UNIVERSITI PUTRA MALAYSIA

DRUG DELIVERY SYSTEMS BASED ON IRON OXIDE MAGNETITE-LAYERED DOUBLE HYDROXIDE NANOPARTICLES FOR LIVER ANTI-CANCER DRUGS

MONA EBADI

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By

MONA EBADI

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

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DEDICATIONS

Dedicated to the kind angels who:
all the unique and beautiful experiences of my life owe their presence; my kind father,
my dear mother and my merciful husband.

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

DRUG DELIVERY SYSTEMS BASED ON IRON OXIDE MAGNETITE-LAYERED DOUBLE HYDROXIDE NANOPARTICLES FOR LIVER ANTI-CANCER DRUGS

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January 2021

Chair : Prof Mohd Zobir Bin Hussein, PhD
Institute : Advanced Technology

The current strategy for cancer treatment focuses on anti-cancer drugs but they have inimitable problems because of adherence to healthy cells. In chemotherapy, if the effect of the medication is specifically restricted to the target cells, it can significantly reduce these detrimental effects.

Lately, iron oxide nanoparticles (FNPs) have received much attention for targeted drug delivery. It has been shown that the chemical binding of the drug to the magnetic nanoparticles which are coated by a biodegradable polymer such as polyethylene glycol (PEG) and polyvinyl alcohol (PVA) and carried by a nanocarrier like layered double hydroxides (LDHs) is a reliable method of delivering the drug.

The purpose of this work is to develop a controlled release anti-cancer drug formulation. For this purpose, FNPs as the core was coated with different biocompatible polymers such as PEG and PVA, and also co-coated by two types of nanocarriers; layered double hydroxides (Mg/Al-LDH and Zn/Al-LDH) as the shell, loaded with different anti-cancer drugs; 5-fluorouracil (5-FU) and sorafenib (SO). Both active drugs were encapsulated separately onto iron oxide which is coated with PEG or PVA and Mg/Al-LDH or Zn/Al-LDH to form 8 different magnetic nanoparticles; iron oxide-polyethylene glycol-5-fluorouracil-Mg/Al-LDH (FPEGFU-MLDH), iron oxide-polyethylene glycol-5-fluorouracil-Zn/Al-LDH (FPEGFU-ZLDH), iron oxide-polyvinyl alcohol-5-fluorouracil-Mg/Al-LDH (FPVAFU-MLDH), iron oxide-polyvinyl alcohol-5-fluorouracil-Zn/Al-LDH (FPVAFU-ZLDH), iron oxide-polyethylene glycol- sorafenib-Mg/Al-LDH (FPEGSO-MLDH), iron oxide-polyethylene glycol-sorafenib- Zn/Al- LDH (FPEGSO-ZLDH), iron oxide-polyvinyl alcohol-sorafenib-Mg/Al-LDH (FPVASO-MLDH) and iron oxide-polyvinyl alcohol-sorafenib-Zn/Al-LDH (FPVASO-ZLDH), respectively.

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The results of XRD, TGA, and FTIR analyses of the magnetic nanoparticles showed the presence of the coating layers on the surface of the FNPs for all the as-synthesized samples. The VSM analysis showed that the magnetic nanoparticles retain their superparamagnetic property. FESEM, DLS, and HRTEM, and it was found that the sizes of all the synthesized nanoparticles were in the nanoscale range. The coating effect on a drug release, the loading efficiency, and percentage loading of drugs were also investigated using the HPLC and UV-Vis in two different phosphate buffer solutions at pH 4.8 and 7.4 and demonstrated that polymer coverage was one of the effective strategies in controlling the drug release and enhanced the percentage of drug loading. The cytotoxicity studies revealed that the anticancer nanodelivery systems show a much better anticancer activity of the magnetic-based nanoparticles compared to their counterparts, the free drugs on HepG2 cells. At the same time, it also found that the nanoparticles are less toxic compared to the normal fibroblast, 3T3 cells.

Based on the results obtained in this work, the novel co-coated magnetic nanoparticles with two carriers were found to be suitable for drug delivery. It is anticipated that the nanoparticle developed in this work is non-toxic, non-immunogenic, biocompatible, biodegradable, and has a longer retention time in the body, therefore improve efficacy and bioavailability.

