UNIVERSITI PUTRA MALAYSIA

FABRICATION, CHARACTERIZATION AND FUNCTIONALIZATION OF SINGLE-WALLED CARBON NANOTUBE CONJUGATED WITH TAMOXIFEN AND ITS ANTICANCER POTENTIAL AGAINST HUMAN BREAST CANCER CELLS

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ITMA 2018 24

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By

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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

FABRICATION, CHARACTERIZATION AND FUNCTIONALIZATION OF SINGLE-WALLED CARBON NANOTUBE CONJUGATED WITH TAMOXIFEN AND ITS ANTICANCER POTENTIAL AGAINST HUMAN BREAST CANCER CELLS

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Chairman : Assoc. Prof Khamirul Amin Matori, PhD
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Even though progress has been made in decreasing breast cancer mortality, it is still one of the major causes of death worldwide. Chemotherapy the most common cancer treatment has severe and lethal side effects. This thesis reports, the use of a drug delivery system for cancer treatment and single wall carbon nanotubes (SWCNT) employed as novel one-dimensional nanomaterials as a drug vehicle. The advantage of SWCNT is, they are capable of delivering therapeutic agents and imaging agents, having the ability to overcome various biological barriers and to localize into the target tissue. This approach not only resulted in enhanced efficacy of the drug but also minimized drug toxicity to the healthy tissues and organs. Due to the importance of cancer treatment and seeking for the safe alternative drug delivery vehicle this comprehensive study was started with the fabrication of SWCNT, its purification, characterization, functionalization followed by its toxicity evaluation (human hepatocyte) and anticancer potential determination against human breast cancer cells.

In this study, the SWCNT was fabricated using modified chemical vapor deposition (CVD) method and the fabricated SWCNT subjected to the two-step acid purification technique. The results of Raman spectrometry, SEM, TEM, HRTEM microscopy and TGA confirmed the success of highly pure SWCNT synthesis. Moreover, the biocompatibility and toxicity of fabricated SWCNT to the human hepatocyte (Chang ATCC: CCL-13) was evaluated *in vitro*. The toxicity evaluation of SWCNT against human hepatocyte cells indicated that concentrations below 50 µg/ml of SWCNT appeared to be nontoxic to the human hepatocyte cells. With regard to the potential of SWCNT in the delivery of cancer drugs, it seems this concentration of SWCNT could be promising for the delivery

of cancer drugs. In the next step, the SWCNT was functionalized to contain free carboxylic acid and hydroxyl groups to be loaded with tamoxifen (SWCNT-PEG). Then, the functionalized SWCNT (SWCNT-PEG) conjugated with tamoxifen (SWCNT-PEG-TAM) and further characterized using Fourier-transform infrared spectroscopy (FTIR) and nuclear magnetic resonance spectroscopy (NMR). The functionalization of SWCNT was performed by oxidizing of SWCNT, attachment of polyethylene glycol (PEG) to oxidized SWCNT, attachment of azelaic acid to the polyethylene glycol group. As result, the SWCNT with free functional carboxylic acid and hydroxyl groups (SWCNT-PEG) was developed. The SWCNT-PEG was then conjugated with tamoxifen (SWCNT-PEG-TAM). The FT-IR together with NMR results confirmed the conjugation of tamoxifen to functionalized SWCNT (SWCNT-PEG-TAM). Finally, the anticancer potential of SWCNT-PEG-TAM was determined against human breast cancer cells (MCF-7 ATCC: HTB22) as compared to the free tamoxifen. The cytotoxic concentrations (CC_{50}, the concentration at which 50% of cells survive) of SWCNT-PEG, tamoxifen, and SWCNT-PEG-TAM were >100, 12.67±2.69, and 5.49±1.34 µg/ml, respectively. The linking of tamoxifen to functionalized SWCNT enhanced the cytotoxic action of tamoxifen against breast cancer cells up to 2.3 times. The results of the morphological examination and cytotoxicity assay confirmed the higher cytotoxic action of SWCNT-PEG-TAM as compare to free tamoxifen. Consequently, the results obtained in this study indicated that the delivery of tamoxifen through SWCNT-PEG-TAM enhanced the therapeutic effects and anticancer potential of tamoxifen against human breast cancer cells.

