UNIVERSITI PUTRA MALAYSIA

DEVELOPMENT OF TAPERED OPTICAL FIBER-BASED SENSOR FOR DETECTION OF DENGUE II E PROTEINS

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By

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

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DEVELOPMENT OF TAPERED OPTICAL FIBER-BASED SENSOR FOR DETECTION OF DENGUE II E PROTEINS

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April 2018

Chairman : Muhammad Hafiz Bin Abu Bakar, PhD
Faculty : Engineering

The escalating cases of dengue around the globe has become a major public health concern with an estimation of 300 million infections, annually. Due to the absence of a cure and a narrow time window for successful detection, survival relies heavily on sensitive, reliable, rapid and accurate diagnostics that would facilitate better clinical management and control over the epidemic. The underlying problem in managing the disease heightens when conventional diagnostics that are available today have crucial set-backs impeding efficient surveillance of the disease. For the past decade, tapered single-mode fibers have exhibited versatility and enticing sensitivity towards changes of its surrounding refractive index, making it favorable to be employed in sensing systems. The research work demonstrates the development of label-free tapered optical fiber-based sensor for the detection of dengue II E proteins. The sensing principle lies within the reaction of evanescent waves driven from the tapering of the optical fiber, towards changes within the external surrounding, in which would produce measurable response that enables to determine the concentration of the proteins. To ensure its selectivity, dengue II E protein complimentary antibodies were immobilized onto the surface of the tapered fiber. The proposed setup obtained a comparable sensitivity of 5.44 nm/nM with a detection limit of 1 pM within a short response time. For further performance enhancement of the sensing system, graphene oxide (GO) and polyamidoamine (PAMAM) dendrimer were integrated to promote higher surface to volume ratio, homogenous adhesion and better molecular orientation. The characteristics of these two nanomaterials are expected to increase the sensitivity of the sensor and its affinity towards dengue II E proteins. With both nanomaterials tested individually as enhancement layers onto the tapered fiber, better sensitivity was obtained when compared to the sensitivity obtained before, with values for PAMAM and GO at 19.53 nm/nM and 12.77 nm/nM, respectively. However, when both layers were applied onto the same tapered fiber, the performance of the sensor was not as satisfactory as PAMAM alone, as it only managed to achieve a sensitivity

value of 13.25 nm/nM. Noting that optical fibers are inexpensive, flexible, and now has shown promising performance in the detection of the dengue virus, it is anticipated of this work to be the first vital steps towards the development of better dengue diagnostics.

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

PEMBANGUNAN SENSOR BERPANDUKAN GENTIAN OPTIK TIRUS UNTUK PENGESANAN PROTEIN DENGGI II E

Oleh

YASMIN MUSTAPHA KAMIL

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Kes-kes denggi terlonjak meningkat serata dunia mengakibatkan 300 juta jangkitan setiap tahun telah menjadi satu kebimbangan kesihatan yang utama. Disebabkan ketiadaan penawar, kemandirian bergantung khusus pada kaedah diagnostik yang sensitif, tepat dan mudah untuk dikendalikan. Masalah dalam menguruskan wabak ini memuncak apabila diagnostik lazim yang ada pada hari ini didapati gagal untuk memastikan pemantauan yang cekap. Untuk beberapa dekad yang lalu, gentian optik tirus telah menunjukkan kebolehan dan kepekaan terhadap perubahan indeks biasan didalam medium menyebabkan penggalakan untuk diterapkan dalam mekanisma sistem deria. Kerja penyelidikan ini memperagakan kemajuan sistem deria berasaskan gentian optik tirus tanpa penanda untuk pengesanan protein Denggi II E. Prinsip pengesanan tersebut terletak pada reaksi gelombang evanesent didorongi daripada proses penirusan gentian optik. Perubahan pada sekeliling gentian optik tersebut akan menghasilkan respon yang boleh diukur untuk mengenalpasti kepekatan protein. Untuk memastikan daya pengesanannya, pelengkap antibodi protein Denggi II akan diterapkan ke atas permukaan gentian optik tirus. Keputusan yg diperoleh menyatakan nilai sensitiviti setinggi 5.02 nm/nM dengan had pengesanan 1 pM dalam tempoh masa 15 minit. Untuk meningkatkan daya pengesanan sistem deria dengan selanjutnya, kajian diteruskan dengan penerapan Grafin oksida (GO) dan dendrimer Polyamidoamine (PAMAM) sebagai lapisan aktif diatas permukaan gentian optik tirus. Ciri-ciri kedua-dua nanomaterial tersebut adalah dijangka untuk meningkatkan kepekaan sensor tersebut dan daya afiniti ke arah protein Dengi II E. Dengan menguji kedua-dua nanomaterial secara berasingan sebagai lapisan aktif ke atas gentian tirus tersebut, daya pengesanan yang lebih baik dapat diperoleh berbanding dengan yang diperoleh tanpa lapisan aktif, dimana nilai sensitiviti PAMAM dan GO ialah 19.53 nm/nM dan 12.77 nm/nM masing-masing. Walaubagaimanapun, apabila kedua-dua lapisan diletak bersama, prestasi sensor tidak memberangsangkan dengan nilai sensitiviti 13.45nm/nM. Mengambil kira bahawa gentian optik adalah murah, anjal,