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

SISTEM PENGHANTARAN DADAH BERDASARKAN NANOPARTIKAL OXIDA BESI MAGNETIT-HIDROXIDA BERLAPIS GANDA UNTUK DADAH ANTI-KANSER HATI

Oleh

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Strategi semasa untuk rawatan barah memberi tumpuan kepada ubat-ubatan anti-kanser sitotoksik tetapi ubat-ubatan ini mempunyai masalah yang tidak dapat diatasi yang disebabkan terutamanya oleh kecacatan kualiti pengedaran yang seragam dan kesan sampingan kerana terlekatan ubat tersebut kepada sel-sel yang sihat. Dalam kemoterapi, jika kesan ubat secara khusus dibatasi pada sel sasaran, ia dapat mengurangkan keberkesananya secara signifikan. Akhir-akhir ini, nanopartikel superparamagnetik besi oksida (FNP) mendapat banyak perhatian untuk penyampaian ubat kepada sasaran kerana. Telah ditunjukkan bahawa ikatan ubat ke nanopartikel magnetik yang dilapisi oleh kimia polimer seperti polietilena glikol (PEG) dan polivinil alkohol (PVA) yang boleh terurai dan dibawa oleh nanokarrier seperti hidroksida berlapis ganda (LDH) adalah kaedah yang boleh dimanfaatkan untuk penyampaian ubat.

Tujuan penyelidikan ini adalah untuk mengubah dan mengembangkan formulasi penyampaian ubat anti-barah. Untuk tujuan ini, superparamagnetik besi oksida sebagai teras, dilapisi dengan polimer serasibio yang berbeza seperti PEG dan PVA, dan juga dilapisi oleh dua jenis nanokarrier; hidroksida berlapis berlapis (Mg/Al-LDH dan Zn/Al-LDH) sebagai cengkerang yang dimuat dengan ubat-ubatan anti-kanser yang berbeza iaitu 5-fluorouracil (5-FU) dan sorafenib (SO). Kedua-dua ubat aktif digabungkan secara berasingan kepada nanopartikel besi oksida yang dilapisi dengan PEG atau PVA dan Mg/Al-LDH atau Zn/Al-LDH untuk membentuk 8 nanopartikel magnet baru; besi oksida-polietilena glikol-5-fluorouracil-Mg/Al-LDH (FPEGFU-MLDH), besi oksida-polietilena glikol-5-fluorouracil-Zn/Al-LDH (FPEGFU-ZLDH), besi oksida-polivinil alkohol-5-fluorouracil-Mg/Al-LDH (FPVAFU-MLDH), besi oksida-polivinil alkohol-5-fluorouracil-Zn/Al-LDH (FPVAFU-ZLDH), besi oksida-polietilena glikol-sorafenib-Mg/Al-LDH (FPEGSO-MLDH), besi oksida-polietilena glikol-sorafenib-Zn/Al-LDH (FPEGSO-ZLDH), besi oksida-polivinil alkohol-sorafenib-Mg/Al-LDH (FPVASO-MLDH) dan besi oksida-polivinil alkohol-sorafenib-Zn/ Al-LDH (FPVASO-ZLDH).

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Hasil analisis XRD, TGA dan FTIR daripada nanopartikel magnetik menunjukkan adanya nanopartikel magnetit, polimer, LDH dan ubat-ubatan untuk semua sampel yang telah disintesis. Analisis VSM bagi sampel yang akhir iaitu yang mengandungi ubatan menunjukkan bahawa nanopartikel magnetik mengekalkan sifat superparamagnetiknya. FESEM, DLS dan TEM, didapati bahawa ukuran semua nanopartikel yang disintesis berada dalam julat skala nano. Kesan lapisan pada pelepasan ubat, kecekapan pemuatan dan pemuatan peratusan ubat juga telah dikaji menggunakan UV-Vis dan HPLC. Hasil kajian ini menunjukkan bahawa liputan polimer adalah salah satu strategi berkesan dalam mengawal pelepasan ubat dan meningkatkan peratusan pemuatan ubat. Kajian sitotoksisiti menunjukkan bahawa sistem penyampaian nano antikanser menunjukkan aktiviti antikanser yang lebih baik pada sel HepG2 bagi nanopartikel berasaskan magnet, berbanding dengan rakan sejenisnya, ubat bebas. Pada masa yang sama, juga didapati bahawa nanopartikel kurang beracun terhadap ujian sel fibroblas normal, 3T3.

Berdasarkan penyelidikan ini, nanopartikel yang telah diubahsuai adalah yang paling sesuai digunakan untuk penyampaian ubat, terutamanya nanopartikel magnetik yang bersalut dengan polimer. Dijangkakan bahawa nanopartikel yang telah diubahsuai hasil daripada penyelidikan ini tidak beracun, tidak imunogenik, serasibio, biodegradasi dan mempunyai masa pengekalan yang lebih lama dalam badan, dan meningkatkan keberkesanan dan ketersediaan bio.

