POLYVINYL ALCOHOL-GRAFTED-MULTIWALLED CARBON NANOTUBES AS A DELIVERY SYSTEM FOR CURCUMIN IN H_2O_2-INDUCED DAMAGED NEUROBLASTOMA SH-SY5Y CELLS

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Specially dedicated to *Babah* and *Mama,*

my husband and sons,

my sisters and brother,

for their love, support and tolerance

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ABSTRACT

Treating neurodegenerative disease using Curcumin, a pigment from turmeric is found difficult due to its low bioavailability. To overcome this problem, polyvinyl alcohol multi-walled carbon nanotubes (PVA-MWCNT) was developed to improve its delivery and uptake by the brain cells. It was first prepared by oxidizing pristine MWCNT (p-MWCNT) in 3:1 sulfuric and nitric acid mixture. Three methods were employed to optimize production of oxidized MWCNT (ox-MWCNT); which is stirring and sonication for 2 and 6 hours. The selected ox-MWCNT with minimal structural damage was then functionalized with PVA via carbodiimide esterification, and confirmed by field-emission scanning electron microscopy (FESEM), Fourier transform infra-red (FTIR) spectroscopy, dispersion test and thermal gravimetric analysis (TGA). Next, Curcumin was loaded onto PVA-MWCNT, p-MWCNT and ox-MWCNT, and evaluated their adsorption capacity and behaviour using adsorption kinetics, isotherm and thermodynamic studies. Percentage of Curcumin desorbed from the MWCNT was analyzed in physiological buffers of pHs 7.4 and 5.5. Lastly, potential of Curcumin loaded on PVA-MWCNT (Cur-PVA-MWCNT) to protect neurons was screened in neuroblastoma SH-SY5Y cells, including other Cur-loaded MWCNT samples. The cells were pre-incubated with hydrogen peroxide (H_2O_2) at half the maximal inhibitory concentration (IC_{50}) for 1 hour, before concurrent treatment of the samples. Cell survival was compared to controls treated with Curcumin-unloaded MWCNT, i.e. PVA-MWCNT, ox-MWCNT and p-MWCNT. From the results, MWCNT was oxidized with minimal structural damage using stirring method. The evidence of PVA grafting was confirmed through the presence of matrix polymer embedded on ox-MWCNT in FESEM, high stability in water, identification C=O stretching of ester group at 1736 cm^{-1} in FTIR and its stable structure compared to ox-MWCNT and p-MWCNT in TGA. PVA-MWCNT adsorbed Curcumin at only 5.1 mg/g, which follows the Freundlich isotherm model (physisorption), while the highest amount was loaded on ox-MWCNT at 714 mg/g that follows the Langmuir model (chemisorption). Although Curcumin adsorption on PVA-MWCNT was only at minimal amount, it showed the most efficient desorption occurred at pH 5.5 (25%) rather than pH 7.4 (3%) with sustained release over a 3-day incubation. This suggests Curcumin weak binding through physisorption to the PVA-MWCNT facilitated its release at lower pH. Cur-PVA-MWCNT also protected SH-SY5Y cells from H_2O_2-induced oxidative stress most significantly at 100 ng/ml, 1 μg/ml and 10 μg/ml compared to PVA-MWCNT. Cur-ox-MWCNT and Cur-p-MWCNT indicated no obvious difference as compared to their controls. The change in the cell environment after damage perhaps encouraged the pH to become acidic which may facilitate Curcumin release from PVA-MWCNT. Overall, PVA-MWCNT was considered promising for loading and the release of Curcumin. The efficacy of the system in *in vitro* cell lines was also enhanced, demonstrating it as a prospective carrier for Curcumin in the treatment of neurodegenerative disease.

