UNIVERSITI PUTRA MALAYSIA

DEVELOPMENT OF ANTI-CANCER AND ANTI-HYPERTENSIVE NANODELIVERY SYSTEMS USING MAGNETITE IRON OXIDE-POLYMERIC NANOPARTICLES

DENA DORNIANI

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By

DENA DORNIANI

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

March 2015

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DEDICATED

To my Mom, Dad and my sister whose valuable support and belief gave me strength to complete my study

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

DEVELOPMENT OF ANTI-CANCER AND ANTI-HYPERTENSIVE NANODELIVERY SYSTEMS USING MAGNETITE IRON OXIDE-POLYMERIC NANOPARTICLES

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March 2015

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

Nanoscience and nanotechnology have received considerable attention due to their benefits to many areas of research and application such as pharmaceutical industry, medicine, electronics and tissue engineering. Much of nanoscience and nanotechnologies are concerned with producing new materials especially for use as diagnosis, and drug delivery systems.

According to the World Health Organization and Cancer Research UK, the top two causes of death in the world are due to the hypertension (one of the primary risks factors for cardiovascular diseases) and different known cancers that affect humans.

As such, different types of carriers have been used to design different anti-cancer and anti-heypertensive therapeutic and diagnostic agents. The new developing drug delivery system has capability in which the drugs can be released in a sustained manner over long periods of time into the targeted tissue. Therefore, it enable an almost constant level of drug to be kept in the bloodstream (by injection method) or delivering it to a specific region of the gastrointestinal tract, orally for treatment of cancers and cardiovascular diseases.

In order to reduce the toxicity of uncoated magnetite nanoparticles and prevent their aggregation which occurs due to dipole-dipole attraction of magnetic particles different biocompatible polymers were used as a coating material. One of the polymer that was used as a coating material for nanoparticles is a natural polymer, chitosan. Due to NH_3^+ groups of chitosan, it can be attracted by by $-OH^-$ groups of iron oxide nanoparticles to inhibit the nuclear growth of iron oxide. The other polymer known as poly ethylene glycol (PEG) which is soluble in both polar and nonpolar solvents due to the presence of polar oxygen atom and nonpolar $(CH_2)_2$ group in it. Also, because of coating the nanoparticles with a neutral and hydrophilic compound such as PEG and polyvinyl alcohol (PVA), the circulatory half-life can be increased from minutes to hours or days.

This study aimed at the synthesis and development of several anti-cancer and an anti-hyperthensive nanodelivery formulations using iron oxide nanoparticles (FNPs) coated

with different biocompatible polymers such as chitosan (C), PEG and PVA, loaded with different active drugs namely gallic acid (GA), 6-mercaptopurine (MP) and perindopril erbumine (PE). A total of 7 nanocomposites based on the aforementioned anti-cancer drugs; GA and MP and anti-hyperthensive drug; PE were prepared by co-precipitation method to increase the residence time in the body via a sustained release formulation to increase the clinical efficacy. All the three (3) active drugs (GA, MP and PE) were integrated separately into iron oxide-chitosan and iron oxide-PEG to form 6 new nanocomposites; FCG, FCMP-D, FCPE, FPEGG, FPEGMP-2 and FPEGPE, respectively. The active drug gallic acid (GA) was also loaded onto iron oxide nanoparticles-polyvinyl alcohol (FNPs-PVA) to form FPVAG nanocomposite.

The release behaviour of the drugs from the nanocomposites in human body simulated phosphate buffer solutions (PBS) of intercellular lysosomal pH 4.8 and human blood pH 7.4 was found to be of sustained manner. The release of the drugs from FCG, FCMP-D, FCPE, FPEGG, FPVAG, FPEGMP-2 and FPEGPE nanocomposites in human body simulated phosphate buffer solutions (PBS) of human blood pH 7.4 is 1600, 6300, 5631, 6905, 6594, 5520 and 4223 minutes respectively, compared to 1300, 2500, 2743, 5775, 3045, 4440 and 1231 minutes respectively, at pH 4.8 (human body simulated PBS of intercellular lysosomal). It was found that all the nanocomposites were more biocompatible compared to free drugs although the choice of coating materials as well as loading percentages of active drugs on the nanocarrier was found to be affected by the activity of the resulting materials.