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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 Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

3T3	Normal Human Fibroblast
5-FU	5-Fluorouracil
EDX	Energy Dispersive X-ray
FESEM	Field Emission Scanning Electron Microscopy
FNPs	Superparamagnetic Iron Oxide Nanoparticles
FPEGFU-MLDH	Iron Oxide nanoparticles coated with Polyethylene Glycol and Magnesium-Aluminum-Layered Double Hydrate -loaded with 5-Fluorouracil
FPEGFU-ZLDH	Iron Oxide nanoparticles coated with Polyethylene Glycol and Zinc-Aluminum-Layered Double Hydrate -loaded with 5-Fluorouracil
FPEGSO-MLDH	Iron Oxide nanoparticles coated with Polyethylene Glycol and Magnesium-Aluminum-Layered Double Hydrate-loaded with Sorafenib
FPEGSO-ZLDH	Iron Oxide nanoparticles coated with Polyethylene Glycol and Zinc-Aluminum-Layered Double Hydrate-loaded with Sorafenib
FPVAFU-MLDH	Iron Oxide nanoparticles coated with Polyvinyl alcohol and Magnesium -Aluminum-Layered Double Hydrate -loaded with 5-Fluorouracil
FPVAFU-ZLDH	Iron Oxide nanoparticles coated with Polyvinyl alcohol and Zinc-Aluminum-Layered Double Hydrate-loaded with 5-Fluorouracil
FPVASO-MLDH	Iron Oxide nanoparticles coated with Polyvinyl alcohol and Magnesium-Aluminum-Layered Double Hydrate-loaded with Sorafenib
FPVASO-ZLDH	Iron Oxide nanoparticles coated with Polyvinyl alcohol and Zinc-Aluminum-Layered Double Hydrate-loaded with Sorafenib

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FTIR	Fourier Transform Infrared
HepG2	Human Hepatocellular Carcinoma Cells
HPLC	High-Performance Liquid Chromatography System
HRTEM	High-resolution Transmission Electron Microscopy
ICP-OES	Inductively Coupled Plasma Optical Emission Spectrometry
MLDH	Magnesium-Aluminum-Layered Double Hydrate
MNPs	Magnetic Iron Oxide Nanoparticles
MTT	Methylthiazol tetrazolium
PEG	Polyethylene glycol
PSA	Particle Size Distribution Analysis
PVA	Poly vinyl alcohol
SO	Sorafenib
TGA/DTG	Thermogravimetric and Differential Analysis
UV-VIS	Ultra violet-visible
VSM	Vibrating Sample Magnetometer
XRD	X-Ray Diffraction
ZLDH	Zinc-Aluminum-Layered Double Hydrate

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CHAPTER 1

INTRODUCTION

1.1 Background of study

In recent years, research on nanosized materials and manufacturing processes, design and the development of nanoparticles are increasing. Nanomaterials are used in a variety of fields; engineering, nanotechnology and nanoscience, biotechnology, pharmacy and medicine, etc (Bayda, Adeel, Tuccinardi, Cordani, & Rizzolio, 2020; Patra et al., 2018). One of the new applications of nanomaterials is in the field of medicine, or the so-called nanomedicine. Currently, many researchers are exploring and developing the properties and applications of nanoparticles in the medical area, especially for cancer treatment (Boulaiz et al., 2011).

According to medical reports, one of the largest and common causes of death in human society is cancer. Researchers have explored different ways to treat cancer (Gmeiner & Ghosh, 2014). Chemotherapy has been used to treat cancer for almost 50 years and significant progress in drug manufacturing for a variety of cancer has resulted in the improvement of the understanding of the physico-chemical properties of drug molecules and the identification of cellular uptake mechanism (DeVita & Chu, 2008). This method has an influence on the cell genetic system through the destruction of cellular structures, cell growth inhibition and prevents the proliferation of cancer cells. Although this method has a role to treat cancer, short half-life in blood, low-efficiency of cell entry and the effect on other healthy parts of the body next to the cancerous tissue and limited side effects is some of the main disadvantages of this method (Cheng, Hsieh, & Tsai, 2018). To overcome this problem, researchers have been designed a targeted drug delivery system that can deliver effective amounts of the drug to the target cells. For this purpose, nanomaterials and in particular iron oxide nanoparticles have received much attention due to their high chemical stability, simple and low-cost manufacturing process, as well as unique intrinsic properties (A. Ali et al., 2016). Additionally, magnetic iron oxide nanoparticles are very widespread due to their non-toxicity and surface reactivity which are easily modified via biocompatible coatings agents (A. Ali et al., 2016; Hernández‐Hernández, Aguirre‐Álvarez, Cariño‐Cortés, Mendoza‐Huizar, & Jiménez‐Alvarado). Polymers are widely used as coating agents. Neutral, hydrophobic, biodegradable, non-toxic and safe polymers such as polyvinyl alcohol (Brady, Dürig, Lee, & Li, 2017; Fujii, 2008) and polyethylene glycol (Antarnusa, 2020; Wei et al., 2016) are generally used for this purpose. PVA and PEG can control drug release and increase the blood circulation half-life over an extended period of time and inhibit excessive drug dosage.