ABSTRAK

Pengubatan penyakit neurodegeneratif menggunakan Curcumin, pigmen dari kunyit didapati sukar kerana bioketerdapatannya yang rendah. Untuk mengatasinya, polivinil alkohol tiub nanokarbon berbilang dinding (PVA-MWCNT) dibangunkan bagi memperbaiki penghantaran dan pengambilannya oleh sel-sel otak. Penyediaannya dimulai dengan oksidasi pristin-MWCNT (p-MWCNT) di dalam 3:1 campuran asid sulfurik dan nitrik. Penghasilan MWCNT teroksida (ox-MWCNT) dioptimum melalui tiga kaedah; iaitu pengacauan, dan sonikasi selama 2 dan 6 jam. Ox-MWCNT dengan sedikit kerosakan struktur kemudiannya difungsikan dengan PVA melalui pengesteran karbodiimida, dan disahkan melalui mikroskop elektron imbasan pancaran medan (FESEM), spektroskopi Fourier transform inframerah (FTIR), ujian penyebaran dan analisis gravimetri terma (TGA). Seterusnya, Curcumin dimuatkan pada PVA-MWCNT, p-MWCNT dan ox-MWCNT, dan dinilai kapasiti dan tingkah laku jerapan melalui kajian kinetik dan isoterma penjerapan, serta termodinamik. Peratus pelepasan Curcumin dari MWCNT pula dikaji menggunakan larutan tampan pH 7.4 dan 5.5. Terakhir, potensi PVA-MWCNT muatan Curcumin (Cur-PVA-MWCNT) melindungi neuron disaring dalam sel neuroblastoma SH-SY5Y, termasuk sampel MWCNT-muatan Cur lain. Sel diaruh hidrogen peroksida (H_2O_2) pada kepekatan separuh perencatan maksima (IC_{50}) selama 1 jam sebelum diuji serentak dengan sampel. Kebolehhidupan sel dibanding dengan kumpulan kawalan MWCNT-tanpa-muatan-Cur, iaitu PVA-MWCNT, ox-MWCNT dan p-MWCNT. Menurut hasil kajian, teknik pengacauan mengoksidasi MWCNT dengan sedikit kerosakan struktur. Bukti cantuman PVA pada ox-MWCNT ditunjukkan oleh matrik polimer tertanam pada ox-MWCNT dalam FESEM, kestabilan tinggi dalam air, pencaman regangan C=O dari kumpulan ester pada 1736 cm^{-1} dalam FTIR serta kestabilan struktur berbanding ox-MWCNT dan p-MWCNT dalam TGA. PVA-MWCNT menjerap Curcumin hanya pada 5.1 mg/g dan mematuhi model isoterma Freundlich (jerapan fizikal), manakala jumlah tertinggi sebanyak 714 mg/g dimuat keatas ox-MWCNT yang mengikuti model isoterma Langmuir (jerapan kimia). Walaupun jerapan Curcumin oleh PVA-MWCNT di kadar yang rendah, penyahjerapannya didapati paling cekap pada pH 5.5 (25%) berbanding pH 7.4 (3%) dengan pelepasan tertahan yang berterusan selama 3 hari. Ia mencadangkan interaksi lemah Curcumin pada PVA-MWCNT melalui jerapan fizikal menggalakkan pelepasannya pada pH yang rendah. Cur-PVA-MWCNT juga melindungi sel-sel SH-SY5Y dari tekanan oksidatif aruhan H_2O_2 dengan ketara pada 100 ng/ml, 1 μg/ml dan 10 μg/ml berbanding PVA-MWCNT. Cur-ox-MWCNT dan Cur-p-MWCNT pula tidak menunjukkan perbezaan berbanding kumpulan kawalannya. Perubahan persekitaran sel SH-SY5Y setelah aruhan berkemungkinan mempengaruhi pH ke arah keasidan, seterusnya menggalakkan penyingkiran Curcumin dari PVA-MWCNT. Keseluruhannya, PVA-MWCNT berpotensi memuat dan menyahjerap Curcumin. Keberkesanan sistem ini di dalam sel *in vitro* juga menunjukkannya sebagai pembawa prospektif Curcumin bagi rawatan penyakit neurodegeneratif.