Cytotoxicity study of FCG nanocomposite shows greater anticancer activity as was seen in MCF7 cell lines than in HT29 cell lines. Also, after 72 hours of treatment, the FCG nanocomposite was not toxic to a normal human fibroblast (3T3) cell lines in the tested doses.

The FCMP-D nanocomposites, shows better anticancer activity against leukemia cell lines (WEHI-3B) than FCMP and pure drug. The IC_{50} for the FCMP-D is 1.19 ± 0.45 μg/mL compared to 4.94 ± 0.76 μg/mL for FCMP nanocomposite after 72 hours post treatment exposed to 0.47-30 μg/mL concentrations.

It was found that the FPEGG nanocomposite demonstrated higher anticancer effect on the breast cancer cell lines (MCF7) in almost all concentrations tested (0.78-25.0 μg/mL) compared to FPVAG nanocomposite.

Anticancer activity of FPEGMP-2 nanocomposite was found to be slightly higher than FPEGMP-0.5 in a dose-dependent manner on the leukemic cell lines (WEHI-3B) after 72 hours of treatment exposed to 1.9-60 μg/mL concentrations. This may be attributed to the differences in the percentage of 6-mercaptopurine between the two nanocomposites. Also, MP which is loaded into the surface of FNPs-chitosan compared to FNPs-PEG nanocarrier with the same molar ratio, shows better cytotoxicity effect which is due to the role of chitosan.

The whole study shows that, iron oxide nanoparticles had a negligible effect in normal and all cancerous cell lines tested in this study. It was found that between 70-100% of cells remaining viable from 0.47 μg/mL to 60.0 μg/mL concentrations. Thus, the cytotoxicity to cancerous cell lines are likely attributable to release of active drugs (GA and MP) from the nanocarrier rather than the effect of the carrier itself.

Therefore, this study demonstrated that all the new nanocomposites show controlled release property of the active drugs, and therefore can be exploited for drug delivery system. Results from in vitro studies were found to be very encouraging to further conduct the in vivo studies of these novel nanocomposites in the future.

Abstrakt tesis yang dikemukakan kepada Senate of Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor of Falsafah

PEMBANGUNAN ANTI-KANSER DAN ANTI-HIPERTENSI SISTEM PENGHANTARAN NANO MENGGUNAKAN ZARAH NANO MAGNETIT BESI OKSIDA-POLIMERIK

Oleh

DENA DORNIANI

Mac 2015

Pengerusi: Prof. Mohd Zobir Bin Hussein, PhD
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Nanosains dan nanoteknologi telah mendapat perhatian kerana ia membawa banyak manfaat kepada pelbagai bidang penyelidikan dan aplikasi seperti dalam industri farmasi, perubatan, elektonik and kejuruteraan tisu. Sebahagian daripada nanosains dan nanoteknologi adalah mengenai penghasilan bahan-bahan baru terutamanya dalam penggunaan diagnosis penyakit, dan sistem penghantaran ubatan.

Menurut Pertubuhan Kesihatan Sedunia (WHO) dan Penyelidikan Kanser UK, dua penyebab utama kematian di dunia adalah disebabkan oleh hipertensi (salah satu faktor risiko utama untuk penyakit kardiovaskular) dan lebih 200 jenis kanser berbeza yang telah dikenal pasti yang memberi kesan kepada manusia.

Sehubungan dengan itu, pelbagai jenis pembawa telah di gunakan untuk mereka bentuk pelbagai anti-kanser dan terapi anti-hipertensi dan agen diagnosis. Penghasilan ubat-ubatan yang baru boleh di hasilkan secara beransur dalam jangka masa yang panjang kedalam tisu yang di sasarkan. Oleh yang demikian, ianya boleh menghasilkan paras ubat yang malar untuk di simpan dalam aliran darah (melalui kaedah suntikan) atau penggunaannya di tempat tertentu saluran gastrousus, secara oral untuk merawat kanser dan penyakit kardiovaskular.

Untuk merendahkan ketoksikan magnetit butiran/zarah nano yang tidak bersalut dan untuk mencegah agregasi yang belaku di sebabkan oleh penarikan dwikutub magnetit butiran/zarah, bioserasi polimer berlainan boleh di gunakan sebagai bahan salutan.

