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Carbon Nanotubes in Nucleic Acids Delivery

Mohammad A. Obeid[1*], Alaa A. A. Aljabali[1], Haneen Amawi[2] and Shatha N. Abdeljaber[1]

[*1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Yarmouk University, Irbid, Jordan
[2]Department of Pharmacy Practice, Faculty of Pharmacy, Yarmouk University, Irbid, Jordan

ABSTRACT

Carbon nanotubes (CNTs) are type of nano-materials which have interesting physicaland chemical properties such as thermal, magnetic, surface and chemical properties. These properties make CNTs as promising opportunities for biomedical research and applications. Because of these interesting properties, CNTs were investigated for their drug delivery characteristics to deliver many therapeutic agents such as anticancer, peptides, vaccines, and nucleic acids into specific target cells. Results obtained gave the CNTs great interest in pharmaceutical development field as carriers with promising development future. CNTs were found to have large surface area which gives them the ability to traverse amphipathic cell membranes and flexible interactions with their cargo. Moreover, these interesting features give CNTs the ability to deliver many types of nucleic acids effectively into their targets. In this review, we discuss the different aspects and properties of CNTs and the use of different types of CNTs as drug delivery system for the delivery of many nucleic acids such as siRNA and miRNA.

Key words: Carbon Nanotubes, Nucleic Acids, Drug Delivery, Anticancer, Nanoparticles

INTRODUCTION

Carbon nanotubes (CNTs) represents a group of nanotechnology drug delivery systems that have a needle shape, which was increasingly used from the early 19th century. CNTs belong to fullerenes sub-family and they are composed of many sheet layers of graphite. They have several characteristics that make them promising drug delivery system and have the potential to be used in industries [1]. These characteristics include their enhanced mechanical strength, electrical and thermal conductivity, light weight, huge surface, and good electronics [2,3]. The large surface area of CNTs comes from their distinctive length-to-diameter ratio, which reaches to 28,000,000:1. This allows for flexible modifications of their chemical surface to improve their therapeutic application and enhance their interaction with different biological membranes in their application as targeted drug delivery systems for the delivery of therapeutic and imaging agents.

Corresponding Author:
m.obeid[at]yudotedudotjo

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CNTs are graphene molecules that are presented as an empty cylindrical tube-like framework with sp^2 hybridised carbon atoms. These carbon atoms are arranged in a specific hexagonal structural pattern. Each CNT molecule differs from another one by the number of its carbon atoms. They can have C20, C30, C36, C70, as well as C78, where the number here represents the number of carbon atom in each CNT

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molecule [4,5]. CNTs can be classified based on their wall structure as single-walled carbon nanotubes (SWNTs) and multi-walled carbon nanotubes (MWNTs). SWNTs are characterised by one sheet of graphene with a radius up to one nanometre whereas the MWCNTs have multiple graphene sheets ranging from two to ten with an internal diameter around ten or sometimes more depending on the number of the graphene sheets. These structures are presented in Figure-1.

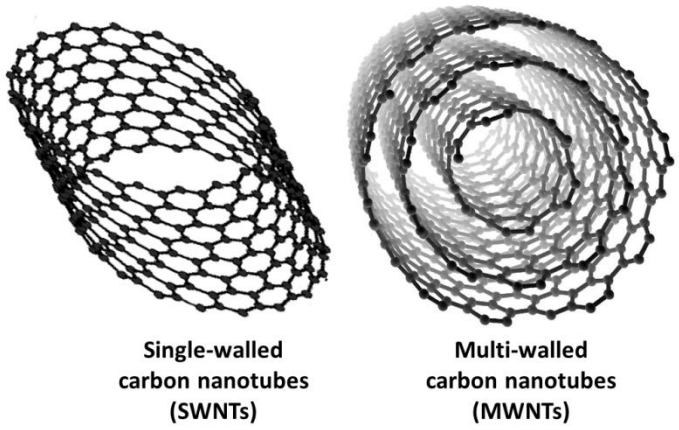

Figure 1: Schematic diagram representing the structures of single-walled carbon nanotubes (SWNTs) and multiwalled carbon nanotubes (MWNTs)

Because of the distinct needle shape of the CNTs, the drug or the imaging contrast can be filled the hollow inner space,and the external surface can be modified by targeting moieties to achieve targeted drug delivery [6]. Currently, CNTs were successfully employed to deliver therapeutic agents in several applications such as central nervous system disorders, anticancer agents delivery, and antimicrobial drugs for the treatment of various infections [7]. Moreover, CNTs have recently being applied for the delivery of several biotechnological agents such as nucleic acids, enzymes, hormones, and vaccines [8-10].