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%	- Percentage
°C	- Degree Celcius
K	- Kelvin
α	- Alpha
β	- Beta
γ	- Gamma
μ	- Micro
n	- Nano
p	- Pico
m	- mass
V	- volume

LIST OF ABBREVIATIONS

ACh	- Acetylcholine
AChE	- Acetylcholinesterase
AChEI	- Acetylcholinesterase inhibitors
AD	- Alzheimer's disease
BBB	- Blood brain barrier
CNT	- Carbon Nanotubes
Cur	- Curcumin
Cur-ox-MWCNT	- Curcumin-loaded on oxidized multi-walled carbon nanotubes
Cur-p-MWCNT	- Curcumin-loaded on pristine multi-walled carbon nanotubes
Cur-PVA-MWCNT	- Curcumin-loaded on PVA-grafted multi-walled carbon nanotubes
CNS	- Central nervous system
Cpt	- Campthothexin
CVD	- Chemical vapour deposition
Da	- Dalton
DDS	- Drug Delivery System
DNA	- Deoxyribonucleic acid
Dox	- Doxorubicin
DWCNT	- Double-walled carbon nanotubes
EDX	- Energy dispersive X-ray
Epi	- Epirubicin hydrochloride
FESEM	- Field emission scanning electron microscopy
FTIR	- Fourier transform infrared
H_2SO_4	- Sulfuric acid

HNO_3	- Nitric Acid
IC_{50}	- Concentration of an inhibitor that reduces response by half
KBr	- Potassium bromide
m	- mol
M	- Molar
mg g^{-1}	- Milligram per gram
MWCNT	- Multi-walled carbon nanotubes
ND	- Neurodegenerative disease
ox-MWCNT	- oxidized multi-walled carbon nanotubes
PD	- Parkinson's disease
PEG	- Polyethylene glycol
PEG-CNT	- Polyethylene glycol grafted on carbon nanotubes
ppm	- Parts per million
PBS	- Phosphate buffer solution
Ptx	- Paclitaxel
PVA	- Polyvinyl alcohol
PVA-MWCNT	- Polyvinyl-alcohol grafted on multi-walled carbon nanotubes
RA	- Retinoic acid
RES	- Reticuloendothelial system
rpm	- Rotation per minute
RNS	- Reactive nitrogen species
ROS	- Reactive oxygen species
SD	- Standard deviation
SDS	- Sodium dodecyl sulphate
SEM	- Standard error mean
SWCNT	- Single-walled carbon nanotubes
t	- time
TGA	- Thermal gravimetric analysis
UV-Vis	- Ultraviolet-visible
V	- Volt
v/v	- Volume per volume
w/w	- Weight per weight

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CHAPTER 1

INTRODUCTION

1.1 Background of study

Curcumin (diferuloylmethane) is a bioactive compound found in turmeric rhizomes of *Curcuma longa linn.* This natural compound has been used for centuries as a spice for cooking curry, as food colouring and as ailments, particularly as an anti-inflammatory agent (Aggarwal *et al.* 2003). It has also shown other pharmacological effects including anti-oxidant, anti-proliferative and anti-angiogenic activities to treat various pathological conditions such as cancer, cardiovascular disease, Alzheimer's disease and so on (Anand *et al.* 2007). Despite such phenomenal advances in medicinal applications, the clinical implication of native Curcumin is hindered by its low solubility, physico-chemical instability, poor bioavailability, rapid metabolism, and poor pharmacokinetics. These problems nevertheless, can be circumvented by utilizing an efficient delivery system (Yallapu *et al*. 2015).