Salah satu polimer yang di gunakan sebagai bahan salutan untuk butiran/zarah nano ialah polimer semula jadi, kitosan. Disebabkan oleh wujudnya kumpulan NH_3^+ dalam kitosan, ia boleh tertarik kepada kumpulan besi oksida butiran/zarah nano $–OH^-$, untuk merencat pertumbuhan nukleus besi oksida. Polimer lain di kenali sebagai poli etilena glikol (PEG) yang larut dalam pelarut berkutub dan pelarut tidak berkutub kerana kehadiran kumpulan atom oksigen berkutub and tidak berkutub $(CH_2)_2$ dalam etilena glikol. Juga boleh digunakan, kerana salutan butiran/zarah nano dengan sebatian semula jadi hidrofilik seperti PEG dan polivinil alkohol (PVA), tempoh separuh hayat boleh meningkat daripada minit ke jam dan ke hari.

Kajian ini di khususkan kepada sistesis dan perkembangan beberapa anti-kanser dan rumusan anti-hipertensi butiran/zarah nano menggunakan besi oksida butiran/zarah nano (FNPs) disaluti dengan bioserasi polimer yang berbeza seperti kitosan (C), PEG dan PVA, sarat dengan ubat-ubat aktif yang berbeza iaitu asid galik (GA), 6-merkaptopurina (MP) dan perindopril erbumin (PE). Sejumlah tujuh (7) komposit nano berdasarkan kepada ubat-ubatan anti-kanser (GA dan MP) dan ubat-ubatan anti-hipertensi (PE) telah di sediakan secara kaedah mendakan bersama untuk meningkatkan masa penempatan di dalam badan melalui formulasi pelepasan secara malar untuk meningkat kemujaraban klinikal. Ketiga-tiga (3) ubat aktif (GA, MP dan PE) telah dikamirkan secara berasingan ke dalam besi oksida-kitosan, dan besi oksida-PEG untuk membentuk enam (6) komposit nano baru: masing-masing FCG, FCMP-D, FCPE, FPEGG, FPEGMP-2 dan FPEGPE. Ubat aktif asid galik (GA) juga telah dimuatkan ke dalam besi oksida butiran/zarah nano–polivinil alkohol (FNPs-PVA) untuk membentuk FPVAG komposit nano.

Cara pembebasan ubat-ubatan dari komposit nano ke dalam tubuh badan manusia dalam sebatian penimbal fostat (PBS) lisosom intersel pH 4.8 dan darah manusai pH 7.4 telah di dapati berada dalam keadaan malar. Pembebsan ubat-ubatan daripada komposit nano FCG, FCMP-D, FCPE, FPEGG, FPEGMP-2 dan FPEGPE ke dalam tubuh badan manusia dalam sebatian penimbal fostat (PBS) darah manusia pH 7.4 masing-masing ialah 1600, 6300, 5631, 6594, 6905, 5520 dan 4223 minit, berbanding dengan masing-masing 1300, 2500, 2743, 5775, 3045, 4440 dan 1231 minit pada pH 4.8 (badan manusia merangsang PBS lisosom intersel). Telah di depati bahawa komposit nano lebih bioserasi berbanding dengan ubat-ubatan yang bebas walaupun pilihan bahan salutan serta peratusan pemuatan ubat-ubatan aktif bagi pembawa nano di dapati terjejas oleh aktiviti daripada bahan-bahan yang terhasil.

Kajian kesitotoksikan daripada FCG komposit nano menunjukkan, aktiviti anti-kanser lebih tinggi daripada sel MCF7 berbanding sel HT29. Juga, selepas rawatan selama 72 jam, FCG komposit nano menunjukkan ia tidak toksik kepada sel fibroblast (3T3) manusia normal dalam dos yang diuji.

Komposit nano FCMP-D menunjukkan aktiviti anti-kanser yang lebih baik berbanding sel leukemia (WEHI-3B) daripada FCMP dan ubat asli. IC_{50} untuk FCMP-D ialah 1.19 ± 0.45 μg/mL berbanding 4.94 ± 0.76 μg/mL untuk FCMP komposit nano selepas 72 jam pasca rawatan setelah terdedah kepada 0.47-30 μg/mL kepekatan.

