UNIVERSITI PUTRA MALAYSIA

SYNTHESIS, CHARACTERIZATION AND CYTOTOXICITY EVALUATION OF CARBOXYLATED CARBON NANOTUBES FUNCTIONALIZED WITH SILIBININ, BETULINIC ACID AND LEVODOPA FOR DRUG DELIVERY

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By

JULIA TAN MEIHUA

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

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

SYNTHESIS, CHARACTERIZATION AND CYTOTOXICITY EVALUATION OF CARBOXYLATED CARBON NANOTUBES FUNCTIONALIZED WITH SILIBININ, BETULINIC ACID AND LEVODOPA FOR DRUG DELIVERY

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Chairman: **Professor Mohd Zobir bin Hussein, PhD**
Faculty: **Institute of Advanced Technology**

Current methods of conventional drugs administered via liquids or tablets are often faced with problems like inefficient biodistribution, low solubility, poor bioavailability, long term toxicity and limited drug efficacy. As a result, many efforts have been carried out in the past to overcome the above mentioned limitations. This has led to the development of nanomaterial-based carrier as novel drug delivery system. In this study, commercially available carboxylated carbon nanotubes (CNTs) were used as the nano drug carrier due to their attractive physico-chemical properties which facilitate functionalization of therapeutic molecules onto their external walls or being encapsulated inside the nanotubes. Therefore, the main objective of the present work was to develop drug delivery formulation for silibinin (SB), betulinic acid (BA) and levodopa (LD) with carboxylated single walled (SWCNTs-COOH) and multiwalled carbon nanotubes (MWCNTs-COOH) separately for enhanced delivery efficiency into targeted cells with sustained-release effect.

The resulting five nanohybrids, namely SWCNTs-SB, MWCNTs-SB, SWCNTs-BA, MWCNTs-BA and SWCNTs-LD, were prepared by non-covalent method via π-π and hydrogen bonds as well as hydrophobic interactions without the use of any cross-linker agent. The physico-chemical properties of the resulting nanohybrids, *i.e.* chemical interaction, elemental composition, crystallinity, thermal property, surface morphology, drug loading capacity and drug releasing characteristic were studied using Fourier transform infrared (FTIR) and Raman spectroscopies, elemental analysis (CHN-S), powder X-ray diffractometry (PXRD), thermogravimetric analysis (TGA), transmission electron microscopy (TEM), field emission scanning electron microscopy (FESEM) and ultraviolet-visibile spectrophotometry (UV-Vis). In order to assess the cytotoxicity characteristic of the synthesized nanohybrids, human cancer cell lines HepG2 (human liver hepatocellular carcinoma cell lines) and A549 (human lung adenocarcinoma epithelial cell lines) were used in comparison to normal cell lines MRC-5 (human lung cell lines), 3T3 (mouse fibroblast cell lines) and PC12 (rat neuronal cell lines).

The loading of drug in SWCNTs-SB, MWCNTs-SB, SWCNTs-BA, MWCNTs-BA and SWCNTs-LD nanohybrids was estimated to be around 46.0, 35.1, 20.0, 14.8 and 38.2 w/w%, respectively as determined by UV-Vis, and these values have been verified by TGA. Both FTIR and Raman spectroscopy studies confirmed that the conjugation process has taken place between drugs and the nanocarriers. The PXRD results showed that tubular structures of the nanocarriers were not affected by drug loading mechanism. Drug release profiles have been investigated at different pH values, showing the influence of pH on the drug release process. In addition, the synthesized nanohybrids possessed favourable sustained-release property to be used in a controlled-release formulation, with satisfactory coefficients conformed well to the *pseudo*-second order release kinetic model.

Preliminary *in vitro* cytotoxicity studies suggest that the drug-loaded nanohybrids (*i.e*. SWCNTs-SB, MWCNTs-SB, SWCNTs-BA and MWCNTs-BA) are not acutely toxic while significantly inhibiting the growth of cancer cells in comparison with pure drugs after 72 hours of treatment using MTT [3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide] assay. Cell viability assay was also performed in PC12 cell lines, a widely used *in vitro* Parkinson's model for neurotoxicity study, in order to investigate their potential effects on normal neuronal cells. It was found that the synthesized SWCNTs-LD did not compromise the cell viability of PC12 cells but remain stable throughout the experiment.

