Carbon Nanotubes in Nucleic Acids Delivery

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ABSTRACT
Carbon nanotubes (CNTs) are type of nano-materials which have interesting physical and 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.

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.
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)](image)

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 RNA 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].
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 Acids 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 represent the 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
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 polyethylenimine (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


