Functionalization of multi-walled carbon nanotube (MWCNT) with CTACe surfactant and polyethylene glycol as potential drug carrier

D Primastari S¹, Y Kusumastuti¹*, M Handayani², Rochmadi¹
¹Department of Chemical Engineering, Universitas Gadjah Mada, Jl. Grafika, 55281 Yogyakarta, Indonesia
²Research Center for Materials Science and Metallurgy, National Research and Innovation (BRIN), 470 Building, Puspiptek Area, Serpong, Tangerang Selatan, Indonesia
* Corresponding author: yuni_kusumastuti@ugm.ac.id

Abstract. Multi-walled Carbon Nanotube (MWCNT) pure is easy to form aggregate, making it difficult to apply as a drug carrier since it can be toxic to the body. It can be overcome by functionalization using surfactants, like cetyltrimethyl ammonium trichlorobromocerate (CTACe) and polyethylene glycol (PEG). First, MWCNT was functionalized with CTACe surfactant, then further PEG 6000 was used with several MWCNT-CTACe ratios. The functionalization was conducted under ultrasonic treatment, then followed by filtration, washing, and drying. The functionalized MWCNT underwent dispersion tests using water and dimethyl sulfoxide (DMSO) as the solvents. A dispersion test with water solvent shows that the functionalized MWCNT still forms aggregates within a few minutes. Whereas, in DMSO solvent, the functionalized MWCNT can be stabilized for more than five days without forming aggregates. FTIR results show a new peak at 1105 cm⁻¹ and an increased peak intensity around 3432 cm⁻¹, corresponding to C-N and hydrogen bonding of N-H vibration from the CTACe. The FTIR from PEG addition shows an increase in the wavenumbers around 3432,87 cm⁻¹, indicating the strength of O-H/N-H intermolecular hydrogen interactions of O-H PEG with N-H surfactant ether bonds.

1. Introduction
Drug delivery systems (DDS) are designed to increase the effectiveness and efficiency of drug release. DDS is achieved because drug delivery systems can reduce the amount of drug consumed in achieving the therapeutic effect of treatment and target drug delivery only to the desired tissue [1]. Currently, the drug loading capacity of the drug delivery system is still below 10% [2], and the drug release time is still relatively fast at the beginning (initial burst release) [3]. The improvement of this system is to find and modify materials that have the potential as drug carrier materials. One promising material for drug carriers is carbon nanotubes (CNT).

CNT are nanometer in size and are long cylindrical formed by covalent bonds between carbons. CNT has a large ratio of length to diameter so that it can provide a large surface area. It is easy for CNT to absorb...
drugs, DNA, vaccines, or antibodies on the surface or cavity of the tube [4][5][6]. There are two kinds of CNT: single-walled carbon nanotubes (SWCNT) and multi-walled carbon nanotubes (MWCNT). Compared with SWCNT, MWCNT has mechanical properties greater than SWCNT. These superior mechanical properties of MWCNT can improve material properties and chemical interactions of the polymer matrix [7]. In addition to the mechanical properties of MWCNT, the production of MWCNT is cheaper than SWCNT [8]. Although MWCNT has potential as a drug carrier, MWCNT also has a weakness, namely low dispersion ability in the aqueous environment because MWCNT is hydrophobic. This causes MWCNTs to tend not to be biocompatible and toxic, thus limiting their application in the biomedical field. Functionalization on the MWCNT surface can be done to improve the characteristics of the MWCNT material.

The surface functionalization of MWCNTs is classified into two, namely covalent and non-covalent functionalization. Covalent functionalization is the most common and relatively easy. This functionalization is by using an oxidizing agent (oxidative treatment). The oxidizing agents that have been used include H2SO4, HNO3 [9], HClO4, KMnO4, and H2O2 [10]. Functionalization will activate functional groups on the surface of the MWCNT and damaged/defective parts of the MWCNT tube. The functional groups are carboxylate, hydroxyl, enone, formyl (-CHO), epoxide, and quinoidal and ester groups [11]. Structurally, this covalent functionalization can damage the aromatic structure [12], and there is a slight change in the molecular structure when the drug molecule covalently binds to the MWCNT [13]. Therefore, MWCNT functionalization is mostly non-covalent. Non-covalent functionalization is a process of physical adsorption of MWCNT surface attachment with other molecules such as surfactants and/or polymers through π-π interactions, Van der Walls interactions, and hydrophobic interactions to facilitate the dispersion of MWCNT in water without damaging the characteristics of the MWCNT material.