With the addition of the surface coating agents, the initial burst of drugs was dramatically improved and thus, resulted in a more prolonged and sustained release fashion. In general, the coated nanohybrids exhibit a *pseudo*-second-order release kinetics which was driven by the ion exchange process between the ionized nanohybrids and the anions in the release medium. On top of that, it was noted that the surfactant and polymer coating improved the biocompatibility of the drug-loaded nanohybrids significantly in comparison to the uncoated ones.

In conclusion, the findings from this work indicate that the carboxylated CNTs with the desired properties could be developed as an efficient drug nanocarrier to non-covalently conjugate poorly water-soluble drug for effective drug delivery in cancer chemotherapies and the treatment of neurodegenerative diseases.

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

SINTESIS, PENCIRIAN DAN PENILAIAN KESITOTOKSIKAN NANOTIUB KARBON TERKARBOKSILAT DENGAN FUNGSIAN SILIBININ, ASID BETULINIK DAN LEVODOPA UNTUK PENYAMPAIAN UBAT

Oleh

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Ogos 2015

Pengerusi: **Profesor Mohd Zobir bin Hussein, PhD**
Fakulti: **Institut Teknologi Maju**

Kaedah semasa pengurusan ubat konvensional yang diberikan melalui cecair atau pil sering berhadapan dengan masalah seperti bioserakan yang kurang cekap, kelarutan yang rendah, bioketersediaan yang rendah, ketosikan jangka panjang dan kerbekesanan ubat yang terhad. Akibatnya, banyak usaha telah dilakukan pada masa lalu untuk mengatasi kekurangan yang dinyatakan di atas. Ini telah membawa kepada pembangunan pembawa ubatan berdasarkan bahan nano sebagai sistem penyampaian ubat baru. Dalam kajian ini, nanotiub karbon terkarboksilat (CNTs) yang diperolehi secara komersial telah digunakan sebagai pembawa ubat nano, disebabkan oleh sifat fizik-kimia mereka yang menarik, memudahkan pemfungsian molekul terapeutik ke atas dinding luar atau terkapsul di dalam nanotiub. Justeru itu, objektif utama kajian ini adalah untuk merumuskan formulasi penyampaian ubat untuk silibinin (SB), asid betulinik (BA) dan levodopa (LD) dengan nanotiub karbon berdinding tunggal terkarboksilat (SWCNTs-COOH) and berdinding pelbagai (MWCNTs-COOH) secara berasingan untuk mempertingkatkan kecekapan penghantaran ubat ke dalam sel-sel sasaran dengan kesan pembebasan yang berterusan.

Sebanyak lima jenis hibrid nano, iaitu SWCNTs-SB, MWCNTs-SB, SWCNTs-BA, MWCNTs-BA dan SWCNTs-LD telah disediakan dengan kaedah bukan kovalen melalui interaksi ikatan π-π, hidrogen dan hidrofobik tanpa menggunakan sebarang ejen rangkaian silang. Sifat-sifat fizik-kimia hibrid nano yang dihasilkan, iaitu interaksi kimia, komposisi keunsuran, kehabluran, sifat terma, morfologi permukaan, keupayaan muatan ubat dan ciri pembebasan ubat telah dikaji dengan spektroskopi inframerah transformasi Fourier (FTIR) dan Raman, analisis unsur (CHN-S), kajian pembelauan sinar-X (PXRD), analisis termogravimetri (TGA), mikroskopi elektron pancaran (TEM), mikroskopi elektron imbasan (FESEM) dan spektrofotometri ultraungu-nampak (UV-Vis). Sebagai usaha untuk menilai ciri kesitotoksikan hibrid nano yang disintesiskan, titisan sel kanser manusia HepG2 (titisan sel karsinoma hepatoselular hati manusia) dan A549 (titisan sel epitelium adenokarsinoma paru-paru manusia) telah digunakan sebagai perbandingan kepada titisan sel normal MRC-5 (titisan sel paru-paru manusia), 3T3 (titisan sel fibroblas tikus) dan PC12 (titisan sel neuronal tikus).