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

FABRIKASI, PENCIRIAN DAN PEMFUNGSIAN TIUB NANO KARBON BERDINDING TUNGGAL YANG BERKONJUGAT DENGAN TAMOXIFEN DAN KEUPAYAAN ANTIKANSERNYA UNTUK MELAWAN SEL-SEL KANSER PAYUDARA MANUSIA

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Terdapat banyak kemajuan telah dibuat dalam penyelidikan untuk mengurangkan kematian kanser payudara, namun ia masih menjadi punca utama kematian di seluruh dunia. Rawatan kanser melalui proses kemoterapi yang biasa digunakan mempunyai kesan sampingan yang tidak baik dan boleh menyebabkan kematian. Tesis ini melaporkan secara terperinci tentang penggunaan sistem penyampaian ubat untuk rawatan kanser mengunakan nanotiub karbon tunggal (SWCNT) yang digunapakai untuk novel bahan nano satu dimensi sebagai medium penghantaran ubat. Kelebihan SWCNT adalah, bahan ini mampu menyampaikan ejen terapeutik dan ejen pengimejan, yang mempunyai keupayaan untuk mengatasi pelbagai halangan biologi dan untuk menuju ke dalam kawasan sasaran. Pendekatan ini bukan sahaja menyebabkan keberkesanan ubat dapat dipertingkatkan tetapi juga mengurangkan peratusan keracunan ubat kepada tisu dan organ yang sihat. Oleh kerana pentingnya rawatan kanser dan mencari medium penghantaran ubat secara lebih selamat, kajian secara komprehensif ini bermula dengan pembuatan SWCNT, penambahbaikan, pencirian fungsi dan diikuti dengan penilaian ketoksikan dalam sitem badan manusia dan penentuan potensi anti-kanser terhadap sel kanser payudara manusia.

Dalam kajian ini, SWCNT dibuat menggunakan kaedah pemendapan wap kimia (CVD) yang telah diubahsuai dan SWCNT dihasilkan dengan teknik dua medium pembersihan asid. Keputusan spektrometri Raman, SEM, TEM, mikroskopi HRTEM dan TGA mengesahkan kejayaan sintesis SWCNT yang sangat tulen. Selain itu, biokompatibiliti dan ketoksikan SWCNT yang direka untuk hepatosit manusia (Chang ATCC: CCL-13) dinilai secara *in vitro*. Penilaian toksisitas SWCNT terhadap sel-sel hepatosit manusia menunjukkan bahawa konsentrasi di

bawah 50 μg / ml SWCNT kelihatan nontoxic pada sel-sel hepatosit manusia. Berhubung dengan potensi SWCNT dalam penyampaian ubat kanser, keputusan eksperimen menunjukkan konsentrasi SWCNT ini boleh menjanjikan penyebaran ubat kanser secara berkesan. Dalam langkah seterusnya, SWCNT telah difungsikan untuk mengandungi asid karboksilik bebas dan kumpulan hidroksil yang akan dimuatkan dengan tamoxifen (SWCNT-PEG). Kemudian, SWCNT yang berfungsi (SWCNT-PEG) dikaitkan dengan tamoxifen (SWCNT-PEG-TAM) dan selanjutnya dicirikan menggunakan spektroskopi infra merah inframerah (FTIR) dan spektroskopi resonans magnetik nuklear (NMR). Fungsi onalisasi SWCNT dilakukan dengan mengoksidasi SWCNT, lampiran polietilena glikol (PEG) ke SWCNT teroksida, lampiran asid azelaik kepada kumpulan polietilen glikol. Hasilnya, SWCNT dengan asid carboxylic dan kumpulan hidroksil berfungsi secara bebas (SWCNT-PEG) telah dibangunkan. SWCNT-PEG kemudiannya dikaitkan dengan tamoxifen (SWCNT-PEG-TAM). FT-IR bersama-sama dengan keputusan NMR mengesahkan konjugasi tamoxifen untuk SWCNT yang berfungsi (SWCNT-PEG-TAM). Akhirnya, potensi antikanker SWCNT-PEG-TAM ditentukan terhadap sel-sel kanser payudara manusia (MCF-7 ATCC: HTB22) berbanding dengan tamoxifen percuma. Kepekatan sitotoksik (CC50, kepekatan di mana 50% sel bertahan) SWCNT-PEG, tamoxifen, dan SWCNT-PEG-TAM masing-masing> 100, 12.67 ± 2.69, dan 5.49 ± 1.34 μg / ml. Penyambungan tamoxifen kepada SWCNT yang berfungsi meningkatkan ketoksikan tamoxifen terhadap sel kanser payudara sehingga 2.3 kali. Keputusan ujian morfologi dan sitotoksisiti mengesahkan tindakan sitotoksik yang lebih tinggi dari SWCNT-PEG-TAM sebagai membandingkan dengan tamoxifen percuma. Hasilnya, hasil yang diperolehi dalam kajian ini menunjukkan bahawa penghantaran tamoxifen melalui SWCNT-PEG-TAM meningkatkan kesan terapeutik dan potensi antikanker tamoxifen terhadap sel-sel kanser payudara manusia.

