UNIVERSITI PUTRA MALAYSIA

SYNTHESIS AND CHARACTERIZATION OF GADOLINIUM AND GOLD-DOPED LAYERED DOUBLE HYDROXIDE AND GRAPHENE OXIDE NANOCOMPOSITES FOR THERAPEUTIC AGENT DELIVERY

MUHAMMAD SANI USMAN

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By

MUHAMMAD SANI USMAN

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

July 2018

DEDICATION

This thesis is dedicated to my beloved parents Dr. Sani Dawaki Usman and Dr. (Mrs) Yalwa Usman

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

SYNTHESIS AND CHARACTERIZATION OF GADOLINIUM AND GOLD-DOPED LAYERED DOUBLE HYDROXIDE AND GRAPHENE OXIDE NANOCOMPOSITES FOR THERAPEUTIC AGENT DELIVERY

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Chairman: Professor Mohd Zobir bin Hussein, PhD
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Multimodal delivery system (MDS) or theranostic delivery system (TDS) is still at its infancy. In this work, the concept of MDS was employed, where magnesium/zinc aluminium-layered double hydroxides (Zn/Mg-Al LDH) and graphene oxide (GO) were used as nanocarriers (host) to intercalate and adsorb therapeutic agents (chlorogenic acid, prochatetuic acid and gallic acid), and contrast agents; gadolinium (Gd) as well as gold nanoparticles (AuNPs) as guest molecules. The Gd contrast agent was used as the main contrast agent for magnetic resonance imaging (MRI) and the AuNPs served as supporting contrast agent.

The therapeutic and contrast agents were used to develop various the LDH and GO-based nanocomposites. The agents were developed based on ion exchange interaction in the LDH and non-covalent π-π stacking bonding and OH/COOH hydrogen bonding in the GO. The synthesis routes adopted were the Hummer's modified method for GO and co-precipitation for LDH. The mechanism and physico-chemical properties of the nanocomposite formation were studied via characterization processes, such as transmission electron microscopy (TEM) and field emission scanning electron microscopy (FESEM), which were used for shape, size and morphological studies. Fourier transformed-infrared spectroscopy (FTIR) and Raman spectroscopy were used for chemical interaction studies. Inductive coupled plasma emission spectroscopy (ICP–ES), carbon, hydrogen, nitrogen and sulphur analysis (CHNS) and energy-dispersive X-ray (EDS) were used to study the composition as well as purity of the samples. The crystallinity and phase change was studied with X-ray diffraction (XRD) and the ultra violet – visible spectroscopy (UV-Vis) was used for drug release study. The anticancer

efficacies of the nanocomposites and the pure phases were evaluated using human liver cancer cell lines (HepG2) and mouse fibroblast cell lines (3T3) were used in cytotoxicity studies. The inherent signal optimization was done on a 3 Tesla MRI machine, to determine the diagnostic properties of the nanocomposites.

Subsequent amounts of the loaded therapeutic agents were estimated between 15-60%, depending on the nanocarrier and the therapeutic agent. All the pharmacokinetic releases of the therapeutic agents were best fitted to the pseudo-second order kinetic model. The XRD analysis results confirmed the drug intercalation in the LDH galleries and adsorption on the GO surface. Similarly, the FTIR and Raman spectroscopy confirmed the bonding that occurred between the host and guest molecules. CHNS, ICP–ES and EDX equally showed the presence of all the intended compounds and elements in the nanocomposites. The AuNPs grown on the LDH and GO nanocomposites as observed from TEM and FESEM micrographs were poly-dispersed with various shapes and sizes (2-120 nm).

The nanocomposites were observed to inhibit growth of HepG2 cells and showed less toxic in the 3T3 cell lines. Preliminary MR imaging contrast properties test conducted showed enhanced T1 and T2 signals in the samples containing the nanocomposites.

Based on the highlighted results, TDS could serve as potential replacement for the incumbent toxic anticancer agents, which could be used simultaneously in diagnosis.