Kandungan ubat dalam hibrid nano SWCNTs-SB, MWCNTs-SB, SWCNTs-BA, MWCNTs-BA dan SWCNTs-LD masing-masing adalah dianggarkan di sekitar 46.0, 35.1, 20.0, 14.8 dan 38.2 w/w% sepertimana yang ditentukan dengan kaedah UV-Vis, dan nilai-nilai ini telah disahkan oleh TGA. Kedua-dua kajian spektroskopi FTIR dan Raman mengesahkan bahawa proses konjugasi telah berlaku di antara ubat dan pembawa nano. Keputusan PXRD menunjukkan bahawa struktur pembawa nano berbentuk tiub tidak dipengaruhi oleh mekanisma muatan ubat. Profil pembebasan ubat telah disiasat pada nilai-nilai pH yang berbeza, menunjukkan pH mempunyai pengaruh ke atas proses pembebasan ubat. Di samping itu, hibrid nano yang disintesiskan mempuyai sifat pembebasan berterusan yang sesuai untuk digunakan dalam formulasi pembebasan terkawal, dengan pekali-pekali memuaskan yang mematuhi model kinetik pembebasan *pseudo*-kedua.

Kajian kesitotoksikan *in vitro* awal mencadangkan bahawa hibrid nano muatan ubat (iaitu SWCNTs-SB, MWCNTs-SB, SWCNTs-BA dan MWCNTs-BA) adalah tidak toksik secara akut sementara menghalang pertumbuhan sel-sel kanser nyata sekali berbanding dengan ubat tulen selepas 72 jam rawatan menggunakan assai MTT [3-(4,5-dimetilthiazolil-2)-2,5-difeniltetrazolium bromida]. Assai kebolehhidupan sel juga dilakukan pada sel PC12, satu model Parkinson *in vitro* yang digunakan secara meluas untuk kajian neurotoksisiti, sebagai usaha untuk menyiasat kesan potensi mereka pada sel-sel neuronal yang normal. Didapati bahawa SWCNTs-LD yang disintesiskan tidak menjejaskan kebolehhidupan sel-sel PC12, tetapi kekal stabil sepanjang eksperimen.

Dengan penambahan ejen salutan permukaan, kesan awal pecahan ubat telah dipertingkatkan secara dramatik dan justeru itu, mengakibatkan pelepasan yang lebih berpanjangan dan berterusan. Secara umumnya, hibrid nano tersalut mempamerkan kinetik pelepasan *pseudo*-kedua yang disebabkan oleh proses pertukaran ion antara hibrid nano terion dan anion dalam medium pelepasan. Selain itu, didapati bahawa salutan surfaktan dan polimer meningkatkan biokompatibiliti ubat-muatan hibrid nano dengan ketara berbanding dengan sampel yang tidak bersalut.

Kesimpulannya, hasil dari kajian ini menunjukkan bahawa CNTs terkarboksilat dengan ciri-ciri yang diingini boleh dibangunkan sebagai pembawa ubat nano yang berkesan untuk aplikasi penyampaian ubat dalam kemoterapi kanser dan rawatan penyakit neurodegeneratif.

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I certify that a Thesis Examination Committee has met on 6 August 2015 to conduct the final examination of Julia Tan Meihua on her thesis entitled "Synthesis, Characterization and Cytotoxicity Evaluation of Carboxylated Carbon Nanotubes Functionalized with Silibinin, Betulinic Acid and Levodopa for Drug 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 degree of Doctor of Philosophy.

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Date: 22 September 2015

The 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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Supervisory Prof. Dr.
Committee: Hairuszah Ithnin

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LIST OF ABBREVIATIONS

AFM	Atomic force microscopy
ANG	Angiopep-2
ANOVA	Analysis of variance
ATCC	American Type Culture Collection
AZ	Azithromycin
A549	Human lung adenocarcinoma epithelial cell line
BA	Betulinic acid
BET	Brunauer-Emmett-Teller
BSA	Bovine serum albumin
CAR	Carvedilol
CHI	Chitosan
CIS	Cisplatin
CLC	Carbon nanotubes-liposomes conjugate
CNTs	Carbon nanotubes
DAU	Daunorubicin
D-band	Disorder-induced mode
DL	Drug loading
DMEM	Dulbecco's Modified Eagle Medium
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOX	Doxurubicin
DPI	Dry powder inhaler
e.g.	Exempli gratia
EGF	Epidermal growth factor
et al.	Et alia
etc.	Et cetera
FA	Folic acid
FBS	Foetal bovine serum
f-CNTs	Functionalized carbon nanotubes
FDA	United States Food and Drug Administration
FESEM	Field emission scanning electron microscopy
FITC	Fluorescein isothiocyanate
FTIR	Fourier transform infrared spectroscopy
G-band	Tangential displacement mode
GEM	Gemcitabine
HA	Hyaluronan
HCC	Hydrophilic carbon clusters
HepG2	Human liver hepatocellular carcinoma cell line
HUVEC	Human umbilical vein endothelial cells
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est
IR	Infrared
KBr	Potassium bromide
LD	Levodopa
LRP	Lipoprotein receptor-related protein
MRC-5	Normal human lung cell line

MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MWCNTs	Multiwalled carbon nanotubes
MWCNTs-BA	Betulinic acid-loaded multiwalled carbon nanotubes
MWCNTs-COOH	Carboxylic acid-functionalized multiwalled carbon nanotubes
MWCNTs-SB	Silibinin-loaded multiwalled carbon nanotubes
NIR	Near Infrared
NMR	Nuclear magnetic resonance
OD	Optical density
PAMAM	Polyamidoamine
PBS	Phosphate buffered saline
PC12	Rat neuronal cell line
PD	Parkinson's disease
PEG	Polyethylene glycol
PL	Phospholipid
PLGA	Poly(lactide-*co*-glycolide) acid
PLL	Poly-L-lysine
PTX	Paclitaxel
PXRD	Powder X-ray diffractometry
QD	Quantum dot
RBM	Radial breathing mode
rpm	Rotation per minute
SB	Silibinin
S_{BET}	Specific surface area
SD	Standard deviation
SEM	Scanning electron microscopy
STEM	Z-contrast scanning transmission electron microscopy
STM	Scanning tunnelling microscopy
SWCNTs	Single walled carbon nanotubes
SWCNTs-BA	Betulinic acid-loaded single walled carbon nanotubes
SWCNTs-COOH	Carboxylic acid-functionalized single walled carbon nanotubes
SWCNTs-LD	Levodopa-loaded single walled carbon nanotubes
SWCNTs-SB	Silibinin-loaded single walled carbon nanotubes
TEM	Transmission electron microscopy
TGA	Thermal gravimetry
T20	Tween 20
T80	Tween 80
UV-Vis	Ultraviolet-visible spectrophotometer
W	Weight
XPS	X-ray photoelectron spectroscopy
XRD	X-ray diffractometry
3T3	Mouse fibroblast cell line

CHAPTER 1

INTRODUCTION

1.1 Background of Study

There are various definitions currently circulating when it comes to the term nanotechnology. The prefix "nano" is actually originated from the Greek word "nanos" for dwarf and technology refers to the application of science in a particular subject (Buzea *et al*., 2007). One nanometer (nm) is equal to one billionth of a meter and a meter is approximately 39 inches long. According to the declaration made by the United States National Nanotechnology Initiative, nanotechnology involves research and development at the atomic, molecular, or macromolecular levels at dimensions between 1 and 100 nm to create structures, devices, and systems that are enabled for novel applications.

In recent years, nanobiotechnology (a combination of nanotechnology and biotechnology) especially in medicine, or the so-called nanomedicine, has emerged as one of the most advanced and promising areas in drug delivery application. The application of nanotechnology in drug delivery involves the use of carriers and therapeutic agents. Nanoscale drug carriers can significantly enhance the bioavailability and therapeutic efficacy of drugs with reduced side effects. Therapeutic agents are drugs or biologically active materials (*e.g*. nucleic acids and proteins) which can be entrapped, intercalated, encapsulated, dissolved, adsorbed, or attached onto the drug carriers, which can then be tailored for controlled and sustained-release formulations.

1.2 Problem Statement

The polyphenolic phytochemical silibinin (SB, 2,3-dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-6-(3,5,7-trihydroxy-4-oxobenzopyran-2-yl) benzodioxin, Figure 1.1) is the main constituent of the silymarin mixture extracted from the seeds, fruits, and leaves of milk thistle (*Silybum marianum* L.) plant (Verschoyle *et al*., 2008). This lignoflavonoid has been used traditionally for more than 2000 years as herbal remedy for the treatment of hepatic disorders (Hruby *et al*., 1983). Even though SB has poor oral bioavailability due to poor aqueous solubility, most of the findings in the past demonstrated that SB exhibits anti-proliferative, anti-inflammatory, anti-fibrotic, anti-oxidant, anti-carcinogenic, membrane stabilizing and liver regeneration effects (Karim *et al*., 2013; Sonnenbichler *et al*., 1999) in both pharmacological and experimental research.