Non-covalent functionalization of MWCNTs needs to be conducted to improve MWCNT dispersion and the performance of MWCNTs as drug carriers. This study carried out the non-covalent functionalization of MWCNTs by combining cationic surfactant CTACe and PEG polymer. The use of surfactants provides faster and more efficient dispersion results, and the presence of cationic groups from the surfactants will give hydrophilic properties (polar groups) on the MWCNT surface [14]. The addition of PEG as a strategy to increase MWCNT dispersion reduces the cytotoxicity of MWCNT, and the presence of PEG provides a longer circulation time in the blood [15].

2. Material and methods

2.1 Materials

Multi-walled Carbon Nanotube (MWCNT) purchased from Cheap Tubes, USA (purity >90%). Cetyltrimethyl Ammonium Bromide (CTAB) from Loba Chemie, and CeCl.7H2O from Sigma Aldrich, PEG (MW = 6000 Da), Dimethyl sulfoxide (DMSO), Methanol, and Ethyl Acetate from Merck & Co., Inc.

2.2 Synthesis CTACe

CTAB and CeCl.7H2O are dissolved in the molarity ratio (1:1) in methanol and stirred for 12 hours at room temperature. Then the solution was transferred to a petri dish to evaporate the solvent. Evaporation was performed at room temperature in a fume hood. After that, the samples were dried using a vacuum oven for 24 hours. The result obtained is a white solid known as a cetyltrimethyl ammonium tri-chloro-monobromo-cerate (CTACe).

2.3 Functionalization of MWCNT- CTACe

Zero point two mg/ml Raw MWCNT dispersed in a 3 mmol/L solution Cetyltrimethyl Ammonium Trichloro-Monobromo-Cerate (CTACe) (C16H33N+(CH3)3[CeCl3Br]) using an ultrasonic bath for 1 hour [5]. Then the MWCNT-CTACe solution was centrifuged at a speed of 4500 rpm ± for 1 hour. After that, samples were filtered and rinsed with distilled water. Results solids were dried using a vacuum oven temperature of 80°C for 3 hours.
2.4 Functionalization of MWCNT-CTACe-PEG

Zero point five grams of PEG in 10 ml of ethyl acetate solvent, then added solid MWCNT-CTACe. The solution was stirred for 8 hours at 60°C. Then filtered and rinsed with distilled water. The resulting solid was dried by using a vacuum oven to 80°C for 3 hours. Formula of

| Sample Code | MWCNT-CTACe (g) | PEG (g) |
|-------------|-----------------|---------|
| C           | 1               | 100     |
| D           | 1               | 50      |
| E           | 1               | 25      |
| F           | 1               | 17      |
| G           | 1               | 5       |

2.5 Dispersion of MWCNT-CTACe-PEG

Water solvents and DMSO were used as MWCNT dispersion media. Five mg of MWCNT was dispersed in 10 ml of solvent. Then it was sonicated for 10 minutes [9].

2.6 MWCNT Characterization

Fourier transform infrared (FTIR) spectroscopy used Nicolet Avatar 360 IR was used to determine the functional groups resulting from MWCNT functionalization and Scanning electron microscopy (SEM) analysis used Hitachi STA200RV for observed surface area.

3. Results and discussion

In this study, several characterization tests were conducted to obtain information on the dispersion, structure, and morphology of MWCNT functionalization with CTACe and PEG. The characterization test was carried out using FTIR spectroscopy, Scanning Electron Microscopy (SEM). A dispersion characterization test was carried out on raw MWCNT, MWCNT-CTACe and MWCNT-CTACe functionalization with all mass variations from the addition of PEG. Meanwhile, the tests using FTIR and SEM for mass variation samples with PEG used sample code “C”, which has the most addition of PEG mass.

3.1 Dispersion of MWCNT-CTACe-PEG

The dispersion of synthetic MWCNT-CTACe-PEG in water and DMSO can be seen in figure 1. Dispersion in aqueous solvent (figure 1a) shows the functionalized of MWCNT with CTACe surfactant (B) and MWCNT functionalized with CTACe-PEG (C-G) still has a low dispersion ability compared to raw MWCNT (A). The aggregation in figure 1a is formed after one minute of dispersion. Aggregation appears in the presence of CTACe surfactant on the MWCNT surface. Surfactants can solidify MWCNT by self-assembling them into micelles around the MWCNT surface. Thus making the intermolecular charge repulsion low and significantly making the MWCNT-CTACe precipitate [5]. The presence of micelles is identical to precipitation. Then, the functionalization of MWCNT-CTACe with PEG addition did not significantly increase the dispersion ability of MWCNT in water. It is possible that the electrical ratio (the number of ionized surfactant groups per the number of ionized groups of the polymer) is equal to one so that the complex formed becomes insoluble and precipitates [16]. In addition, the large molecular weight of 6000 PEG molecules decreased the binding constant value [17].

