HETERO-LIGAND PEPTIDE FUNCTIONALIZATION OF GOLD NANOPARTICLES FOR SELECTIVE DETECTION OF COBALT (II) IONS

By

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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Chair : Amir Syahir Amir Hamzah, PhD
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Cobalt (II) ions, Co^{2+} represents one of the heavy metals that poses contamination to the environment. Despite being an essential element, over exposure to Co^{2+} can be detrimental to human health. To combat Co^{2+} contamination, monitoring the level of Co^{2+} with a fast detection technique is of utmost importance. Current techniques for Co^{2+} detection such as inductively coupled plasma spectroscopy, atomic absorption spectrometry and voltammetry are sophisticated, expensive, and laboratory bound. Thus, to overcome this, nanomaterials was often used as probe for the development of colorimetric detection approach due to its simplicity, rapidity, and effectiveness. This research focusses on exploiting the gold nanoparticles (AuNPs) with unique plasmon surface property. The approach involves functionalizing the AuNPs with hetero-ligand peptide owing to its excellent capability for metal ion detection. Herein, the successful functionalization of AuNPs were achieved with the integration of a mono- (GCH-AuNPs and HCH-AuNPs respectively) and hetero-ligand peptide (GCH+HCH-AuNPs). Both peptide ligands were synthesized using solid phase synthesis approach. As both surface ligands of AuNPs formed complexes with Co^{2+}, the synergistic effect of hetero-ligand peptide exhibits excellent colorimetric sensing performances where the sensor produced a color change from red to blue could be observed by the naked eye and UV–visual spectroscopy. There is a shift from 530nm (red) to 660nm (blue) which arises from aggregation effect of the AuNPs. The colorimetric sensing using hetero-ligand was selective towards Co^{2+} at as low as 100 ppb level. The colorimetric sensing towards Co^{2+} also achieved a linear detection range from 100-1000 ppb (R^2 =0.9433) with detection limit was calculated to be at 300 ppb level. The characterization and comparison of the mono-ligand and hetero-ligand system was also supported by the analysis of dynamic light scattering and transmission electron microscope to determine the changes in size of 20 nm AuNPs when exposed to Co^{2+}. This study have demonstrated a great potential of exploiting mixed ligand peptide on nanomaterials in improving the performance of colorimetric sensor of metal ions with high selectivity and sensitivity.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PEFUNGSIAN PEPTIDA LIGAN HETERO TERHADAP NANOPARTIKEL EMAS UNTUK PENGESANAN SELEKTIF ION KOBALT (II)

Oleh

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Ion kobalt (II), Co^{2+} merupakan salah satu logam berat yang menimbulkan pencemaran kepada alam sekitar. Sungguhpun ia adalah elemen penting, pendedahan berlebihan terhadap Co^{2+} boleh memudaratkan kesihatan manusia. Untuk memerangi pencemaran Co^{2+}, pemantauan tahap Co^{2+} dengan teknik pengesanan pantas adalah sangat penting. Teknik semasa untuk pengesanan Co^{2+} seperti spektroskopi plasma yang digabungkan secara induktif, spektrometri penyerapan atom dan voltametri adalah canggih, mahal, dan terikat dengan makmal. Oleh itu, untuk mengatasinya, bahan buatan nano sering digunakan sebagai proba untuk pembangunan pengesanan kolorimetrik kerana kesederhanaan, kepantasan dan keberkesanannya. Penyelidikan ini memberi tumpuan kepada mengeksploitasi nanopartikel emas (AuNPs) dengan sifat permukaan plasmon yang unik. Pendekatan ini melibatkan fungsi AuNPs dengan peptida hetero-ligan kerana keupayaannya yang sangat baik untuk pengesanan ion logam. Di sini, pefungsian AuNP telah berjaya dicapai dengan penyepaduan peptida mono- (GCH-AuNPs dan HCH-AuNPs masing-masing) dan hetero-ligan (GCH + HCH-AuNPs). Kedua-dua ligan peptida telah disintesis menggunakan pendekatan sintesis fasa pepejal. Oleh kerana permukaan kedua-dua ligan terhadap AuNPs telah membentuk kompleks dengan Co^{2+}, kesan sinergistik peptida hetero-ligan mempamerkan prestasi penderiaan kolorimetrik yang sangat baik di mana sensor menghasilkan perubahan warna daripada merah kepada biru dapat diperhatikan oleh mata kasar dan spektroskopi UV-visual. Terdapat peralihan daripada 530nm (merah) kepada 660nm (biru) yang timbul daripada kesan pengagregatan AuNPs. Penderiaan kolorimetrik menggunakan hetero-ligan adalah selektif terhadap Co^{2+} pada paras serendah 100 ppb. Penderiaan kolorimetrik ke arah Co^{2+} juga mencapai julat pengesanan linear dari 100-1000 ppb (R^2=0.9433) dengan had pengesanan dikira pada tahap 300 ppb. Pencirian dan perbandingan sistem mono-ligan dan hetero-ligan juga disokong oleh analisis penyebaran cahaya dinamik dan mikroskop elektron penghantaran untuk menentukan perubahan saiz AuNPs 20 nm apabila terdedah dengan Co^{2+}. Kajian ini menunjukkan potensi yang besar

untuk mengeksploitasi peptida ligan campuran pada bahan nano untuk meningkatkan prestasi pengesanan kolorimetrik ion logam dengan selektiviti dan kepekaan yang tinggi.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science in Nanobiotechnology. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