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

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LIST OF ABBEREVIATIONS

CNT	Carbon Nanotube
MWCNT	Multi Wall Carbon Nano Tubes
SWCNT	Single Wall Nano Tubes
ECCVD	Ethanol Catalytic Chemical Vapor Deposition
SEM	Scanning Electron Microscopy
TEM	Transmission Electron Microscopy
ADDS	Advance Drug Delivery System
CVD	Chemical Vapor Deposition
ECCVD	Ethanol Chemical Vapor Deposition
PEG	Poly Ethylene Glycol
DIC	Diisopropylcarbodiimide
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
SDS	Sodium Dodecyl Sulphate
Tam	Tamoxife

CHAPTER 1

INTRODUCTION

1.1 Overview

Cancer has been reported to be the main reason of death worldwide while its global prevalence is increasing as well. As projected by the American Cancer Society which is a pioneering health organization, cancer caused 7.6 million deaths all around the world in the year 2015, which is itself a case of 20,000 cancer deaths per day. Moreover, over 12 million humans would discover having the disease. This has to be accepted as the contemporary status of cancer despite the fact there have been progressing to a certain degree in minimizing the cancer-related deaths. Indeed, the most extensively used methods for treating the cancer are restricted to radiation, chemotherapy, and surgery (Azimzadeh et al. 2016). As such, the advanced drug delivery system (ADDS) has been found to play a major role in upgrading the cancer outcomes, and possibly in preventing it (DeSantis et al. 2014). ADDS is such a system that can transport and deliver one or more bioactive molecules, such as the therapeutic agents and imaging contrast enhancers for the biomedical applications. Moreover, the ADDS can counter the effect of diverse biological obstructions, localizing into the target tissue (Vivek et al. 2014). Having this in mind, nanotechnology has been proven effective in treating cancer and the idea of adopting it in medical research and clinical practice is referred to as bionanotechnology (Allen & Cullis 2013). An ADDS is commonly intended to enhance a drug molecule's pharmacological and therapeutic profiles.

Bionanotechnology is emerging as a new interdisciplinary research area in cancer treatment, amalgamating the disciplines of biology, physics, chemistry, engineering, and medicine. Bionanotechnology is expected to lead to major advances in cancer detection, diagnosis, and treatment (Hughes & King 2012). ADDS mainly consists of a therapeutic and a guidance mechanism attached/encapsulated to a carrier known as the delivery vehicle (Parhi et al. 2012). Site-specific targeting is one of the most important advantages of nanoscale drug delivery system which lead to, increase the drug concentration at desired sites of action and reduce systemic levels of drug and its toxic collateral in healthy tissues and improve solubility of the chemotherapeutic to facilitate parenteral drug administration and also, increase drug stability to maximize drug action.

Breast cancer is a major cause of cancer death in women in the USA, with an estimated 207,090 new cases and 39,840 deaths in 2012 (Ma & Jemal 2013). Due to improvement in treatment and prevention, the number of deaths caused by breast

cancer is decreasing, but the number of new diagnoses still continues to rise. Approximately one-third of all breast cancer patients and two-thirds of postmenopausal breast cancer patients have estrogen-dependent (ER+) breast cancer. Estrogen receptors (ERs), ER-alpha and ER-beta, are overexpressed in more than 75‑80% of breast tumor cells, and estrogen plays a vital role in the development and progression of cancer (El-Aneed 2004). Thus, the ER has been the most important target for breast cancer therapy. Therefore, efforts were made to develop an antiestrogen, which can block the mechanism of action of estrogen by competing with it for binding to estrogen receptors (Seigel & Jemal 2015). The antiestrogen tamoxifen is the most widely used drug in estrogen-dependent breast cancer therapy, and it has made a considerable contribution to reducing the mortality rate due to breast cancer. However, its use is associated with tumor resistance and increased levels of uterine and endometrial cancer (Cuzick et al. 2010).