Telah di dapati bahawa FPEGG komposit nano menunjukkan kesan anti-kanser yang lebih tinggi pada sel barah payudara (MCF-7) dalam hampir semua kepekatan yang diuji (0.78-25.0 μg/mL) berbanding FPVAG komposit nano menunjukkan aktiviti anti-kanser yang lebih baik selepas 72 jam rawatan.

Aktiviti anti-kanser FPEGMP-2 komposit nano di dapati sedikit lebih tinggi daripada FPEGMP-0.5 dalam dos terkawal bagi sel leukemia (WEHI-3B) selepas 72 jam rawatan terdedah kepada kepekatan 1.9-60 μg/mL. Ini menyumbang kepada perbezaan peratusan 6-merkaptopurina di antara dua komposit nano. Juga, MP yang di muatkan ke dalam permukaan FNPs-kitosan berbanding pembawa nano FNPs-PEG dengan nisbah molar yang sama, menunjukkan kesan kesitotoksikan yang lebih baik di sebabkan oleh peranan kitosan.

Keseluruhan kajian menunjukkan, butiran/zarah nano besi oksida mempunyai kesan yang boleh diabaikan didalam sel kanser biasa dan semua, di antara 70-100% sel berdaya hidup selebihnya daripada kepekatan 0.47 μg/mL ke 60.0 μg/mL. Oleh itu, kesitotoksikan pada sel kanser mungkin boleh dikaitkan dengan perlepasan ubat-ubatan aktif (GA dan MP) daripada pembawa berbanding dengan kesan pembawa itu sendiri.

Oleh itu, kajian ini menunjukkan bahawa kesemua komposit nano dapat mengawal sifat pembebasan ubat-ubatan aktif, dan dengan itu boleh di eksplotasi untuk sistem perubatan. Keputusan dari kajian in vitro di dapati amat menggalakkan untuk meneruskan kajian in vitro bagi komposit nano ini pada masa akan datang.

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I certify that a Thesis Examination Committee has met on 25 March 2015 to conduct the final examination of Dena on her thesis entitled "Development of Anti-Cancer and Anti-Hypertensive Nanodelivery Systems Using Magnetite Iron Oxide-Polymeric Nanoparticles" 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.

Members of the Thesis Examination Committee were as follows:

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Date: 17 June 2015

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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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

GA	Gallic acid
MP	6-Mercaptopurine
ACE	Angiotensin-converting enzyme
FNPs	Iron oxide nanoparticles
PE	Perindopril erbumine
C	Chitosan
FC	Iron oxide nanoparticles coated with chitosan
FCG	Iron oxide nanoparticles coated with chitosan-loaded with gallic acid
FCMP	Iron oxide nanoparticles coated with chitosan-loaded with 6-mercaptopurine which is dissolved in hot ethanol
FCMP-D	Iron oxide nanoparticles coated with chitosan-loaded with 6-mercaptopurine which is dissolved in dimethyl sulfoxide
MP-D	6-Mercaptopurine dissolved in dimethyl sulfoxide
FCPE	Iron oxide nanoparticles coated with chitosan-loaded with perindopril erbumine
FPEGG	Iron oxide nanoparticles coated with polyethylene glycol-loaded with gallic acid
FPVAG	Iron oxide nanoparticles coated with polyvinyl alcohol-loaded with gallic acid
FPEGMP-0.5	Iron oxide nanoparticles coated with polyethylene glycol-loaded with 0.5% of 6-mercaptopurine
FPEGMP-2	Iron oxide nanoparticles coated with polyethylene glycol-loaded with 2% of 6-mercaptopurine
FPEGPE	Iron oxide nanoparticles coated with polyethylene glycol-loaded with perindopril erbumine
M_s	Saturation magnetization
M_r	Remanent magnetization
H_C	Coercive field

MNPs	Magnetic nanoparticles
NPs	Nanoparticles
BSA	Bovine serum albumin
MPS	Mononuclear phagocytic system
GI	Gastrointestinal
DMSO	Dimethyl sulfoxide
PBS	Phosphate buffer silane solutions
FBS	Fetal bovine serum
PXRD	Powder X-ray diffraction
FTIR	Fourier transform infrared spectroscopy
TGA/DTG	Thermogravimetric and differential thermogravimetric
VSM	Vibrating sample magnetometer
FESEM	Field emission scanning electron microscope
TEM	Transmission Electron Microscopy
UV-VIS	Ultraviolet-Visible Spectrophotometer
ATCC	American tissue center

CHAPTER 1

INTRODUCTION

1.1 Background of study

Nanotechnology is the ability of controlling and manipulating matter at atoms and molecules scale that help to understand fundamental physics, chemistry, biology and technology of nanometer-scale objects.