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

SINTESIS DAN PENCIRIAN KOMPOSIT NANO DWI HIDROKSIDA BERLAPIS DAN GRAPHENE OKSIDA YANG DIDOP GADOLINIUM DAN EMAS UNTUK PENGHANTARAN AGEN TERAPEUTIK

Oleh

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Sistem penghantar multimodal (MDS) atau sistem penghantar teranostik (TDS) untuk penghantaran ubat masih di peringkat awal. Konsep sistem penghantar multimodal telah digunakan di dalam projek ini di mana zink/magnesium dwi-hidrokdsida berlapis (Zn/Mg-Al LDH) dan graphene oksida (GO) telah digunakan sebagai '*nanocarriers*' atau hos. *Nanocarriers* tersebut bertindak sebagai platform untuk interkalasi dan penyerapan agen terapeutik (asid klorogenik, asid prochatetuic dan asid gallic) beserta agen kontras iaitu; gadolinium (Gd) dan partikel nano emas (AuNPs) sebagai molekul tetamu. Agen kontras Gd telah digunakan sebagai agen kontras utama untuk pengimejan resonans magnet (MRI) dan nano partikel emas bertindak sebagai agen kontras sokongan.

Agen-agen terapeutik dan kontras tersebut telah digunakan untuk mensintesis pelbagai nanokomposit dwi-hidrokdsida berlapis (LDH) dan nanokomposit graphene oksida (GO). Agen-agen tersebut telah disintesis berasaskan interaksi pertukaran ion di dalam LDH, ikatan tidak kovalen □-□ dan ikatan hydrogen OH/COOH di dalam GO. Kaedah sintesis yang telah digunakan adalah kaedah Hummer diubahsuai untuk GO dan kaedah pemendakan bersama untuk LDH. Mekanisma formasi dan ciri-ciri fiziko-kimia nanokomposit telah dikaji menggunakan pelbagai kaedah pencirian. Mikroskopi transmisi electron (TEM) dan mikroskopi imbasan elektron pemancaran medan (FESEM) digunakan untuk kajian bentuk, saiz dan morfologi.

Spektroskopi transformasi Fourier inframerah (FTIR) dan spektroskopi Raman digunakan untuk kajian interaksi kimia. Spektrometri pancaran plasma gandingan aruhan (ICP-EOS), analysis unsur CHNS dan pengimbas serakan tenaga sinar X (EDX) turut digunakan untuk mengkaji komposisi dan ketulenan sampel. Kristaliniti dan perubahan fasa dikaji menggunakan pembelauan sinar X (XRD), seterusnya spektroskopi ultraungu tampak (UV-VIS) digunakan untuk kajian pelepasan ubat. Kesan anti-kanser nanokomposit dan fasa tulen telah dinilai menggunakan sel kanser hati manusia (HepG2) dan kajian sitotoksisiti dijalankan menggunakan sel fibroblast tikus (3T3). Pengoptimuman isyarat yang wujud telah dilakukan menggunakan mesin MRI 3 Tesla untuk menentukan ciri diagnostik nanokomposit yang telah disintesis.

Jumlah agen terapeutik yang telah dimuatkan di dalam hos dianggarkan antara 15 – 60% berdasarkan *nanocarrier* dan agen terapeutik yang digunakan. Pelepasan farmakokinetik untuk semua agen terapeutik adalah didapati mengikut model kinetik tertib pseudo kedua. Keputusan XRD menunjukkan ubat telah diinterkalasi di dalam LDH dan diserap di permukaan GO. Keputusan FTIR dan spektroskopi Raman turut menunjukkan ikatan antara hos dan molekul tetamu. Analisis CHNS, ICP-EOS dan EDX semua menunjukkan kehadiran setiap elemen dan sebatian yang dikehendaki di dalam nanokomposit. AuNPs yang disintesis di atas nanokomposit LDH dan GO telah dianalisis melalui TEM dan FESEM dan didapati terdiri daripada pelbagai bentuk dan saiz (2 – 20nm).