Figure 1b shows the dispersion of MWCNT-CTACe-PEG in DMSO solvent. The results showed that MWCNTs functionalized with CTACe surfactants and CTACe-PEG (figure 1b. B-G) had better dispersion abilities than raw MWCNTs (figure 1b. A). The low dispersion of raw MWCNT in DMSO solvent is due to the high polar nature of DMSO, which tends to stabilize the liquid state compared to interacting interface
with MWCNT. At the same time, MWCNT functionalized with CTACe surfactant (figure 1b. B) gives good dispersion results. The presence of DMSO as a solvent may provide a competitive interaction with the various functional groups of the surfactant, thereby giving a change in the aggregate shape of the surfactant molecule. In other words, DMSO has a significant influence on the micelle properties of surfactants [18]. In addition, MWCNT-CTACe functionalization followed by PEG functionalization (figure 1b. C-G) gave similar dispersion results to MWCNT-CTACe. It is possible that in the presence of active groups, sulphur (S), oxygen (O), and two methyl groups of DMSO, the solvent interacts with the functional groups of PEG. So that DMSO is straightforward to disperse the PEG polymer bound to the MWCNT surface [19].

3.2 Characteristics FTIR

FTIR spectra is applied to determine the interaction pattern of MWCNT functionalization with CTACe and PEG surfactants. Figure 2 shows the FTIR spectra of raw MWCNT, MWCNT-CTACe, and MWCNT-CTACe-PEG. When compared to the three spectra, it appears that all three have similar absorption patterns. In particular, the FTIR spectrum of MWCNTs before functionalization (figure 2a) shows a broad peak at wavenumber 3441.10 cm\(^{-1}\) which refers to the OH stretch of the hydroxyl group which may originate from the carboxyl group on the surface of the raw MWCNT from the production process and MWCNT purification [20, 21, 22].

Furthermore, the presence of a typical CTACe surfactant (figure 2b) is characterized by the appearance of amine peaks around the wave numbers 1210-1150 cm\(^{-1}\), 1650-1550 cm\(^{-1}\), and 1650-1590 cm\(^{-1}\) in the form of tertiary amines, from C-N stretching vibrations, secondary amines from the N-H bond, and primary amines from the N-H bond. Furthermore, the sharp peak of 3432.87 cm\(^{-1}\) is the area of the amine group with N-H stretching vibrations around the area of 3500-3100 cm\(^{-1}\). The second functionalization with PEG addition did not show a new dominant peak, but a widening of the peak in the 3500-3100 cm\(^{-1}\) area and an increase in wavenumbers from 3432.87 cm\(^{-1}\) (figure 2, b) to 3434.40 cm\(^{-1}\) (figure 2c). This may be due to strengthening the intermolecular hydrogen interactions O-H/N-H from O-H PEG and N-H from CTACe surfactants. An increase in frequency indicates a change in the shape of the structure. In addition to wavenumbers, there is a change in intensity, where with CTACe and PEG, there is an increase in transmission percent, which means that the energy used by the free functional groups becomes smaller due to the interaction between MWCNT, CTACe surfactants, and PEG [23].
Figure 2. FTIR spectra of raw MWCNT (a), MWCNT functionalized CTACe (b) and functionalization of MWCNT-CTACe-PEG (c)

| Raw MWCNT | MWCNT-CTACe | MWCNT-CTACe-PEG |
|-----------|-------------|-----------------|
| ![Image](image1) | ![Image](image2) | ![Image](image3) |

Figure 3. SEM images of raw MWCNTs, MWCNT-CTACe, MWCNT-CTACe-PEG with magnifications of 3000x (a), 7500x (b), and 10000x (c)
3.3 Characteristics SEM

SEM images for raw MWCNTs before being functionalized with CTACe surfactants and PEG show a real difference (see figure 3). Before functionalization, MWCNTs looked like rolled-up clusters of MWCNTs. After the surfactant functionalization treatment, the bundling effect began to decrease. In addition, this synthesis process experienced a destructive effect indicated by the MWCNTs being truncated and shorter in size (figure 3c, white arrow). It is possible the influence of surfactants as well as the ultrasonication process [22]. The addition of PEG polymer to the MWCNT-PEG functionalization did not significantly alter the outer surface of the MWCNT. However, the addition of PEG showed a more even distribution of MWCNTs in the polymer matrix [24]. In addition, the addition of a polymer may change the structure of the MWCNT in the presence of an interconnected structure with the polymer [25].