Nanotechnology and nanoscience have been developed in many areas of research since the last decade, to synthesize and characterize different nanoparticles for various applications (Choo et al., 2011; J. Kim et al., 2009; Mulder et al., 2009; Subramani & Ahmed, 2011) such as electronics, pharmaceutical industry, medicine and tissue engineering. This technology is concerned with producing new materials especially in medicine which caused the growth of global market.

New technology is developed and changed the medical world due to the combination of nanotechnology and medicine named as nanomedicine. Most of applications of nanomedicine is currently developed and concerned with producing new nanomaterials especially for the disease diagnosis (Kabanov & Gendelman, 2007), deliver drugs, heat, light or other substances to targeted specific sites in the human body and molecular imaging. To minimize the damage cells to the healthy cells in the body in this way needs the appropriate engineering particles to allow detection and/or treatment of diseases or injuries within the targeted cells (Kumar & Jee, 2013).

Researchers study on molecular and cellular levels to produce different nanoparticles, due to limitations of conventional chemotherapy such as general systemic distribution of drug and targeted to the tumor site. Therefore, choosing the correct nanoparticles for the suitable methods of drug delivery is very important (Kayal & Ramanujan, 2010).

One of the most common worldwide disease is hypertension which is a risk factor in kidney and cardiovascular diseases (Brás et al ., 2014). Management of hypertension needs long-term treatment which involves frequent multi-drug dosage, side effects and noncompliance of patients to the treatment. Therefore, design a new drug delivery offer many advantages such as targeted delivery and protection of drugs from physic-chemical degradation, prolonged therapeutic effect in a sustained manner (Bonadio et al., 1999), decreasing the frequency dosage, reduced side effects, improved bioavailability, better patient compliance and easy termination of drug therapy (Ahad et al., 2014).

Nanoparticles can enhance the selectivity for eliciting cancer cell death and minimizing toxicity on noncancerous cells therefore, different types of nanoparticles have been used to design anti-cancer and anti-hypertensive therapeutic and diagnostic agents (Koh et al., 2010; Riaz & M Ashraf, 2013). The new nanoparticles should enable an almost constant level of drug to be kept in the bloodstream (by injection method) or delivering it to a specific region of the gastrointestinal tract, orally for treatment of cancers and cardiovascular diseases.

Nowadays, nanoparticles have been used as delivery vehicles based on polymeric or inorganic formulations or a combination of both. This is due to many advantages such as longer retention time in the tissue and increasing the circulatory half-life from minutes to hours or days. This allows for the prolonged release of the loaded compound (Niven, 1995; Tsapis et al., 2002). Among the different types of nanoparticles, polymeric magnetite nanoparticles have considered to be the promising candidates due to their superparamagnetic behaviour of iron oxide nanoparticles and surface-modification properties which has the ability to target drugs and reducing toxic side effects on healthy cells and tissues.

Functionalized biodegradable nanoparticles have the potential to be used in different biological and medical applications such as hyperthermia (Jordan et al., 1999a), magnetic resonance imaging (Allen & Cullis, 2004; Prabaharan & Mano, 2004), cell separation (Wang, D. et al., 2004), diagnostic tests assays for early detection of diseases and targeted drug delivery systems (Yang et al., 2011) to minimize secondary systemic negative effects (Aprahamian et al., 1987). In order to reduce the toxicity of uncoated magnetite nanoparticles and prevent their aggregation which occurs due to dipole-dipole attraction of magnetic particles different biocompatible polymers can be used.