Nucleic Acids Therapy

Nucleic acids are among the therapeutic agents that could be delivered to their target sites using CNTs. Nucleic acids include antisense oligonucleotides (ODNs), plasmid DNA (pDNA), DNA or RNA aptamers, small-interfering RNAs (siRNA), messenger RNA (mRNA),and short hairpin RNA (shRNA). Nucleic acids are used in specific disorders for the replacement of specific genes or the inhibition of specific target proteins [11]. siRNAis approximately 21 nucleotides which represent a promising therapeutic agent where it can inhibit any vital protein of known sequence in the target cells through its integration with the RNA-induced silencing complex (RISC) in the cytoplasm of the target cells and the subsequent cleavage of the mRNA which is complementary to the siRNA antisense strand [12]. This will result in the interference of the protein translation process and protein production knockdown. The process of the use of protein production inhibition through the use of siRNA is referred to as RNAi interference or siRNA silencing [13]. miRNAs are also typed of nucleic acids with 18-28 nucleotides in length and are involved in regulating various gene expression at the post-transcriptional stage in the treatment of most cancers where it can act as suppressors for tumours and oncogenes [14]. miRNA will also be is aligned with the RISC and result in degradation or destabilisation of the target mRNA [15].

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The main limitations for the extensive application of the nucleic acids are the limited stability and cellular uptake. Nucleic acids are highly susceptible to degradation by nucleases enzymes in the plasma and the subsequent rapid elimination. Moreover, they have poor cellular uptake due to their substantial molecular weight and their negative charge. Therefore, the successful application of these nucleic acids therapies for the treatment of various diseases is hampered by the use of effective drug delivery system that can encapsulate, protect, and enhance the uptake of the loaded nucleic acids into the target cells [13].

Nucleic Aacids Delivery with CNTs

Several types of viral and non-viral nanocarriers were investigated as potential delivery systems for nucleic acids delivery with many promising outcomes. These nanoparticles include liposomes niosomes, gold nanoparticles, polymeric nanoparticles, and many others [11,16-20]. CNTs are also investigated widely as promising drug delivery systems for the delivery of different types of siRNAs and miRNAs. The advantages of using CNTs as a potential carrier for nucleic acids include the ability to functionalised their outer surface for targeted drug delivery, their simple transportation through the cell membrane, their light weight, and the possibilities for large scale production of CNTs.

The loaded nucleic acids will be complexed with the CNTs structure, and a targeting moiety can be attached to the outer surface to form a specific drug delivery system as presented in Figure-2.

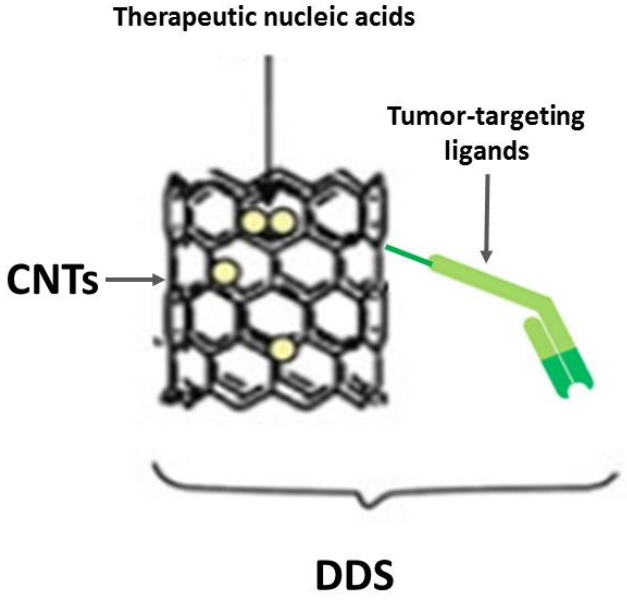

Figure: 2 Schematic diagram representthe design of CNTs targeted drug delivery system designed for nucleic acids delivery

Several researchers investigated the potential of CNTs as a delivery vector for various types of nucleic acids either *in vitro* or *in vivo*. For example, in the work of Bartholomeusz et al., siRNA targeting hypoxia-inducible factor 1 alpha (HIF-1α) was complexed to SWNTs [21], and the formulation was transfected into human pancreatic carcinoma cells (MiaPaCa-HRECells) and a significant specific inhibition HIF-1α was achieved *in vitro*. Moreover, this formulation was administered to mice bearing MiaPaCa-2/HRE

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tumours through intratumoral administration,and the tumour growth was significantly inhibited [22].
Guo et al. designed a cationic MWCTs for the delivery of apoptotic siRNA targeting polo-Like Kinase (PLK1) in Calu6 tumour xenografts by direct intratumoral injections and reported a significant tumour eradication was due to PLK1 knockdown [23,24]. In the work of Wang et al., siRNA was successfully transfected into PC-3 cells using SWNTs functionalised with polyethyleneimine (PEI) (SWNTs-PEI). siRNA transfection resulted in a significant tumour cell growth inhibition as both in vitro and in vivo as confirmed by the polymerase chain reaction (PCR) and the Western blotting results [25,26].