Nanokomposit diperhatikan telah menghalang pertumbuhan sel HepG2 dan adalah didapati kurang toksik terhadap sel 3T3. Ujian awal ciri kontras pengimejan resonans magnet menunjukkan peningkatan isyarat T1 dan T2 di dalam sampel yang mengandungi nanokomposit.

Berdasarkan keputusan yang telah diketengahkan, TDS menggunakan nanokomposit berasaskan Zn/Mg LDH atau GO berpotensi untuk menggantikan agen antikanser toksik yang sedia ada dan pada masa yang sama turut boleh digunakan untuk tujuan diagnosis.

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I certify that a Thesis Examination Committee has met on 5 July 2018 to conduct the final examination of Muhammad Sani Usman on his thesis entitled "Synthesis and Characterization of Gadolinium and Gold-Doped Layered Double Hydroxide and Graphene Oxide Nanocomposites for Therapeutic Agent Delivery" 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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LIST OF ABBREVIATIONS

AgNPs	Silver nanoparticles
AuNPs	Gold nanoparticles
CuNPs	Copper nanoparticles
CA	Chlorogenic acid
LHs	Layered hydroxides
LDH	Layered double hydroxides
GO	Graphene oxide
DNA	Deoxyribonucleic acid
MRI	Magnetic Resonance Imaging
UV	Ultraviolet -Visible
LHs	Layered hydroxide salt
WHO	World Health Organization
DOX	Doxorubicin
MTX	Methotrexate
5-Flu	5-Fluorouracil
CPT	Camptothecin
PCA/PA	Protocatechuic
GA	Gallic acid
FRA	Ferulic acid
DFUR	Doxifluridine
CET	Cetirizine
HA	Hippuric acid
CFX	Ciprofloxacin
CA	Chlorogenic acid
ET	Etopoxide
PPT	Podophyllotoxin
TEM	Transmission electron microscopy
PET	Positron emission tomography
CT	Computed tomography
Gd	Gadolinium
FA	Folic acid
T1	Spin–lattice relaxation
T2	Spin–spin relaxation
Gd-DTPA	Gadopentetate dimeglumine
DTPA	Diethylenetriaminepentaacetic acid
PET-CT	Positron emission tomography-computed tomography
PEG	Polyethylene glycol
3T3	Normal fibroblast cell lines
Hela	Cervical cell lines
HepG2	Human liver hepatocellular carcinoma cell lines
MDA-MB-231	Breast cancer cell lines

T	Tesla
NGO	Nanographene oxide
DMSO	Dimethyl sulfoxide
DEMEN	Dulbecco's Modified Eagle Medium
MTT	(3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide)
PBS	Phosphate-buffered saline
$KMnO_4$	Potassium Permanganate
H_3PO_4	Ortho-phosphoric acid
HCl	Hydrochloric acid
MAPGA	Protocatechuic Acid/Gadolinium-Mg/Al LDH
MAPGAu	Protocatechuic Acid/Gadolinium-Mg/Al LDH/AuNPs
GOGPA	Graphene oxide-gadolinium and protocatechuic acid nanocomposite
GOGPAu	Graphene oxide-gadolinium and protocatechuic acid nanocomposite/AuNPs
ZAGCA	Chlorogenic acid/gadolinium-Zn/Al LDH nanocomposite
ZAGCAu	Chlorogenic acid/gadolinium-Zn/Al LDH nanocomposite/AuNPs
GOGCA	Chlorogenic Acid /Gadolinium-Graphene oxide
GOGCAu	Chlorogenic Acid /Gadolinium-Graphene oxide/AuNPs
GOGGA	Gallic Acid/Gadolinium-Zn/Al LDH
GOGGAu	Gallic Acid/Gadolinium-Zn/Al LDH/AuNPs
EDS	Energy dispersive X-ray spectroscopy
FTIR	Fourier-transform infrared
ICP–ES	Inductively coupled plasma atomic emission spectrometry
CHNS	Carbon, Hydrogen, Nitrogen, and Sulphur Analysis
MDS	Multimodal delivery systems
XRD	X-ray diffraction
TGA/DTG	Thermogravimetric and Differential thermogravimetric analyses
SPC	Supramolecular chemistry
GOGPAU	Graphene oxide-based theranostic nanodelivery system
TDS	Theranostic delivery systems
BIT	Bimodal theranostic nanodelivery system
FBV	Fetal bovine serum