dan telah menunjukkan prestasi yang mempunyai harapan dalam pengesanan virus Denggi, kerja penyelidikan ini adalah dijangkakan sebagai langkah pertama yang penting ke arah kemajuan untuk diagnostik Denggi yang lebih berkualiti.

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I certify that a Thesis Examination Committee has met on 25 April 2018 to conduct the final examination of Yasmin binti Mustapha Kamil on her thesis entitled "Development of Tapered Optical Fiber-Based Sensor for Detection of Dengue II E Proteins" 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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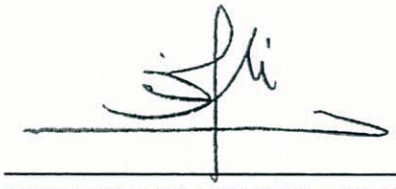

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The thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Declaration by graduate student

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AFM	Atomic force microscope
APTES	(Aminopropyl) triethoxysilane
ASE	Amplified spontaneous emission
ASE	Amplified spontaneous emission
C-H	Methyl
DENV	Dengue virus
DHF	Dengue hemorrhagic fever
DSS	Dengue shock syndrome
C	Capsid
PrM	Protein membrane
NS	Non-structural protein
ELISA	Enzyme linked immunosorbent assay
PCR	Polymerase chain reaction
RT-PCR	Real-time polymerase chain reaction
LSPR	Long surface plasmon resonance
Ge	Germanium
SiO_2	Silicon oxide
HF	Hydrofluoric acid
CO_2	Carbon dioxide
LP_{01}	Fundamental mode
EDX	Energy-dispersive X-Ray
FESEM	Field emission scanning electron microscope
FSR	Free spectral range
G	Generation

GO	Graphene oxide
LOD	Limit of detection
NaCl	Sodium hydroxide
NaOH	Sodium hydroxide
OH	Hydroxyl
OSA	Optical spectrum analyzer
PAMAM	Polyamidoamine
PBS	Phosphate buffer solution
RMS	Root mean square
Si	Silicon
SMF	Single-mode tapered optical fiber
ssDNA	Single-stranded deoxyribose nuclease

CHAPTER 1

INTRODUCTION

1.1 Research Background

The arthropod-borne flavivirus, dengue (DENV), is one of the world's major concerns causing approximately 300 million infections per year [1]. Infection by any of its four distinct serotypes (DENV-1, DENV-2, DENV-3 and DENV-4) may lead to clinical manifestations ranging from asymptomatic infection to more severe and fatal types of dengue fever; dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).

Conventional methods in dengue detection often rely on the presence of immunological proteins. A primary dengue infection usually triggers a slow and low titre production of IgM and IgA antibodies on the 5th day of infection, followed by a surge production of IgG a week later. On the contrary, secondary infection would be countered with a more rapid immune response as antibody titres would shoot up three days after the onset of a common fever [2]. However, the crucial set back of detecting immunological proteins is its absence during the acute phase of infection. Thus, methods as such can only detect primary infection patients with DENV from the 5^{th} day onwards after the onset of symptoms.

For early detection of the disease, diagnostics are now employing sensing systems which target antigenic determinants. It is known that DENV produces 10 different types of proteins with its 11 000 nucleotide-based genome. Three of the proteins are structural proteins for the capsid (C), membrane (prM) and envelope (E) glycoprotein, leaving the remaining 7 as non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) [2]. Given by its name, structural proteins would give rise to the formation of the virion itself. 180 identical copies of the envelope glycoproteins, for example, form the outer membrane of the virion that will facilitate the attachment of the virus to the host cell. Similar to the aforementioned invention, detection kits targeting NS1 proteins have been reported and are available in the market [3]. However, they are purely qualitative restricting its use solely for initial detection, thus, clinical monitoring and progression analysis of the infection are not possible.