Many other researchers have optimised various CNTs formulations for the delivery of miRNA. This can be seen in the work of Celluzziet al. where polyamine-coated CNTs were developed for the miRNAs delivery into human cells, which was intended to optimise the transfection efficiency of these compounds as an effective drug delivery systems in biomedical applications [27].

CONCLUSION

Recently, CNTs were studied extensively as a promising drug delivery system to be used for the delivery of different therapeutic agents such as peptides, anticancer agents, and nucleic acids.
In the field of nucleic acids delivery, various formulations of CNTs have been developed and proved to enhance the delivery and the uptake of different nucleic acids types such as siRNA and miRNA.
These significant targeted results of nucleic acids delivery with CNTs represents a crucial advance in the field of gene therapy with promising future formulations to be developed as an approved medicine for controlled treatment of many diseases after conducting the required clinical studies to test the true value of CNTs in nucleic acids delivery.
Although many obstacles still need to be overcome in order to effectively translate CNTs-based drug delivery formulations into clinical usage, adequately developed and tested CNTs still represent a promising alternative drug delivery system to deliver therapeutic agents into specific target inside the body.

REFERENCES

1. Obeid MA, Khadra I, Albaloushi A, Mullin M, Alyamani H, Ferro VA. Microfluidic manufacturing of different niosomes nanoparticles for curcumin encapsulation: Physical characteristics, encapsulation efficacy, and drug release. Beilstein journal of nanotechnology. 2019 Sep 5;10(1):1826-32.
2. Lu F, Gu L, Meziani MJ, Wang X, Luo PG, Veca LM, Cao L, Sun YP. Advances in bioapplications of carbon nanotubes. Advanced Materials. 2009 Jan 12;21(2):139-52.
3. Obeid MA, Gany SA, Gray AI, Young L, Igoli JO, Ferro VA. Niosome-encapsulated balanocarpol: compound isolation, characterisation, and cytotoxicity evaluation against human breast and ovarian cancer cell lines. Nanotechnology. 2020 Feb 20;31(19):195101.
4. Beg S, Rizwan M, Sheikh AM, Hasnain MS, Anwer K, Kohli K. Advancement in carbon nanotubes: basics, biomedical applications and toxicity. Journal of pharmacy and pharmacology. 2011 Feb;63(2):141-63.
5. Obeid MA, Al Qaraghuli MM, Alsaadi M, Alzahrani AR, Niwasabutra K, Ferro VA. Delivering natural products and biotherapeutics to improve drug efficacy. Therapeutic delivery. 2017 Nov;8(11):947-56.
6. Hasnain MS, Nayak AK. Carbon nanotubes for targeted drug delivery. Springer; 2019 Nov 8.
7. Obeid MA, Elburi A, Young LC, Mullen AB, Tate RJ, Ferro VA. Formulation of Nonionic Surfactant Vesicles (NISV) prepared by microfluidics for therapeutic delivery of siRNA into cancer cells. Molecular pharmaceutics. 2017 Jul 3;14(7):2450-8.
8. Brandelli A. Nanostructures as promising tools for delivery of antimicrobial peptides. Mini reviews in medicinal chemistry. 2012 Jul 1;12(8):731-41.
9. Vashist SK, Zheng D, Pastorin G, Al-Rubeaan K, Luong JH, Sheu FS. Delivery of drugs and biomolecules using carbon nanotubes. Carbon. 2011 Nov 1;49(13):4077-97.