CHAPTER 1

INTRODUCTION

1.1 Background

The concept of “nanotechnology” was first introduced by an American physicist known as Richard Feynman as far back as 1959 [1, 2]. The concept of Nanotechnology is still being utilized in various fields of science and other areas of researches, such as nanomedicine, despite age of its inception. As a matter of fact, new research areas such as theranostics, that are currently emerging are based on nanotechnology theory. Nanotechnology is a simple term in any area of science or technology that involves the use of materials within the nanoscale dimensions (nanomaterials).

Nanomaterials are generally considered materials with at least a dimension within the nanoscale. The generally accepted nanoscale is 1-100 nm [3].

1.2 Nanomedicine

Nanomedicine is considered as any field or area of nanotechnology that is applied to prevent or treat human diseases. "Nanomedicine" was first reported by Drexler et al., 1991 [4]. Nanomedicine is vast and covers a wide range of research areas, from materials to engineering, so long the materials used are within the nanoscale [5]. One of the most promising areas of nanomedicine is in novel therapeutics and drug delivery systems, which has reached the level of clinical in some areas of the advanced world [6-8]. Nevertheless, the use nanotechnology in multifunctional delivery for targeting of specific diseases or multiple diseses across biological barriers is still at its infancy stage. Consequently, there is yet to be an established framework for administering dose for nanomaterials-based drug [9].

1.3 Nanodelivery Systems

Nanodelivery system refers the use of nanomaterials or nanostructured as delivery agents for materials, mainly therapeutic agents, diagnostic or the combination of both (theranostic), and other food bioactives [10]. The system offers an opportunity for stability, solubility improvement and control, bioavailability as well as reduction in toxicities of therapeutic agents [11, 12].

Multimodal or multifunctional nanodelivery systems are very much at early stage. The system encompasses therapeutic and diagnostic agents with morethan one imaging applications [13]. As mentioned earlier, the most important aspect of nanoscience in nanomedicine is the area of drug delivery; the purpose of drug targeting is to enable site-specific delivery of the drugs, which would help in doing away with unwanted side-effects. The nanocarrier can easily be used in drug dosage control since the drugs will be delivered to a specific target. Lately, nanotechnology is being applied in the simultaneous diagnosis and treatment of cancer related diseases in theranostic delivery systems [14]. The system is derived from the wide knowledge of molecular science of human body. The therapeutic agents used in this work are listed below:

Gallic acid (GA) is naturally occurring polyhydroxyl phenolic compound that can be found in different varieties of fruits. It has medicinal and disease preventive properties, such as anti-inflammatory, antibacterial and antiviral. The natural product has anticancer properties, which makes it good candidate for cancer chemotherapy. [15, 16]. However, the anticancer properties of the plant-based material is yet to be fully explored.

Protocatechuic acid (PA) is a natural product of numerous medicinal plants sources. The plants include *hibiscus sabdariffa* L, *hypericum perforatum* L and *Ginkgo biloba* L, whereas the pharmacological properties of the protocatechuic acid include, anti- antimicrobial [17], inflammatory [18], cardioprotective and antigenotoxic [19], antimutagenic [20], and most importantly anticancer [21] and antitumor [22]. The therapeutic agent has potentials of being a worthy anticancer agent.