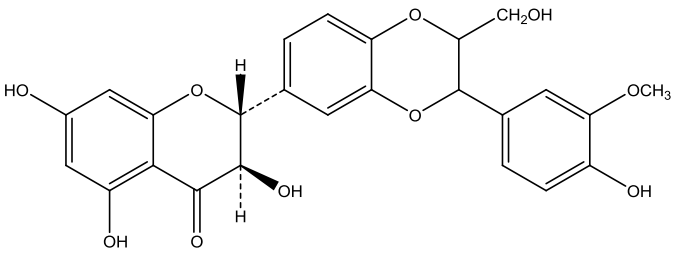

Figure 1.1. Chemical structure of silibinin.

Betulinic acid (BA, 3β-hydroxy-lup-20(29)-en-28-oic acid, Figure 1.2) is a naturally occurring pentacyclic lupane-type triterpene extracted from numerous botanical sources found widely distributed in the plant kingdom. It has been used traditionally as a folk remedy by the Native Americans to treat intestinal problems like dysentery and diarrhea. Recent studies reported that BA possesses many favourable therapeutic activities such as anticancer, hepatoprotective potential, antimalarial, anti-inflammatory, antihuman immunodeficiency virus, anthelmintic, and antioxidant effects (Baratto *et al*., 2013; Jain *et al*., 2012). BA was also well known for its high selective cytotoxic activity against human melanoma derived cell lines (Kommera *et al*., 2010) as well as other types of cancerous tumours (Sun *et al*., 2013; Chintharlapalli *et al*., 2011). Healthy, normal cells like peripheral blood lymphoblasts, melanocytes, normal human fibroblasts, and astrocytes were also reported to be resistant against BA treatment *in vitro* (Selzer *et al*., 2000). However, its optimum potential is greatly limited by poor solubility in aqueous solvents. As such, an ideal delivery system can further enhance the bioavailability of BA as a potent anticancer agent.

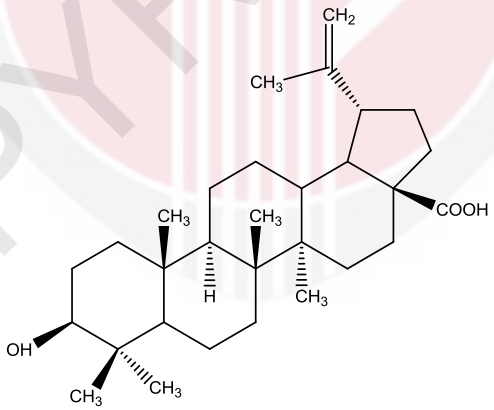

Figure 1.2. Molecular structure of betulinic acid.

Levodopa (LD, 3-(3,4-dihydroxyphenyl)-L-alanine, Figure 1.3), an anti-Parkinson drug, is the most effective and widely prescribed oral administration due to its ability to cross the blood brain barrier. However, long term responsive patients treated with LD therapy may experience a decrease in the duration of responsiveness to the treatment and resulting in motor fluctuation (dyskinesia) side effects (Modi *et al*., 2009).

Moreover, once LD is administered orally into the body, the drug is immediately metabolized and only a small amount of drug reaches the central nervous system. To prevent LD from being rapidly metabolized before it reaches the brain, carbidopa, an inhibitor of dopamine decarboxylase, is commonly used in combination with LD to enhance the effectiveness of LD peripherally (Okereke *et al*., 2004). Therefore, in order to achieve the desired effect with a lower therapeutic dose of LD, one will have to take several combinations of these medications which further increases inconvenience in patients.

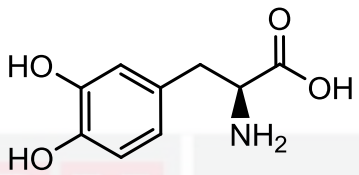

Figure 1.3. Structure of levodopa.

Current methods of conventional drugs administered via liquids or pills are generally less efficient and suffered from poor biodistribution, low solubility, long term toxicity, and limited drug efficacy (Del Valle *et al*., 2009). This has caused the pharmaceutical industry to develop novel drug delivery systems using a wide range of biocompatible drug carriers with the aim to improve therapeutic efficacy and reduced toxicity. In meeting this demand, various forms of efficient and biocompatible drug delivery systems have been developed extensively and can be generally classified into four major categories: nanomaterials (Saifullah *et al*., 2013; Hariharan *et al*., 2012), viral carriers (Teunissen *et al*., 2013; Zeng *et al*., 2013), organic cationic compounds (Tseng *et al*., 2013; Salomon and Ehrhardt, 2012), and recombinant proteins (Hofer *et al*., 2012; Teng *et al*., 2011).