Better clinical monitoring would require quantitative assessment where clinical laboratories opt for the enzyme-linked immunosorbent assay (ELISA) technique, or specifically MAC-ELISA (IgG/IgM antibody capture ELISA). The method fundamentally operates on the changes of absorbance based on the ligand-targeted antibody interaction bound on the sensing solid phase. Commercial ELISA kits today offer a detectable range of 1 – 75 ng/ml with a reported detection limit of 1 ng/ml [4]. In spite of the method's enticing capability, such an option requires a complex laboratory infrastructure, technical expertise, time consuming and financial capacity which may be limited in many countries where DENV is endemic. Real-time

polymerase chain reaction (PCR) is also another alternative for quantitative measurement of DENV as it targets the viral genome in the patient's serum [2]. However, due to the method's complexity and high cost, they have yet to be commercialized.

1.2 Problem statement and motivation

Dengue is not a foreign crisis for those who are living in the tropical region. In Malaysia, the infestation of the viral infection continues to worsen ever since its onset back in 1901. All four serotypes have been found to be co-circulating in this country with DENV II being the dominant strain [5]. As we have yet to find a specific vaccine for the virus, controlling the DENV epidemic depends solely on appropriate clinical management that should commence during the acute phase of the viral infection, which is the first three days of infection. Thus, survival of dengue patients depend highly on early, rapid and accurate diagnosis within that narrow time window. Conventional dengue diagnostics include qualitative strip kits and complex techniques like PCR and ELISA which have been found to be unreliable, time-consuming and expensive. These limitations create unnecessary delay which sadly is responsible for 70% of deaths caused by the virus and that is a serious problem [6]. It is inevitable to deny that there is still a significant need for an improved diagnostic method. The complications to the development of a robust dengue diagnostic system left medical institutes no other choice but to monitor the progression of the infection through a general blood analysis which includes platelet, white blood cell, and haematocrit counts. Although the analysis is undoubtedly helpful as supportive data, in actual, it not specific for DENV and does not represent the effect of all DENV serotype infections. Therefore, there is a need for an approach that is able to achieve greater specificity and sensitivity within a shorter amount of time and a more portable setup when compared to conventional methods namely detection strips and ELISA.

1.3 Research objectives

The research work is focused on the development of an optical sensor for sensing DENV II E protein using a functionalized single-mode tapered fiber. The objectives of the study are:

i. To design and fabricate a single-mode tapered fiber with optimized parameters for sensing bulk solutions.
ii. To design and develop a single-mode tapered fiber sensor for the detection of DENV II E proteins.
iii. To design and develop DENV II E protein sensor integrating sensing layers of graphene oxide (GO) and polyamidoamine (PAMAM) dendrimer.
iv. To analyse and compare the performance of both developed sensors

1.4 Research scope

The deployment of tapered optical fiber in sensing systems is particularly enticing as it brings forth an alternative with established compact characteristics and microstructure. Not only that, the exposed nature of tapered optical fiber creates vast opportunities of customisation and integration with other materials to fit the demands of the sensor field, today. The research work looks into the quantitative sensing of DENV II E proteins using a functionalized single-mode tapered optical fiber. DENV II strain was chosen as it has been reported to be the dominant strain in Malaysia. The selectivity of the sensor is determined by surface functionalization of bio-recognition molecules on to the tapered region, whereby in this case, Anti-DENV II E protein specific antibodies are used. For further performance enhancement of the sensing system, GO and PAMAM dendrimer are integrated individually to promote higher surface to volume ratio, homogenous adhesion and better molecular orientation. GO was chosen due to its strong core structure and the abundance of oxygenated groups on the carbon lattice network. On the other hand, the branched-like structure of PAMAM molecules terminated with amino-functional groups is predicted to provide better interaction between the immobilized protein; Anti-DENV II E protein; and the fiber surface. Both materials have great potential in facilitating a more congruent and homogeneous attachment of antibodies onto the tapered fiber. Here, the effects of GO and PAMAM towards the performance of the sensor is observed and compared by testing with different concentrations of monoclonal DENV II E protein solutions. The assessment includes measuring the sensitivity, limit of detection, dissociation constant of the sensor towards the targeted determinant, DENV II E protein, and detection time. These parameters are chosen as they are essential traits in an improved dengue diagnostic system to curb the unreliable and time-consuming methods we have today. It is to be acknowledged that assessing the shelf-life of the sensor and testing the sensor with real serum samples would strengthen the work. Unfortunately, the requirement of certain medical facilities and certification are not available for the time being. The research scope of the work is summarized in Figure 1.1.