Therapeutic drug delivery via a guidance mechanism, by being attached or encapsulated on a carrier vehicle, offers new directions for more effective diagnosis and therapy of cancer. This not only leads to improved efficacy of the drug but also minimizes its toxicity to healthy tissues (Danhier et al. 2010). In the last few years, a number of different nanoscale drug delivery vectors have been evaluated, including emulsions, polymers, quantum dots, silica nanoparticles, dendrimers, micelles, carbon nanotubes, molecular conjugates, and liposomes. Among these, single wall carbon nanotubes (SWCNT) offer more potential as a drug delivery vehicle, and therefore, they are of considerable interest in this regard. The bioavailability of drugs from functionalized SWCNT is increased by two of their characteristics: (1) their unique ability to incorporate multiple functionalizations on their surfaces gives high cargo loading (2) their intrinsic stability and structural modifiability to produce a long circulation time in the body (Liu et al. 2011). Simple strategies are available to functionalize SWCNT with biomolecules, such as proteins, DNA, and drug molecules. These strategies solubilize them, enabling them to enter cells efficiently by endocytosis or other mechanisms. Reports suggest that functionalized and solubilized SWCNT can transport peptides, proteins, genes, and DNA across the cell membrane with very little toxicity (Elhissi et al. 2011). Enhanced permeability and retention effect favor the increased and preferential accumulation of these conjugates at tumor sites *in vivo*. The ligand or antibody-directed delivery of drugs to tumors by binding to cancer cell surface receptors or antigens facilitates delivering therapeutic drugs more safely and effectively in the cells, which makes them ideal candidates for drug delivery (Ji et al. 2010).

The extraordinary physiochemical properties of carbon nanotubes facilitate their application for photothermal therapy in the field of cancer. Due to their strong optical absorbance in near-infrared (NIR) and radiofrequency regions, SWCNT release a great amount of heat, rendering them capable of thermal destruction of cells during near-infrared laser or radiofrequency irradiation (Robinson et al.

2010). Biological systems are transparent to 700‑1,100 nm NIR light, whereas SWCNT absorb light in this region, enabling them to trigger an endosomal rupture by a NIR laser pulse. For the purpose of increasing drug selectivity and decreasing toxicity to normal tissues, SWCNT were targeted to the tumor site for the NIR-mediated killing of tumor cells by coating SWCNT with cell binding ligands, such as peptides or antibodies, via covalent or non-covalent binding. This thermal therapy by SWCNT is considered to be a harmless, noninvasive, and exceedingly efficient technique (Liu et al. 2011).

Henderson et al. (2010) were the pioneers in fabricating the SWCNT from disproportionation of the carbon monoxide at 1200 °C in the company of molybdenum nanoparticles. Subsequently, by making use of diverse catalysts the SWCNT were fabricated from benzene, acetylene, ethylene, methane, cyclohexane, and fullerene (Kumar & Ando 2010).

In line with this, high-purity SWCNT were synthesized by See and Harris (2007) from alcohol on Fe-Co-impregnated zeolite support at a low temperature. From that point, ethanol turned into the most common CNT precursor in the chemical vapor deposition method all around the world (MacKenzie et al. 2010). In recent times, Song (2007) indicated that intermittent supply of acetylene in ethanol CVD can meaningfully help ethanol maintain the catalyst's activity, which therefore boosts the CNT growth rate (Song et al. 2007).

The mode of action of the breast cancer drug tamoxifen is through binding to the estrogen receptor site. Similar to other members of the hormone receptor family, ERs exist not only intracellularly but also on the cell membrane (Georgakilas et al. 2010). Tamoxifen–gold nanoparticle conjugates show drug potency 2.7 times greater than free tamoxifen, due to their selective intracellular delivery to ER(+) breast cancer cells, caused by both receptor and ligand dependence *in vitro* (Yaron et al. 2011). However, the analogous SWCNT–tamoxifen conjugates were not yet synthesized and evaluated. This new conjugate comprising both SWCNT and tamoxifen linked by (poly ethylene glycol) (PEG) has potential in breast cancer treatment, due to the advantages of SWCNT in drug delivery systems and photothermal therapy, as well as the recognition properties of tamoxifen as a selective targeting agent and potent endocrine treatment drug (Liu et al. 2008).

