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MODIFIED CARBON NANOTUBES FOR DRUG DELIVERY APPLICATIONS

MISS CHULARAT IAMSAMAI

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY PROGRAM IN NANOSCIENCE AND TECHNOLOGY
(INTERDISCIPLINARY PROGRAM)

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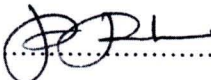
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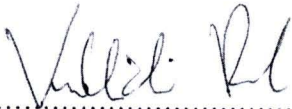
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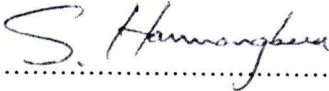
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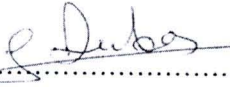
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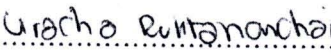

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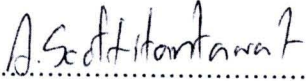
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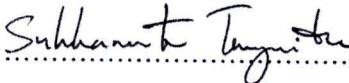

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การดัดแปรพื้นผิวของท่อคาร์บอนนาโนผนังหลายชั้น (MWCNTs) แบบนอนโควาลেন্ট โดยการเคลือบพื้นผิวแบบชั้นเดียวด้วยโคโคซานได้ถูกนำเสนอในงานวิจัยนี้ ระดับการกำจัดหมู่อะซิทิล (%DD) ของโคโคซาน (61%, 71%, 78%, 84%, 90% และ 93%) และความเข้มข้นของโคโคซานที่แตกต่างกัน มีผลต่อความสามารถในการกระจายตัวและความเสถียรของท่อคาร์บอนนาโนผนังหลายชั้น ผลการทดลองแสดงว่า โคโคซานที่มีระดับการกำจัดหมู่อะซิทิลต่ำที่สุด (61%) สามารถปรับปรุงการกระจายตัวของท่อคาร์บอนนาโนผนังหลายชั้น จากการวัดค่า zeta potential ยืนยันได้ว่า โคโคซานที่มีระดับการกำจัดหมู่อะซิทิล 61% สามารถปกคลุมพื้นผิวท่อคาร์บอนนาโนผนังหลายชั้นได้สูงกว่าสองเท่าเมื่อเทียบกับโคโคซานที่มีระดับการกำจัดหมู่อะซิทิล 93% เพื่อศึกษาโคโคซานซึ่งเป็นพอลิแซ็กคาไรด์ว่าช่วยเพิ่มความสามารถในการกระจายตัวและความเสถียรให้กับท่อคาร์บอนนาโนได้อย่างไร ดังนั้น Molecular Dynamics Simulation ถูกนำมาใช้เพื่อทำการศึกษาระบบ ได้แก่ i) ท่อคาร์บอนนาโนที่ไม่ผ่านการดัดแปรทั้งคู่ (*pCNT-pCNT*), ii) ท่อคาร์บอนนาโนที่ไม่ผ่านการดัดแปรกับโคโคซานที่มีระดับการกำจัดหมู่อะซิทิล 60% (*pCNT-cwCNT*) และ iii) ท่อคาร์บอนนาโนที่ผ่านการดัดแปรด้วยโคโคซานที่มีระดับการกำจัดหมู่อะซิทิล 60% ทั้งคู่ (*cwCNT-cwCNT*) การรวมตัวกันของท่อคาร์บอนนาโนเกิดขึ้นในกรณีที่เป็น *pCNT-pCNT* และ *pCNT-cwCNT* เนื่องจากแรง van der Waals ที่เกิดขึ้นระหว่างวงแหวนอะโรมาติกของท่อคาร์บอนนาโนและการเกาะกันระหว่างท่อคาร์บอนนาโนด้วยโคโคซาน ตามลำดับ ส่วนในกรณี *cwCNT-cwCNT* พบว่า เกิดการผลักกันระหว่างประจุส่งผลให้ท่อทั้งสองแยกออกจากกันและกระจายตัวได้ในสารละลาย แม้ว่าท่อคาร์บอนนาโนผนังหลายชั้นที่ผ่านการดัดแปรโดยการเคลือบพื้นผิวแบบชั้นเดียวด้วยโคโคซานที่มีระดับการกำจัดหมู่อะซิทิลต่ำ จะสามารถปรับปรุงความสามารถในการกระจายตัวของท่อคาร์บอนนาโนผนังหลายชั้นได้ แต่ความเสถียรของท่อคาร์บอนนาโนดัดแปรด้วยโคโคซานดังกล่าวยังไม่เพียงพอต่อการนำมาใช้เพื่อเป็นตัวนำส่งยา ด้วยเหตุนี้เทคนิค layer-by-layer deposition เป็นวิธีที่มีศักยภาพที่ถูกเลือกใช้เพื่อเตรียมฟิล์มบางหลายชั้นระหว่างพอลิ(ไดอัลิลไดเมทิลแอมโมเนียม คลอไรด์) (PDADMAC) และพอลิ(ไครีเนียม 4-สไตรีน ซัลโฟเนต) (PSS) เพื่อเคลือบบนท่อคาร์บอนนาโนที่ผ่านการดัดแปรทางเคมี เป็นที่น่าสนใจว่า การเตรียมฟิล์มบางชั้นที่ 1, 2 และ 3 บนท่อคาร์บอนนาโนที่ผ่านการดัดแปรทางเคมี สามารถเตรียมได้ด้วยวิธีที่ง่ายโดยใช้ “just enough polyelectrolyte” ซึ่งปราศจากการผ่านขั้นตอนการปั่นเหวี่ยง ทำให้ท่อคาร์บอนนาโนดัดแปรด้วยวิธีดังกล่าวมีความเสถียรอยู่ในสารละลายสูง ท่อคาร์บอนนาโนดัดแปรดังกล่าวถูกนำมาใช้เพื่อ load ยาโมเดลที่ละลายน้ำ ได้แก่ ยาเจนเซียนไวโอเลตและยาโคโคทีแนค พบว่า ยาเจนเซียนไวโอเลตสามารถ load ลงบนท่อคาร์บอนนาโนดัดแปรที่มีพื้นผิวเป็นประจุลบได้ดี ในขณะที่ยาโคโคทีแนคไม่สามารถ load ลงบนท่อคาร์บอนนาโนดัดแปรชนิดใดได้เลย ทั้งนี้ท่อคาร์บอนนาโนที่ผ่านดัดแปรด้วยหมู่ดัดแปรที่แตกต่างกันถูกนำมาทดสอบเพื่อประเมินค่าความเป็นพิษต่อเซลล์ L929 ด้วย MTT assay พบว่า ท่อคาร์บอนนาโนที่ผ่านการดัดแปรทางเคมีปริมาณ 25 ไมโครกรัม/มิลลิลิตร มีความเป็นพิษต่อเซลล์ L929 ในขณะที่ท่อคาร์บอนนาโนดัดแปรที่เคลือบหนึ่งชั้นด้วย PDADMAC มีความเป็นพิษต่อเซลล์ L929 ที่ปริมาณ 12.5 ไมโครกรัม/มิลลิลิตร