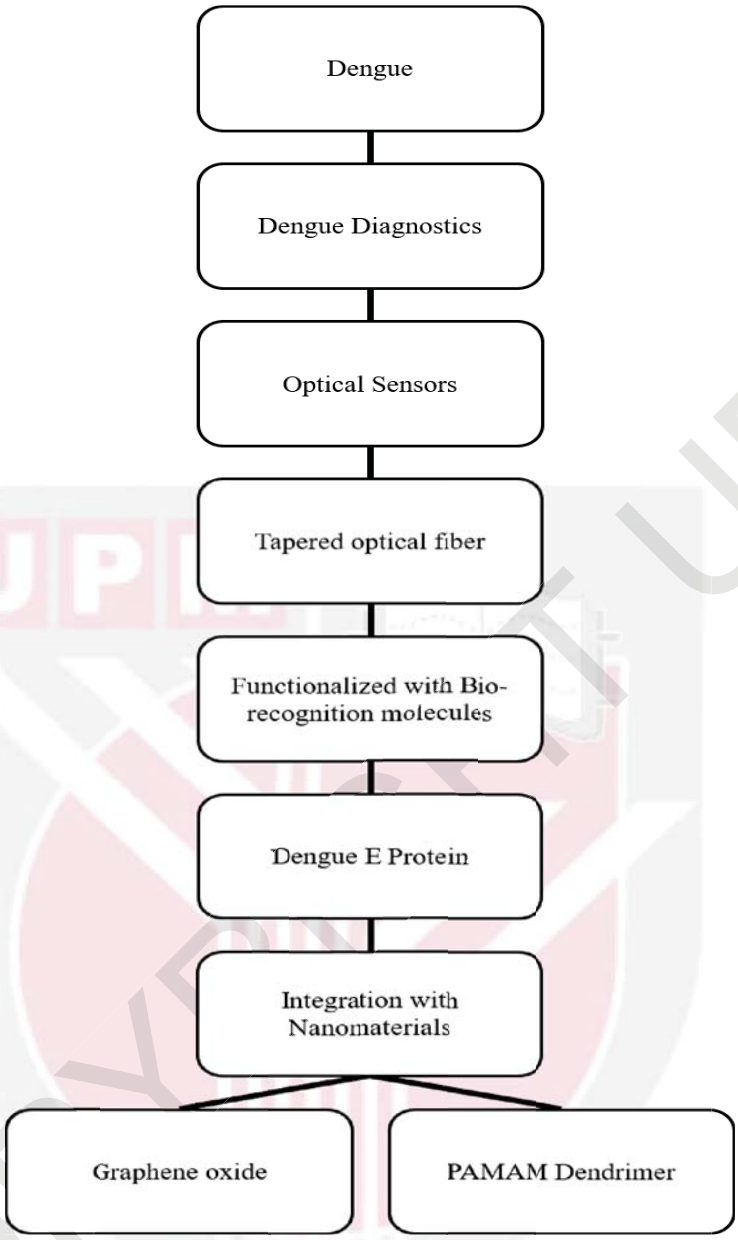

Figure 1.1 : Research scope

1.5 Organization of thesis

The content of the thesis is divided into seven chapters and are outlined as follows:

Chapter 1 delivers a brief overview about the research work. It touches on the current situation of DENV infection, challenges in the dengue diagnostics field, and motivations in conducting the work.

Chapter 2 describes the conventional methods and current trends in dengue diagnostics. Following that is an extensive review on the sensing mechanism of tapered optical fiber based sensors as well as previous studies that are relevant. The emerging technology of nanomaterial integration within optical sensing systems and its applications are also presented in this chapter.

Chapter 3 elaborates on the fabrication of the tapered optical fibers and the characterization of its geometrical dimension to obtain optimum sensitivity. Here, the effects of waist diameter and waist length towards the performance of the tapered optical fiber sensor are experimentally investigated.

Chapter 4 discusses on the functionalization of bio-recognition molecules onto the surface of the tapered optical fiber in order to enhance the selectivity of the sensor. Acknowledging that fact that promoting molecular assembly on the tapered optical fiber is a delicate process, preliminary investigation and optimization of the surface modification method are conducted with Silane-PEG-Biotin and Avidin first before the immobilization of recombinant DENV antibodies.

Chapter 5 describes the subsequent step to what has been discussed in chapter 4, where recombinant DENV II E protein specific antibodies are immobilized onto the tapered optical fiber. It also highlights the performance of the functionalized tapered optical fiber in sensing DENV II E proteins at different concentrations. The performance of the sensor is analyzed by measuring the sensitivity and limit of detection.

Chapter 6 elaborates on the performance of the sensor when integrated with GO and PAMAM dendrimer, individually. It begins with optimizing the deposition method of both nanomaterials by monitoring wavelength shift throughout time. Performance analysis is also conducted and presented in this chapter.

Chapter 7 concludes the study by summarizing key points of the research and introduces recommendations for future work.

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