Layered double hydroxides (LDHs) are other types of drug carriers that are biodegradable, non-toxic and have a simple production process with two-dimensional non-silicate structures. This compound is comprised of alternating positively charged metal-hydroxide nanolayers (bivalent or trivalent cations) and interlayer anions. LDHs can exchange their interlayer counters anions such as nitrate or phosphate with other

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beneficial anions, such as drugs, fungicides or other active agents (Saifullah, Arulselvan, et al., 2014). The anion-exchange capability of these compounds makes it possible to use as ideal carriers and protective agents for the active agents. These agents are protected from destruction and variation in the body environment by the LDH interlayers and released at the target organ or tissue (Saifullah, Arulselvan, et al., 2014).

According to previous studies and reports, anticancer drug activities when used alone have low efficacy due to less specificity and limited side effects. Although the chemotherapeutic agents rapidly kill cancer cells, however, it kills the normal cells due to its inherent toxicity. Therefore, the side effects commonly occur including the decrease in blood cell production (myelosuppression), digestive inflammatory response (mucositis) and hair loss (alopecia). Additionally, the toxicities associated with chemotherapeutic drugs leads to nausea, vomiting and anemia because of a sudden exposure of drugs to the body organs. Apart from these side effects, the poor solubility in water, low bioavailability reduces the efficacy of anticancer drugs (Senapati et al., 2016). Therefore, the use of a novel drug delivery system including magnetic nanoparticles along with appropriate carriers that can reduce the side effects of the drug seems necessary (Patra et al., 2018). The main goal of the modern targeted drug delivery is to modify the surface of magnetic iron oxide nanoparticles using polymers and other nano-coatings agents along with an anticancer drug that is compatible with the human body conditions (Aguilar, 2012; Tekade, Maheshwari, Soni, Tekade, & Chougule, 2017). One of the important advantages of this new drug delivery system is the maximum efficacy, ease of use, drug dose reduction, avoids unintended side effects in healthy cells and increasing convenience and patient acceptance. Magnetic drug targeting is injected into the body or consumed orally, enters the circulatory system and uses the adsorption properties to the external magnetic field and moves to the target site for complete treatment (Tiwari et al., 2012).

1.2 Problem Statement of study

In recent years, liver cancer cases are the fastest-increasing due to lifestyle changes in modern societies. Perhaps the most common treatment method to treat this disease is chemotherapy. Chemotherapy is a type of drug treatment that applies powerful anti-cancer drugs to kill the cancer cells in the body, but the major problem associated with this treatment method was the poor performance of drugs, adverse and painful side effects.

Due to these problems, studies have been conducted to perform chemical modification of the drug to reduce side effects (Araújo, Martins, Azevedo, & Sarmento, 2018; Juillerat-Jeanneret & Schmitt, 2007) and improve drug efficacy (Huang et al., 2017). On the other hand, previous comprehensive studies revealed that (Hegazy et al., 2017) agglomeration of the iron oxide nanoparticles may pose a negative effect on their potential for drug delivery application (J. Yang, Fan, Xu, & Xia, 2017). To prevent the aggregation of iron oxide nanoparticles, their surface must modify using a coating agent such as polymers and layered double hydroxides. It was found that good magnetic properties of iron oxide nanoparticles with core-shell structure are maintained even after they were coated (Mahmoudi, Shokrgozar, et al., 2009); (Zhou, Yuan, & Wei, 2011).

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In the present study, we synthesized and characterized a novel magnetic drug targeting nanocarrier in which magnetic iron oxide nanoparticles were used as the core, and coated with surface-active agents; polyethylene glycol and polyvinyl alcohol and along with liver anti-cancer drugs; sorafenib and 5-fluorouracil were encapsulated between the magnesium or zinc-aluminium layered double hydroxides interlayers. The proposed nanocarriers are suitable for magnetic targeting drug delivery systems and led to drug activities with controlled release properties, longer circulation time and reduced side effects. Apart from the polymers used in this study, LDHs was also capable of protecting the drug from entering the bloodstream until it reached the target and preventing rapid drug release.