With the development of nanotechnology, a number of formulations have been developed and explored upon achieving successful outcomes for pre-clinical and human clinical trials. They involve the use of adjuvants, stabilizers,

nanoparticles, liposomes, and polymer-drug conjugates (Yallapu *et al.* 2015). Carbon nanotubes (CNT) have recently received considerable attention as an efficient drug delivery carrier due to their unique physicochemical properties. They enable easy surface modification for immobilization of therapeutic molecules, such as drugs, proteins, DNA and antibodies (Zhang *et al.* 2011). Compared to other drug delivery carriers, CNT offers several advantages such as exceptionally high drug loading due to its high surface area (Kushwaha *et al.* 2013). Different kinds of therapeutic molecules can also be incorporated into their inner cavity to improve efficacy, for instance providing protective environment for drugs with poor stability. Many studies show that adsorbed molecules could be released from CNT under different conditions (Zhang *et al.* 2014, Wang *et al.* 2012b, Heister *et al.* 2012) and that it can be controlled by varying pH value, temperature and different diameter type (Kumari *et al.* 2014, Liu *et al*. 2007a). The targeting agents attached to the CNT also enable the molecules, for example drugs, to be selectively transported and released to the diseased sites (Zhang *et al.* 2011).

Other important issues such as opsonisation, phagocytosis by macrophages and sequesterian by the liver and spleen that lead to its eventual elimination from the body need to be taken into account when developing a nanocarrier (Kotagiri and Kim, 2014). Hence, careful strategies in CNT functionalization are required for it to reach its full clinical potential. The design of CNT that combined coatings made of ligands or polymer in a complete and uniform manner helps to stabilize the carrier and prevents non-specific cell uptake in the bloodstream. A famous example is polyethylene glycol (PEG), a known polymeric steric stabilizer in pharmaceutical and food products, including in the development of CNT nanocarriers (Heister *et al*. 2010, Lay *et al.* 2010). The PEG-CNT did not only show good biocompatibility in biological mileu but also demonstrated prolonged blood circulation. As a result, the drug can be released when reaching the targeted cells. Advances using alternative biocompatible polymers incorporated with CNT have been well-described too, such as poly(lactic-co-glycolic acid) (Gupta *et al.* 2015), phosphatidylcholine (PC) and polyvinylpyrrolidone (PVP) (Zhang *et al.* 2014) and polyvinyl alcohol (PVA) (Sahoo *et al.* 2010). Their efficiency to improve stability, loading and release of Curcumin in a slow manner was, however, scarcely reported.

1.2 Problem statement

It was known that many formulations were developed to improve Curcumin delivery, except for CNT where studies are still in its infancy. To date, there is only one report that worked on Curcumin-loaded CNT system, which focused on Curcumin's anti-cancer potential (Zhang *et al.* 2014). The group functionalized single-walled CNT (SWCNT) with PC and PVP polymer for Curcumin loading, and the results showed fast release of the compound to suit its applicability for photothermal therapy.

In this study, the aim is to develop multi-walled CNT (MWCNT) as a carrier for Curcumin towards neurodegenerative treatment. The possible route of administration is through blood circulation; the time taken to reach the blood-brain barrier (BBB) might slow down before the drug can be released. Commonly, CNT was functionalized with PEG, as PEG is the most widely used polymer for increasing various nanocarrier's stability. CNT-PEG was known to provide shielding to the nanotubes to render its resistance to opsonin, macrophage and reticuloenthelial system (RES); showed by its increased blood circulation time in *in vivo* and *in vitro* experiment (Kotagiri and Kim, 2014). The prolonged circulation time of CNT helps the drug to be released effectively at the relevant/ targeted sites, which makes it an ideal drug carrier. In the current situation, there is a need to explore more coating materials that have PEG-like properties due to a number of limitations. First, studies have found anti-PEG antibodies in a population of healthy humans due to an increased exposure of PEG through food product, pharmaceutical formulation and cosmetics (Kinnear *et al.* 2014). These antibodies caused a reduction in circulation time of the PEGylated agent and accelerated clearance from the body due to repeated administration. Secondly, the "stealth" of PEG is potentially undesirable if there is a specific biological target on the carrier, such as the immune system. Also controversial is that PEG requires further synthetic steps to introduce a high number of functional moieties to bind with other therapeutic molecules, such as targeting peptides. The conventional PEG was known to have a low degree of functionality,

where only its end is reactive for attachment. This study has therefore explored new polymer alternatives for functionalization with MWCNT.