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Noncovalent surface modification of multiwall carbon nanotubes (MWCNTs) using chitosan coating as a monolayer is presented. The different degree of deacetylation (%DD) (61%, 71%, 78%, 84%, 90% and 93%) of chitosan and chitosan concentration affected to carbon nanotubes's dispersion efficiency and their stability. Results showed that the dispersion of MWCNTs could be improved when using chitosan with the lowest degree of deacetylation (61%DD). Zeta potential measurements confirmed that the chitosan surface coverage on the MWCNTs was twice as high when modifying the nanotubes surface with the 61%DD than when using the 93%DD chitosan. To study how a chitosan-polysaccharide increases the dispersion efficiency and stability of CNTs, molecular dynamics simulation done on the three models: *i*) two pristine CNTs (*p*CNT-*p*CNT), *ii*) a pristine CNT-a chitosan wrapped CNT (*p*CNT-*cw*CNT) and *iii*) two chitosan wrapped CNTs (*cw*CNT-*cw*CNT). As a result, the CNT aggregation was found in *p*CNT-*p*CNT and *p*CNT-*cw*CNT due to van der Waals interaction between the tube-tube aromatic rings, and intertube bridging by chitosan, respectively. In case of *cw*CNT-*cw*CNT, charge-charge repulsion was found to separate the two tubes and well disperse in aqueous solution. Although the monolayer coating MWCNTs with low %DD chitosan was improved the dispersion of MWCNTs, their stability was insufficient to be used as drug carrier. Therefore, the layer-by-layer deposition technique was selected as a potential method for preparing multilayers between poly(diallyldimethylammonium chloride) (PDADMAC) and poly(sodium 4-styrenesulfonate) (PSS) coating on treated MWCNTs surface. Interestingly, we found the simple method to prepare primary, secondary and tertiary layers on treated MWCNT with "just enough polyelectrolyte" without centrifugation process. Multilayer coating on MWCNT was provided high stability in aqueous solution. Gentian violet and diclofenac were used as hydrophilic model drugs for loading on modified MWCNTs. Gentian violet selectively loaded on negatively charged surface of MWCNT while diclofenac cannot be achieved to load in any kind of MWCNTs. The cytotoxicity of modified MWCNTs with different functional groups was evaluated by MTT assay. Treated MWCNTs were toxic to L929 cells when the concentration reached 25µg/ml while primary coating MWCNTs with PDADMAC was toxic at concentration 12.5µg/ml.

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LIST OF ABBREVIATIONS

CNT(s)	:	Carbon nanotube(s)
MWCNT(s)	:	Multiwall carbon nanotube(s)
SWCNT(s)	:	Singlewall carbon nanotube(s)
DD	:	Degree of deacetylation
PEL	:	Polyelectrolyte
PEM	:	Polyelectrolyte Multilayer Thin Films
LbL	:	Layer-by-Layer technique
ESA	:	Electrostatic self - assembly
PDADMAC	:	Poly(diallyldimethylammonium chloride)
PSS	:	Poly(sodium 4-styrene sulfonate)
RDF	:	Radial Distribution Function
τ	:	Torsion angle
S_g	:	Distance between CNTs surface
C_g	:	Distance between center of mass of CNTs
C_w	:	Chitosan wrapped
p	:	Pristine
mM	:	milli Molar
M	:	Molar
nm	:	nanometer
$\text{\AA}$	:	Angstrom
min	:	minute
ps	:	picosecond
fs	:	femtosecond
<i>et al.</i>	:	<i>et alii</i>