1.3 Hypothesis

The following hypothesis is anticipated in this work,

Using the core-shell type nanodrug delivery system, the functions of the drug can be maximized in terms of therapeutic efficacy and minimized the side effects on the patient's body as a result of the modification of the drug compound.

Optimization of parameters such as the ratio of the carrier to the drugs and types of coating agents, then these nanocarriers could load more drugs and the release of the drugs can be modified by the latter. With the presence of the magnetic iron oxide nanoparticle as the core, this enables the release of the drug at the target sites, thus enhance the therapeutic efficacy and reduce the side effect.

If coating agents are used on the surface of iron oxide nanoparticles for a controlled drug delivery system then, it can increase the drug release capacity, control the period of release time besides protecting the drug among layers of layered double hydroxide.

1.4 Objectives of study

The objectives of this work are as follow:

1. To synthesize 5-fluorouracil or sorafenib coated on the surface of magnetite nanoparticles (core) in the presence of polymer, polyethylene glycol or polyvinyl alcohol (shell) and intercalate between the interlayers of the zinc-aluminum or magnesium-aluminum-layered double hydroxide as new magnetic nanodrug delivery system namely FPEGFU-MLDH, FPVAFU-MLDH, FPEGFU-ZLDH, FPVAFU-ZLDH, FPEGSO-MLDH, FPVASO-MLDH, FPEGSO-ZLDH, and FPVASO-ZLDH.

2. To characterize the synthesized sample characterization, as well as their controlled release properties.

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3. To evaluate the cytotoxicity assay of all the synthesized samples, sheer magnetite nanoparticles, pure 5-fluorouracil and sorafenib, magnetite nanoparticles coated by polymer as well as magnetite nanoparticles co-coated with polymer and layered double hydroxide.

4. To evaluate the toxicity profiles of naked 5-fluorouracil and sorafenib as well as pure magnetite nanoparticles, magnetite nanoparticles coated by polymer and magnetite nanoparticles co-coated by polymer and layered double hydroxide towards HepG3 (cancer cell line) and 3T3 (normal cell line).

5. To develop magnetic nanoparticles using LDHs as co-coated agents to protecting the drug and preventing rapid drug release upon administration in the bloodstream until reaching to the target site.

1.5 Significance of study

The finding of studies will be contributed to the advancement of liver cancer treatment of better efficacy compared to the counterpart. Traditionally, many ways for treatments of liver cancer have been practiced but their beneficial values have been not well-documented. The present study was performed to develop several new liver anti-cancer nanodelivery systems with new functionality based on the core, magnetite iron oxide nanoparticles and the shells with good biocompatibility. Several magnetite iron oxide nanoparticles co-coated by polymers and layered double hydroxides were prepared and examined to find new formulations for liver anti-cancer drugs; 5-fluorouracil and sorafenib. A total of eight (8) nanocarriers with good biocompatibility, high drug loading capacity, protection of the drugs into the LDH interlayers, controlled release of the drugs and reduced drug doses will be designed and synthesized. Additionally, they could reduce the side effects of drugs and offering a good cytotoxicity effect on normal cell lines.

1.6 Scopes of study

All the essential elements in nano-drug delivery which are going to be covered in the present study can be found in the following sections: First, co-precipitation as a facile, convenient and the most popular method was used to synthesize magnetite nanoparticles as a core. The reason for choosing magnetite is its magnetic property, which can be directed at the body using a magnetic field, but the allowable amount of magnetite that is not harmful to living organisms must be considered. This amount is not a high value and it is necessary to create a magnetic property in the samples with a small value of magnetite. In addition, there are limits to the supply of external magnetic field equipment that able to move magnetic drugs in the body. Second, the synthesized magnetiticnano drug particles were coated with a polymeric shell as a coating agent and the optimal polymer with the highest performance was studied (polymer PVA and PEG). The selected polymer should create the best bonding between the drug and magnetite, which this issue limits the choice of polymer. Third, magnesium and zinc-aluminium layered double hydroxide (Mg and Zn/Al-LDH) were constructed using the co-precipitation

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method and the suitable LDHs in the drug delivery system was determined. Although the LDHs used for drug protection and controlled drug release, however, the utilization of two coating agents partly reduces the magnetic property of the core (magnetite). Finally, the structural, physico-chemical (XRD, HR-TEM, FESEM, FTIR, TGA) and *in vitro* cell biocompatibility was also evaluated. Additionally, the effects of two prevalent drugs for treating liver cancer (Sorafenib and 5-Fluorouracil) on normal and cancer cells were evaluated in vitro by MTT assay. In this study, it was limited to perform *in vivo* tests on living organisms.

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