1.3 Research objectives

The present study was dedicated to develop nanocarriers using MWCNT and biocompatible PVA for Curcumin delivery. This work is regarded as the first study using MWCNT, with the main aim to graft PVA to ox-MWCNT, achieve stability of the PVA-MWCNT and to successfully load and release the compound in a slow manner. Additionally, the study is also aimed at providing recommendations for its potential implementation as a neuroprotective agent.

The specific objectives of the experimental study are as follows:

i. To develop functionalized MWCNT with PVA for the attachment of Curcumin
ii. To determine loading and release behavior of Curcumin on PVA-MWCNT in comparison to pristine MWCNT (p-MWCNT) and oxidized MWCNT (ox-MWCNT)
iii. To determine neurotoxicity and neuroprotective effect of Cur-PVA-MWCNT, Cur-ox-MWCNT and Cur-p-MWCNT, in comparison to PVA-MWCNT, ox-MWCNT and p-MWCNT using neuroblastoma cell line SH-SY5Y

1.4 Scope of study

This research project investigates the potential of functionalized MWCNT as an effective delivery carrier for Curcumin. In the first step of the study, the p-MWCNT was modified to ox-MWCNT using acid oxidation. The methods include stirring and sonication in the acid mixture and were optimized for its ability to provide substantial functional groups on ox-MWCNT with minimal structural damage. The best method was then selected to reproduce ox-MWCNT for grafting with PVA. Conformation of functional groups generated on ox-MWCNT and PVA-MWCNT were evaluated using field-emission scanning electron microscopy (FESEM), energy dispersive X-ray (EDX), Fourier transform infra-red (FTIR) spectroscopy, dispersion test and thermal gravimetric analysis (TGA). In the second objective, Curcumin was loaded to the PVA-MWCNT, as well as on ox-MWCNT and p-MWCNT for comparison. The Curcumin attached to the MWCNT samples were named Cur-PVA-MWCNT, Cur-ox-MWCNT and Cur-p-MWCNT. Their adsorption behavior was predicted by examining adsorption kinetics, isotherm and thermodynamics using mathematical models. In the drug desorption study, Curcumin's ability to disperse from the MWCNT samples, and its release pattern were determined in physiological buffers. Finally, investigations on neurotoxicity and neuroprotection effect of Cur-PVA-MWCNT, Cur-ox-MWCNT and Cur-p-MWCNT were evaluated using SH-SY5Y cells, which were conducted at Universiti Teknologi MARA, Shah Alam, Selangor. The correlation between Cur-loaded MWCNT and Cur-unloaded MWCNT was statistically validated using paired t-test.

1.5 Significance of study

In developing a CNT-based drug delivery carrier, careful design of functionalization is crucial. Polymer functionalized CNT has been reported to increase its circulation time in blood due to its "stealth", which helps to regulate drug release more

efficiently to cells and tissues. The present study hence optimized MWCNT functionalization strategies using biocompatible PVA. The discovery made from this study will disseminate knowledge that solved fundamental problems in the use of CNT as a drug carrier, such as their water solubility. The PVA that was employed as an alternative polymer for CNT functionalization will also help overcome PEG limitations that were recently reported. This was investigated through drug adsorption and desorption studies that used Curcumin as a drug model. Although there is still a long way to go for practical use, this study helps increase understanding on polymer-functionalized MWCNT for pharmaceutical industries application. The developed PVA-MWCNT before and after loading with Curcumin was studied for neuroprotective capabilities that will be beneficial in neurodegenerative disease treatment.

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