°C	Degree Celsius
%	Percent
Ag	Silver
AgNPs	Silver nanoparticles
As^{3+}	Arsenic (III) ions
ATCUN	Amino terminal copper and nitrogen
Ba^{2+}	Barium (II) ions
Cd^{2+}	Cadmium (II) ions
Co^{2+}	Cobalt (II) ions
COOH	Carboxylic acid
Cr^{3+}	Chromium (III) ions
Cu^{2+}	Copper (II) ions
CuNPs	Copper nanoparticles
DLS	Dynamic light scattering
EPR	Electron paramagnetic resonance
Eq.	Equivalent
FT-IR	Fourier transform infrared
g	Gram
GCH	Glycine-cysteine-histidine
GCH-AuNPs	Glycine-cysteine-histidine functionalized gold nanoparticles
GCH+HCH-AuNPs	Hetero-ligand glycine-cysteine-histidine and histidine-cysteine-histidine functionalized gold nanoparticles
GSH	Glutathione
HCH	Histidine-cysteine-histidine

HCH-AuNPs	Histidine-cysteine-histidine functionalized gold nanoparticles
Hg^{2+}	Mercury (II) ions
HSAB	Hard soft acid base
ITC	Isothermal calorimetry
kV	Kilovolt
LOD	Limit of detection
µM	Micromolar
µL	Microlitre
mg	Milligram
mL	Millilitre
Mn^{2+}	Manganese (II) ions
M	Molar
NH_2	Amine
Ni^{2+}	Nickel (II) ions
nm	Nanometre
nM	Nanomolar
Pb2+	Lead (II) ions
PdI	Polydispersity index
ppb	Part per billion
ppm	Part per million
RP-HPLC	Reversed phase-high performance liquid chromatography
s	Seconds
SH	Thiol/ sulfhydryl
SPPS	Solid phase peptide synthesis
TEM	Transmission electron microscope

UV-vis	Ultraviolet-visible
Zn^{2+}	Zinc (II) ions

CHAPTER 1

INTRODUCTION

1.1 Background study

Heavy metals are regarded as non-biodegradable elements that occurs naturally and can be ubiquitously found throughout the earth crust. They generally have a specific gravity which is greater than 5.0 with relatively high atomic weight (Ali et al., 2019). Some of them serve their purposes for the metallurgical industry such as cadmium and lead, while some of them are critically essential for the biochemical and physiological reaction in human body such as manganese, copper, cobalt, and zinc. For essential elements of heavy metals, small amount is usually required by the body but it would be lethal if their presence is more than the threshold limit (Jaishankar et al., 2014). Other non-essential heavy metals on the other hand are very toxic if exposed even at low level of concentration such as mercury.

Among the heavy metals, cobalt is widely distributed in nature and are part of wastes by-products. Besides known cobalamin, other cobalt compounds have been regarded as toxic for the environment and human body (Beeson et al., 2016). As a result, over exposure to other cobalt compounds may cause detrimental effects such as vasodilation, flushing, and cardiomyopathy in humans (Kuwar et al., 2014). High concentration of cobalt can also cause acute effects of lung toxicity and asthma, inflammation of the lungs and chest tightness (Paustenbach et al., 2013). In addition, the International Agency for Research on Cancer (IARC) has also identified cobalt as a potential carcinogen (International Agency for Research on Cancer, 2006).

Over the past years there exists an increment to the number of health-associated problems pertaining to cobalt contamination. This is not surprising as nowadays cobalt emission is on the rise due to global urbanization and industrialization (Kumar et al., 2017). In fact, most of the cases of cobalt contamination and human exposure has resulted from the anthropogenic activities such as mining and smelting operations, metal based industrial work, sewage treatment and agricultural production. This leads to the accumulations of cobalt contaminants in water, sludge, air, and soils causing pollution of the environment (Ahmed, 2018). In the long run when living organisms continuously ingest these cobalt contaminants, there will be gradual bioaccumulation in their body which could lead to biomagnification; a phenomenon indicating the metal ions particularly cobalt (II) (Co^{2+}) ions were intensified at the highest hierarchy of trophic levels (Verma and Dwivedi, 2013). This condition would cause severe toxicity when the Co^{2+} were absorbed by the human body.