Nanomaterials such as CNTs have been receiving considerable amount of attention as a new, non-viral carrier alternative (Ji *et al*., 2012; Cheng *et al*., 2011a; Li *et al*., 2011a) compared to viral and cationic carrier. These allotropes of carbons are extensively studied and investigated as novel drug delivery vehicles due to their good biocompatibility, ultrahigh surface area, good mechanical strength yet ultralight weight, low cytotoxicity, and excellent chemical and thermal stability. Furthermore, their outer surface can be chemically functionalized with biocompatible materials (Zheng *et al*., 2013), whilst inner volume allows the loading of small biomolecules such as proteins and genes for effective drug delivery (Luo *et al*., 2011). Recently, it was reported that chemically functionalized CNTs can be utilized as a novel form of drug carrier by attaching different range of functional groups to their sidewalls (Liu *et al*., 2008). The research team discovered that the functionalized CNTs were able to cross cell barriers in mice through the enhanced permeability and retention effect without causing any harm to the normal cells. Equipped with all these unique advantages of CNTs and their tremendous breakthroughs in nanomedicine, it is no doubt that CNTs can be used as a promising novel drug delivery system for advanced therapeutic treatment. Therefore, carboxylated CNTs were selected as the nanocarrier for effective delivery of SB, BA and LD in this study.

1.3 Scope of Study

The present study was conducted to develop and determine the physico-chemical properties of carboxylated CNTs-based drug delivery formulation for SB, BA and LD. Secondly, drug loading and release profiles of the synthesized nanohybrids were studied in human body-simulated phosphate buffered saline (PBS) solutions at pH 7.4 and 4.8. pH 7.4 was chosen to demonstrate the drug release in physiological environment, whereas pH 4.8 was selected to mimic the acidic condition of human stomach after food. Finally, in order to assess the cytotoxic characteristics of the drug-loaded nanohybrids, human cancer cell lines HepG2 (human liver hepatocellular carcinoma cell lines) and A549 (human lung adenocarcinoma epithelial cell lines) were used in comparison with normal, healthy cell lines MRC-5 (normal human lung cell lines), 3T3 (mouse fibroblast cell lines) and PC12 (rat neuronal cell lines). In addition to that, further coating steps were taken as an attempt to mask the cytotoxicity of the drug-loaded CNTs nanohybrids and the coating effects were determined on 3T3 cells in detailed. This study however, does not cover the biological aspect of specific cellular uptake mechanism of the resulting nanohybrids and cell interactions due to constraints imposed by time, cost and availability of materials.

1.4 Hypotheses

Carboxylated CNTs can be loaded with SB, BA and LD non-covalently via π-π stacking hydrogen bonding and hydrophobic interactions for advanced drug delivery. The developed CNTs drug-loaded nanohybrids demonstrated controlled and sustained-release properties with enhanced efficiency of the *in vitro* delivery of SB, BA and LD compared with the pure drugs. Due to the carboxylic acid (–COOH) functional groups of carboxylated CNTs which facilitate their solubility in physiological environment, the drug-loaded nanohybrids are not acutely toxic in healthy cells *in vitro*. In addition, they are capable of inhibiting the growth of cancer cells *in vitro* by immobilizing the drugs on the outer wall or by encapsulation inside the nanotubes.

1.5 Objectives

The purpose of the present study is to develop drug-loaded carboxylated CNTs formulation for effective drug delivery. The specific objectives are as follows:

a) to synthesize and characterize the nanohybrids, namely SWCNTs-SB, MWCNTs-SB, SWCNTs-BA, MWCNTs-BA, SWCNTs-LD, SWSB-T20, SWSB-T80, SWSB-PEG, SWSB-CHI, SWBA-T20, SWBA-T80, SWBA-PEG and SWBA-CHI;
b) to investigate the drug loading and release profile of the synthesized nanohybrids at two different pH levels (*i.e*. PBS solutions at pH 7.4 and pH 4.8);
c) to study the cytotoxic activity of the synthesized nanohybrids in normal cell lines (*i.e*. 3T3, MRC-5 and PC12) and human cancer cell lines (*i.e*. HepG2 and A549); and
d) to examine the use of the coating agents in the context of the drug release characteristic and cytotoxic activity in 3T3 cell lines.

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