One of the most commonly used coating materials for nanoparticles is a natural polymer, chitosan. Due to NH_3^+ groups of chitosan, it can be attracted by by $-OH^-$ groups of iron oxide nanoparticles to inhibit the nuclear growth of iron oxide. The other polymer known as poly ethylene glycol (PEG) which is soluble in both polar and nonpolar solvents due to the presence of polar oxygen atom and nonpolar $(CH_2)_2$ group in ethylene glycol (Yousefpour et al., 2015). PEGylation, is the procedure in which the drug molecule can be attached and conjugated to PEG to protect the PEGylated hydrophobic drug from the immune system of the human body. Neutral and hydrophilic compound such as PEG and PVA can enhance the blood circulation half-life from minutes to hours or days (Bunker, 2012) in the physiological environment by minimizing or removing the protein adsorption to the NPs.

Previous studies showed that the choice of carrier used to deliver the drug to the tissue is playing an important role (Iyer et al., 2006). Therefore, the selected carrier must be biocompatible, biodegradable and non-toxic. Due to the limitations of conventional chemotherapy including insufficient local drug concentration in the tumor site, organic-inorganic nanocomposites such as core-shelled magnetic nanoparticles have received considerable attention for the last decade. These magnetic-polymeric nanocomposites can be used as contrast agents, thermal therapy for cancer which can be concentrated to target sites through an external magnetic field.

1.2 Problem statement

Gallic acid, 3,4,5-trihydroxybenzoic acid (GA) (Figure 1.1) is an anticancer drug and a natural product of the hydrolysis of tannins in black tea, gallnut and sumac. Previous studies have been conducted to intercalate the gallate anion with zinc-aluminium-layered double hydroxide (Yeganeh Ghotbi & bin Hussein, 2010) and zinc-layered-gallate nanohybrid (Hussein et al., 2009) as the sustained-release vehicles and structural memory effect, respectively. It was also found that gallic acid (GA) shows a significant inhibition of cell proliferation in a series of cancer cell lines such as A549

(Maurya et al., 2011) and induced apoptosis in esophageal cancer cells (TE-2) but not in non-cancerous cells (CHEK-1) (Faried et al., 2007). Therefore, choosing a proper controlled-release formulation could improve the prolonged release of the loaded compound and the GA anticancer activity.

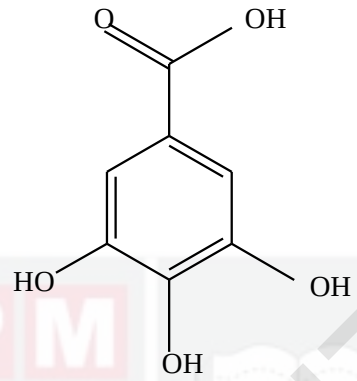

Figure 1.1 Structure of gallic acid

Purine derivatives, 6-mercaptopurine (MP) (Figure 1.2), have been used as an antitumor drug, particularly against leukemia, inflammatory bowel disease and pediatric non-Hodgkin's lymphoma (Dorniani et al., 2013a). Previous studies proved an anticancer activity of 6-mercaptopurine as a synthesized complex with silver and gold in a HeLa (cervical cancer) cell lines (Cuin et al., 2011). In addition, 6-mercaptopurine has currently attracted significant attention as an antineoplastic agent due to the good coordination properties of its nitrogen and sulfur donor sites, which can be bonded at N-1, N-3, N-7, and N-9. Therefore, it has the ability to transform the nitrogen donor sites into the respective ribosides (Selvaraj et al., 2006). Moreover, the acid-base properties of MP, enabling to have a variety of metallic bonding sites which causes to have more anticancer activity than the free drug (R. Acevedo-Chávez et al., 1997; Bariyanga & Luyt, 2001; Selvaraj et al., 2006; M.-H. Sorouraddin et al., 2011). Here, iron oxide nanoparticles (FNPs) coated with chitosan/polyethylene glycol were chosen as the carriers to improve the controlled-release formulation of targeted active drug, MP. The viability of leukemia cell lines (WEHI-3B) and normal mouse fibroblast (3T3) were examined when exposed to these new compounds.