1.2 Problem statement

Before any remediation action can be taken, the presence of Co^{2+} in the environment must be determined. Many techniques have been developed over time to detect Co^{2+} in the environment such as X-ray fluorescence spectrometry, atomic absorption spectrometry, microprobe and inductively coupled plasma (Ghaedi et al., 2007, Abdolmohammad-Zadeh & Ebrahimzadeh, 2010, Hutton et al., 2014, Okano et al., 2015). These methods detect Co^{2+} in the environment with high sensitivity. However, most of them are complex, time-consuming, and costly. So, they are not suitable for in situ analysis. These constraints necessitate the development of simpler and less expensive Co^{2+} detection techniques.

Among the detection techniques, colorimetric method is the most convenient method as it can be done with ease by observing any changes in color using the naked eye without the aid of any advanced instruments (Vilela et al., 2012). Thus, it would be easier to apply on-site for monitoring and detecting the presence of the Co^{2+}. Colorimetric methods are often developed by using colorimetric dyes and chromogenic agents (Liu et al., 2020). As compared to colorimetric dyes and chromogenic agents, detection techniques based on the utilization of nanomaterials is currently preferred due to their large surface area, high catalytic efficiency, high surface reactivity and strong adsorption capacity (Ullah et al., 2018). Owing to their remarkable properties, nanomaterials not only serve as receptors specific to metal ions, but also generate excellent signals corresponding to various technologies.

Nowadays, nanomaterials particularly AuNPs have been given great attention in environmental monitoring as it has been assembled into functional probes for detecting toxins, heavy metal ions, as well as organic and inorganic pollutants. The smaller size of AuNPs allows them to have a large surface area which can lead to rapid responses. AuNPs also possess unique optical property known as surface plasmon resonance (SPR), a remarkable phenomenon linked with metal nanoparticles that occurs when coherent oscillations of conduction band electrons resonate with the frequency of electromagnetic radiation (Hutter & Fendler, 2004). In the presence of target analyte, plasmon coupling will decrease the energy level of the plasmon band that results in a change of absorption maxima of AuNP solution from 520 nm wavelength to a longer wavelength which consequently changes the color of solution from red to blue color (Yu et al., 2020). To make the AuNPs based colorimetric assay having better selectivity and sensitivity towards the target analyte, AuNPs surfaces can be exploited further to function as a sensing platform via surface chemistry or functionalization (Priyadarshini & Pradhan, 2017).

As compared to the functionalization with protein or DNA, peptides are more versatile and powerful ligands molecules to be utilized in biosensing platforms for metal ion detection (Karimzadeh et al., 2018). This is due to the fact that different side chain of 20 naturally occurring amino acids are capable of forming stable complexes with the great majority of metal ions (Sóvágó & Osz, 2006).

For example, imidazole group of histidine, carboxylate group of aspartate and glutamate, phenol ring of tyrosine and thiol groups of cysteine are often involved in the metal ion coordination and chelation as they can be employed as metal-binding sites in protein (Zou et al., 2015). Furthermore, the amino terminal copper and nickel binding (ATCUN) motifs of peptide derivatives with special structural features of free NH_2-terminus, two amide nitrogens and a histidine residue in the third position can also act as ligand for metal ions (Maiti et al., 2020). Thus, through chemical synthesis or enzymatic biocatalysis, a wide range of peptide chain with high specificity and versatility towards metal ions can be exploited, produced and screened to ensure the desirable binding of metal ions with the peptide (Guzmán et al., 2007).

In this regard many of the published work dealing with the usage of colorimetric nanoparticle sensors have revealed the metal nanoparticles were commonly stabilized by a single functional ligand that has high affinity towards targeted analyte. In more recent years, mixed-ligand functionalized nanoparticles have garnered interest among researchers. It was reported that by utilizing mixed-ligand nanoparticle for biosensing, it greatly improves the sensor sensitivity and selectivity due to the combined effects between different ligand domains (Zeiri, 2020). However, there is a limited report on using a combination of two ligand peptide which are derived from ATCUN motif. Thus, the objective of the present research is to investigate the use of novel ATCUN motif tripeptide functionalized AuNPs in providing a better selectivity and sensitivity in detecting Co^{2+}.

1.3 Objectives

The main objective of this study is to develop a highly selective colorimetric assay for detection of Co^{2+} using hetero-ligand peptide functionalized AuNPs. The specific objectives consist of three parts which are:

1. To synthesize and characterize two novel tripeptide sequence using solid phase peptide synthesis technique.

2. To fabricate AuNPs using mono-ligand and hetero-ligand peptide and compare the selectivity of metal ions using the functionalized AuNPs.

3. To evaluate the sensor performance of the fabricated AuNPs using transmission electron microscope (TEM) and dynamic light scattering and determination of limit of detection by concentration dependency of Co^{2+}.

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