4. Conclusion

In brief, MWCNT was successfully functionalized with CTACe surfactant and CTACe-PEG surfactant through a facile method by soluting mixing. The results showed that functionalized MWCNTs had lower dispersion abilities compared to raw MWCNTs in aqueous solvents. Meanwhile, DMSO solvent gives excellent dispersion results and can be dispersed for more than five days. Although the functionalization yield in aqueous solvents is low, the attachment of surfactant-PEG to the MWCNT surface has been successfully carried out. It is hoped this functionalization provides insight into the possibility of further research related to drug attachment and the resulting toxic effects of this functionalization.

5. Reference

[1] Torchilin V P 2010 197
[2] Press D 2017 High drug-loading nanomedicines: progress, current status, and prospects 4085–4109
[3] Sharmeen S, Rahman A F M M, Lubna M M, Salem K S, Islam R and Khan M A 2018 Bioact. Mater. 3 236–244
[4] Saleemi M A, Kong Y L, Yong P V C and Wong E H 2020 J. Drug Deliv. Sci. Technol. 59 101855
[5] Xu L, Feng L, Dong S, Hao J and Yu Q 2018 Colloids Surfaces A Physicochem. Eng. Asp. 559 201–208
[6] Foldvari M and Bagonluri M 2008 Nanomedicine Nanotechnology, Biol. Med. 4 183–200
[7] Venkatesan J, Ryu B M, Sudha P N and Kim S K 2012 Int. J. Biol. Macromol. 50 393–402
[8] Anshori I, Rizalputri L N, Althof R R, Sean S, Harimurti S, Gumilar G, Yuliarto B, Harimurti S, Gumilar G, Yuliarto B and Handayani M 2021 Nanocomposites 7 97–108
[9] Sapalidis A, Sideratou Z, Panagiotaki K N, Sakellis E, Kouvelos E P, Papageorgiou S and Katsaros F 2018 Front. Mater. 5 1–10
[10] Wu K H, Wang D W and Gentle I R 2015 Carbon N. Y. 81 295–304
[11] Chernyak S A, Ivanov A S, Maslakov K I, Egorov A V., Shen Z, Savilov S S and Lunin V V. 2017 Phys. Chem. Chem. Phys. 19 2276–2285
[12] Rastogi V, Yadav P, Bhattacharya S S, Mishra A K, Verma N, Verma A and Pandit J K 2014 J. Drug Deliv. 2014 1–23
[13] Tsai H C, Lin J Y, Maryani F, Huang C C and Imae T 2013 Int. J. Nanomedicine 8 4427–4440
[14] Wulan P P, Wulandari H, Ulwan S H, Purwanto W W and Mulia K 2018 AIP Conf. Proc. 1933
[15] Liu Z, Davis C, Cai W, He L, Chen X and Dai H 2008 Proc. Natl. Acad. Sci. U. S. A. 105 1410–1415
[16] Pojjaźk K, Bertalanits E and Mezőszaźros R 2011 Langmuir 27 9139–9147
[17] Raees K, Ansari M S and Rafiquee M Z A 2020 J. King Saud Univ. - Sci. 32 1182–1189
[18] Kaushal D, Rana D S, Chauhan M S and Chauhan S 2013 Fluid Phase Equilib. 355 123–129
[19] Chalaris M, Marinakis S and Dellis D 2008 Fluid Phase Equilib. 267 47–60
[20] Greta Putri R, Syafara Y, Larasati F, Rosiqoh Eviana Putri N, Handayani M, Rochmadi and Kusumastuti Y 2020 IOP Conf. Ser. Mater. Sci. Eng. 742
[21] Коморников В А, Тимаков И С, Зайнуллин О Б, Гребенев В В, Макарова И П and Селезнева Е В 2018 Кристаллография 63 967–71
[22] Vaisman L, Wagner H D and Marom G 2006 Adv. Colloid Interface Sci. 128–130 37–46
[23] Harish Prashanth K V and Tharanathan R N 2003 Carbohydr. Polym. 54 343–351
[24] Rahman M M, Hussein M A, Abdel Salam M and Asiri A M 2017 New J. Chem. 41 10761–10772
[25] Zawawi N A, Majid Z A and Rashid A N A 2017 Colloid Polym. Sci. 295 1925–1936

Acknowledgments
Thanks to the Ministry of Education and Culture for supporting all activities and financial support for this research. This research granted from “Program Dasar Unggulan Perguruan Tinggi” (PDUPT) Program with funding scheme mentioned on 1718/UN1/DITLIT/DIT-LIT/PT/2021.