Chlorogenic acid (CA) is a phenolic compound that is naturally occurring and originates from coffee. Chlorogenic acid has medicinal properties such as antioxidants and anticancer properties, antiaging and neurodegenerative diseases protective properties [23].

1.4 Problem Statement

Cancer disease remains a major cause of mortality globally. The deaths associated with cancer are increasing yearly, as reported by the world health organisation (WHO) [24]. Although there are various methods of cancer treatment, chemotherapy remains the most utilised form of cancer treatment. This could be due to the availability of varieties of chemotherapeutic agents. However, reports have indicated that most of the chemotherapeutic agents are toxic and had caused various unwanted side-effects, such as vomiting and hair

loss. This is understandably due to non-selective target of cells by the anticancer agents. Thus, the use of these agents poses a threat to human health.

All cancer treatments require prior diagnosis, which are mostly done using molecular imaging techniques. Magnetic resonance imaging (MRI) is often employed for this purpose. However, MRI contrast agents are administered to patients prior to the imaging. The contrast agents have also been reported to be toxic even in their chelate forms and less toxic in nanocomposites form.
A possible solution to this problem is to deliver the therapeutic agents to the cancer cells, which in turn could protect the healthy cells and by extension will eliminate the side-effects. Although some researchers have tried to develop anticancer drug and therapeutic agent's delivery systems via nanocarriers, a universal multi delivery system is still lacking. A holistic delivery system were both the therapeutic and the contrast agents can be delivered to the cancer cells region will be more effective in the treatment of cancer. Therefore, this work is focused on developing a theranostic delivery system where the diagnostic and the therapeutic agents can be delivered using different nano delivery agents.

1.5 Hypothesis

Theranostic nanocomposites will reduces the problem of toxicities of therapeutic and contrast agents towards healthy cells and will provide better cancer diagnosis and treatment than the current toxic chemotherapy treatment and diagnosis with contrast agents. Better yet, it will provide the option of holistic and more precise approach towards treatment of cancer.

1.6 Scope of Study

The inspiration of this study is derived from the fact that anticancer agents currently been used in chemotherapy are toxic and harmful to normal human cells. The MRI contrast agents used in cancer diagnosis are equally toxic to certain extent. This project is aimed at producing unique nanocomposites that will simultaneously deliver both the therapeutic and diagnostic agents to the cancer sites. The theranostic nanocomposites in this work were developed using different nanocarriers, therapeutic agents, and contrast agents. The nanocomposites were tested with cancer and normal cell lines as well as with MR imaging equipment. The nanocomposites could serve as potential theranostic anticancer agents for more efficient and less toxic cancer treatment than the incumbent chemotherapy treatment.

1.7 Objectives

The purpose of this study is to develop theranostic delivery systems for simultaneous delivery of anticancer and MRI contrast agents. The systems will integrate various natural occurring phenolic therapeutic agents [gallic acid (GA), protocatechuic acid (PA) and chlorogenic acid (CA)], and diagnostic agents [gadolinium (Gd) and gold nanoparticles (AuNPs)] loaded on Zn/Mg-Al layered double hydroxide (LDH) and Graphene oxide (GO) nanocarriers. The theranostic systems have the capability to enhance MRI contrast via the T1 signals as well as to deliver the therapeutic agents simultaneously. The general toxicities, if any, of the contrast and therapeutic agents is expected to be reduced in the nanocomposite form.

The specific objectives for the theranostic delivery systems development are highlighted below:

i. To prepare and incorporate the various therapeutic and contrast agents into the nanocarriers.
ii. To characterize the physico-chemical properties of the synthesized nanocomposites loaded with the various therapeutic agents using various characterization techniques.
iii. To study the cytotoxicity and therapeutic agents release pattern of the therapeutic agents loaded nanocomposites.
iv. To evaluate the anticancer activities of the theranostic nanocomposites.
To determine the MRI contrast enhancement properties of the prepared theranostic nanocomposites.

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