ISSN 2397-5547

10. Al Qaraghuli MM, Alzahrani AR, Niwasabutra K, Obeid MA, Ferro VA. Where traditional drug discovery meets modern technology in the quest for new drugs. Annals of pharmacology and pharmaceutics. 2017 Jun 4;2(11):1-5.
11. Obeid MA, Dufès C, Somani S, Mullen AB, Tate RJ, Ferro VA. Proof of concept studies for siRNA delivery by nonionic surfactant vesicles: in vitro and in vivo evaluation of protein knockdown. Journal of Liposome Research. 2019 Jul 3;29(3):229-38.
12. Shrivastava G, Bakshi HA, Aljabali AA, Mishra V, Hakkim FL, Charbe NB, Kesharwani P, Chellappan DK, Dua K, Tambuwala MM. Nucleic Acid Aptamers as a Potential Nucleus Targeted Drug Delivery System. Current Drug Delivery. 2020 Feb 1;17(2):101-11.
13. Obeid MA, Tate RJ, Mullen AB, Ferro VA. Lipid-based nanoparticles for cancer treatment. InLipid Nanocarriers for Drug Targeting 2018 Jan 1 (pp. 313-359). William Andrew Publishing.
14. Ta F, Hoell JI, Tuschl PM. Micrornas in human cancer. Advances in Experimental Medicine. Biology. 2013;774(2):1-20.
15. Ha M, Kim VN. Regulation of microRNA biogenesis. Nature reviews Molecular cell biology. 2014 Aug;15(8):509-24.
16. Aljabali AA, Lomonossoff GP, Evans DJ. CPMV-polyelectrolyte-templated gold nanoparticles. Biomacromolecules. 2011 Jul 11;12(7):2723-8.
17. Zhang J, Li X, Huang L. Non-viral nanocarriers for siRNA delivery in breast cancer. Journal of Controlled Release. 2014 Sep 28;190:440-50.
18. Aljabali AA, Evans DJ. Polyelectrolyte-modified Cowpea mosaic virus for the synthesis of gold nanoparticles. InVirus Hybrids as Nanomaterials 2014 (pp. 97-103). Humana Press, Totowa, NJ.
19. Aljabali AA, Akkam Y, Al Zoubi MS, Al-Batayneh KM, Al-Trad B, Abo Alrob O, Alkilany AM, Benamara M, Evans DJ. Synthesis of gold nanoparticles using leaf extract of Ziziphus zizyphus and their antimicrobial activity. Nanomaterials. 2018 Mar;8(3):174.
20. Aljabali AA, Al Zoubi MS, Al-Batanyeh KM, Al-Radaideh A, Obeid MA, Al Sharabi A, Alshaer W, AbuFares B, Al-Zanati T, Tambuwala MM, Akbar N. Gold-coated plant virus as computed tomography imaging contrast agent. Beilstein journal of nanotechnology. 2019 Oct 7;10(1):1983-93.
21. AA Aljabali A, A Bakshi H, L Hakkim F, Haggag YA, M Al-Batanyeh K, S Al Zoubi M, Al-Trad B, M Nasef M, Satija S, Mehta M, Pabreja K. Albumin nano-encapsulation of piceatannol enhances its anticancer potential in colon cancer via downregulation of nuclear p65 and HIF-1α. Cancers. 2020 Jan;12(1):113.
22. Bartholomeusz G, Cherukuri P, Kingston J, Cognet L, Lemos R, Leeuw TK, Gumbiner-Russo L, Weisman RB, Powis G. In vivo therapeutic silencing of hypoxia-inducible factor 1 alpha (HIF-1α) using single-walled carbon nanotubes noncovalently coated with siRNA. Nano research. 2009 Apr 1;2(4):279-91.
23. Guo C, Al-Jamal WT, Toma FM, Bianco A, Prato M, Al-Jamal KT, Kostarelos K. Design of cationic multiwalled carbon nanotubes as efficient siRNA vectors for lung cancer xenograft eradication. Bioconjugate chemistry. 2015 Jul 15;26(7):1370-9.
24. Obeid MA, Gebril AM, Tate RJ, Mullen AB, Ferro VA. Comparison of the physical characteristics of monodisperse non-ionic surfactant vesicles (NISV) prepared using different manufacturing methods. International journal of pharmaceutics. 2017 Apr 15;521(1-2):54-60.
25. Wang L, Shi J, Zhang H, Li H, Gao Y, Wang Z, Wang H, Li L, Zhang C, Chen C, Zhang Z. Synergistic anticancer effect of RNAi and photothermal therapy mediated by functionalized single-walled carbon nanotubes. Biomaterials. 2013 Jan 1;34(1):262-74.
26. Obeid MA, Teeravatcharoenchai T, Connell D, Niwasabutra K, Hussain M, Carter K, Ferro VA. Examination of the effect of niosome preparation methods in encapsulating model antigens on the vesicle characteristics and their ability to induce immune responses. Journal of Liposome Research. 2020 May 11(just-accepted):1-30.
27. Celluzzi A, Paolini A, D'Oria V, Risoluti R, Materazzi S, Pezzullo M, Casciardi S, Sennato S, Bordi F, Masotti A. Biophysical and biological contributions of polyamine-coated carbon nanotubes and bidimensional buckypapers in the delivery of miRNAs to human cells. International journal of nanomedicine. 2018;13:1.

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