1.2 Problem statement

The breast cancer is the top leading cause of cancer-related death among female worldwide. The surveys revealed that higher incidences of breast cancer are found

in the developed countries as compared to the developing countries. Although the number of people diagnosed with breast cancer is increasing annually, the recent developments in the treatment and diagnosis could hopefully decrease the number of deaths. The chemotherapy with tamoxifen is the common method to treat the breast cancer and improving the therapeutic efficacy of tamoxifen increases the chance of survival in people suffering from breast cancer. Thus, scientists are conducting researches to improve the tamoxifen therapeutic efficacy. In this regard, the nanoscale delivery vectors appeared to be a promising alternative to enhance the treatment of breast cancer using tamoxifen.

The drug delivery through attachment of anticancer molecule to a carrier vehicle opened a new era in cancer treatment strategies. This approach not only resulted in enhanced efficacy of the drug but also minimized drug toxicity to the healthy tissues and organs. In the last decade, various nanoscale vectors for the delivery of drugs have been developed such as dendrimers, liposomes, micelles, silica nanoparticles, emulsions, polymers and quantum dots. However, most of the developed nanoscale vectors so far indicated some shortages such as low purity, little loading capacity, low solubility and cellular penetration, high toxicity, and complicated production and functionalization processes. Among these vectors, single-wall carbon nanotubes (SWCNT) appeared to be promising for the delivery of drugs since the SWCNT capable of penetrating into cells, high biocompatibility, less hydrophobicity and higher loading capacity and therapeutic efficacy. Thus, it is suggested that conjugation of tamoxifen with a highly pure SWCNT not only enhance the tamoxifen cellular penetration, biocompatibility, hydrophobicity and loading capacity but also improve the therapeutic efficacy of tamoxifen against breast cancer cells.

1.3 Hypothesis

The CVD method in combination with two-step purification technique results in fabrication of highly pure SWCNT. After purification, the SWCNT possesses low toxicity to human hepatocyte. The functionalized SWCNT containing free carboxylic acid and hydroxyl groups could be considerably loaded with tamoxifen and finally the functionalized SWCNT loaded with tamoxifen possesses higher anticancer potential against human breast cancer cells as compared to the free tamoxifen.

1.4 Objectives

The present research aimed to fabricate the highly pure single wall carbon nanotube as a drug delivery vehicle and characterized using Raman spectroscopy, SEM, TEM, HRTEM, and TGA. Further, the toxicity and biocompatibility of fabricated SWCNT to the human hepatocytes is determined using cytotoxicity assay. This drug vehicle is (SWCNT) functionalized to be loaded with tamoxifen (SWCNT-PEG) and characterized using FTIR and NMR spectroscopy. The SWCNT-PEG is conjugated to tamoxifen (SWCNT-PEG-TAM) and the loading efficacy of SWCNT is measured using content analysis method. Finally, the anticancer potential of SWCNT-PEG-TAM is evaluated against human breast cancer cells (MFC-7).

This study embarks on the following objectives:

1. To fabricate a highly pure single wall carbon nanotube (SWCNT) in the lab environment and its characterization.
2. To evaluate the toxicity and biocompatibility of fabricated SWCNT to human hepatocyte.
3. To functionalize the fabricated SWCNT for tamoxifen delivery and its characterization.
4. To evaluate the anticancer potential of SWCNT-tamoxifen using *in vitro* cancer cell model.

1.5 Outline of the Thesis

The structure of this thesis is provided as the following chapters:

Chapter 1 gives the introduction to the processes used, hypothesis and objectives of this project. Glancing through the SWCNT fabrication method and a total vision of drug delivery system to cancer cell included in the first chapter.

Chapter 2 discusses the literature review on the works done earlier related to this thesis and includes the describing SWCNT, chemical vapor deposition, drug delivery system, cancer therapy and the latest work is done related to this research work.

Materials and methods/methodology are brought in Chapter 3. Materials, machines, standards, tools, and method of characterization are described in this chapter. Theoretical approaches and experimental designs are included in Chapter 3.

Result and discussion are included in Chapter 4. All findings about the synthesis of SWCNT and its purification, characterization, functionalization elaborated in this chapter. Cytotoxicity assay of functionalized SWCNT has been reported in this chapter as well. Chapter 5 contains conclusions and recommendations for future studies.

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