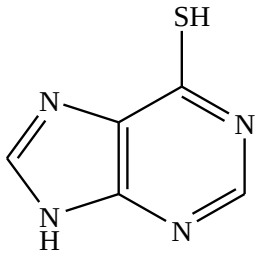

Figure 1.2 Structure of 6-mercaptopurine

Perindopril, (2S, 3As, 7aS)-1-[(2S)-2-[[(2S)-1-ethoxy-1-ox-opentan-2-y1)]amino] propanoyl]-2,3,3a,4,5,6,7,7a-octahydroin-dole-2-carboxilic acid (Figure 1.3), belongs to the class of antihypertensive drugs, that acts by angiotensin-converting enzyme (ACE) inhibitor, which hydrolysis of the ester group after oral administration in the liver into the active diacid, perindoprilat (Pascard et al., 1991). In oral administration, a tablet in a 1:1 ratio of perindopril salt with erbumine (tert-butylamine) is used. Previous studies reported the intercalation of perindopril erbumine (PE) anion with zinc-aluminium-layered double hydroxide and magnesium-aluminium-layered double hydroxide (Al Ali et al., 2012a; Al Ali et al., 2012b) to develop the sustained release formulation, however due to the fast release a proper controlled release system was selected as the system.

Here, PE was used as a model drug to synthesis new nanocomposites, for the improvement of the controlled-release properties.

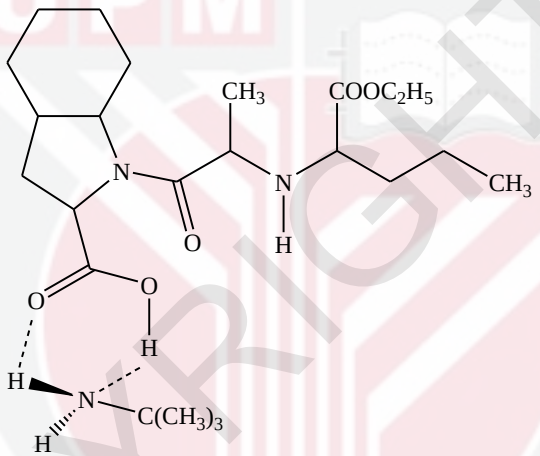

Figure 1.3 Structure of perindopril erbumine

Organic-inorganic nanocomposites such as core-shelled magnetite iron oxide nanoparticles-polymers, enabling to reduce the undesired side effects of drug usage to a specific region of the gastrointestinal tract by oral way and keeping almost constant level of drug in the bloodstream (by injection method). Therefore, the dosage of the drugs in the oral administration can be designed as a single dose rather than the multiple one causes to have new possible controlled-release formulations which help to increase the clinical efficacy of drugs (Rathbone et al., 2002).

An organic polymer which is coated on the surfaces of magnetic nanoparticles can prevent their aggregation and improve their stability and chemical reactivity by adding some specific functional groups which is required for adsorption (L. Chen et al., 2010; R. Y. Hong et al., 2006; Utech et al. 2010; Vidal-Vidal et al., 2006; D.-L. Zhao et al., 2010). Therefore, core-shell magnetic iron oxide nanoparticles which is encapsulated in a polymeric coating, are desired for biomedical applications due to many properties such as the low cost, small sizes (< 100 nm), ease of preparation, drug targeting via external magnetic field, low cytotoxicity, biocompatibility and inert in body fluids.

Therefore, in this work gallic acid, 6-mercaptopurine and perindopril erbumine were coated on the surfaces of encapsulated iron oxide with different polymers such as chitosan, polyethylene glycol and polyvinyl alcohol to get sustained-release formulations.

1.3 Objectives

The objectives of this study are as follows:

1) Preparation of gallic acid, 6-mercaptopurine and perindopril erbumine coated on the surface of encapsulated magnetite iron oxide nanoparticles with chitosan and controlled release study of these nanocomposites

2) Preparation of 6-mercaptopurine and perindopril erbumine coated on the surface of encapsulated magnetite iron oxide nanoparticles with polyethylene glycol to form nanocomposites, FPEGMP-2 and FPEGPE, respectively and study the controlled-release properties.

3) Preparation of gallic acid coated on the surface of encapsulated magnetite iron oxide nanoparticles with polyethylene glycol/polyvinyl alcohol to form two new nanocomposites and comparing them for the controlled-release study

4) Study the cytotoxicity of magnetite iron oxide nanoparticles, iron oxide nanoparticles-chitosan, iron oxide nanoparticles-polyethylene glycol and iron oxide nanoparticles-polyvinyl alcohol, as well as gallic acid and perindopril erbumine

5) Study the toxicity profiles towards leukemia (WEHI-3B) cell lines of 6-mercaptopurine as well as iron oxide nanoparticles and iron oxide nanoparticles-chitosan/polyethylene glycol

1.4 Significance of study

The presented studies in this thesis were performed to develop new anti-cancer and anti-hypertensive nanodelivery systems based on magnetite iron oxide-polymer nanoparticles and composites. Several magnetite iron oxide-polymer nanoparticles and composites were prepared and examined to find new controlled release formulations for drug actives such as gallic acid, 6-mercaptopurine and perindopril erbumine. All seven (7) nanocomposites could enhance the activity of drugs and could be used to reduce the undesired side effects of drug usage to a specific tissue due to the accomplishment of drugs released over long periods of time and showing a good cytotoxicity effect towards normal and anti-cancer cell lines.

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LIST OF PUBLICATIONS

Research publications

Dena Dorniani, Mohd Zobir Bin Hussein, Aminu Umar Kura, Sharida Fakurazi, Abdul Halim Shaari and Zalinah Ahmad. "Preparation of Fe_3O_4 magnetic nanoparticles coated with gallic acid for drug delivery". *International Journal of Nanomedicine*. 2012;7: 5745-5756.

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Dena Dorniani, Aminu Umar Kura, Samer Hasan Hussein-Al-Ali, Mohd Zobir Bin Hussein, Sharida Fakurazi, Abdul Halim Shaari and Zalinah Ahmad. "Release behavior and toxicity profiles towards leukemia (WEHI-3B) cell lines of 6-mercaptopurine-PEG-coated magnetite nanoparticles delivery system". *Scientific World Journal*. 2014;2014:11, Article ID 972501.

Dena Dorniani, Aminu Umar Kura, Mohd Zobir Bin Hussein, Sharida Fakurazi, Abdul Halim Shaari and Zalinah Ahmad. "Controlled-release formulation of perindopril erbumine loaded PEG-coated magnetite nanoparticles for biomedical applications". *Journal of Materials Science*. 2014;49:8487-8497.

Conferences and workshops

Dena Dorniani, Mohd Zobir Bin Hussein, Abdul Halim Shaari, Zalinah Ahmad. "Preparation, characterization and synthesis of Fe_3O_4 magnetic nanoparticles using for drug delivery". International Conference on Nanotechnology 2012 (ICONT 2012), Universiti Malaysia Pahang, Kuantan, Malaysia.

Dena Dorniani, Mohd Zobir Bin Hussein, Abdul Halim Shaari, Zalinah Ahmad. "Synthesis and characterization of magnetic nanoparticles using for drug delivery". Fundamental Science Congeress 2012 (FSC 2012), Universiti Putra Malaysia, Malaysia.

Attendance in the 6th Nanotechnology Cancer Asia-Pacific (NCAP) Network Meeting, (Healthcare session I of APAN 37th Video Conferencing meeting) on 23 January at IDEC Alpha, Video Conference Meeting, 2014, Universiti Putra Malaysia.

Dena Dorniani, Mohd Zobir Bin Hussein, Aminu Umar Kura, Sharida Fakurazi. "Cytotoxic profiles of nanodrug delivery based on 6-mercaptopurine-coated magnetite-PEG nanoparticles towards leukemia (WEHI-3B) cell lines". Scientific Cancer Research Poster Competition in conjunction with Cancer Awareness Carnival 2014, Universiti Putra Malaysia.

Workshop on Advanced Materials and Nanotechnology (WAMN 2011), "Synthesis, characterization and application of carbon nanotubes", Organized by the *Institute of Advanced Technology (ITMA), Faculty of Engineering and Faculty of Science*, 2011, Universiti Putra Malaysia.

Workshop on Cell Culture & Flow-Cytometry 2013, "Cell Culture & Flow-Cytometry workshop 2013", Organized by the *Institute of Bioscience*, Universiti Putra Malaysia.

Workshop on Advanced Materials and Nanotechnology 2014 (WAMN 2014), Organized by the *Institute of Advanced Technology (ITMA)*, Universiti Putra Malaysia.