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Nanomedicine: Carbon Nanotube: A Unique Pharmaceutical Dosage Form

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Abstract

The last few years have witnessed the discovery, development and, in some cases, large-scale manufacturing and production of novel materials that lie within the nanometer scale. Such novel nanomaterials consist of inorganic or organic matter and in most cases have never been studied in the context of pharmaceuticals. Carbon nanotubes (CNTs) are one of them. These tubes were originally called “buckytubes” but now are better known as carbon nanotubes or CNT for short. These molecules are shaped like a tube; imagine a sheet of graphite ("graphene sheet") or chicken wire rolled into a tube. Carbon nanotubes are allotropes of carbon with a nanostructure that can have a length-to-diameter ratio greater than 1,000,000. One of the physical properties of carbon nanotubes is that it’s possible to make them only a single atomic layer thick. This means that they can be about 1/50,000th the thickness of a human hair. The small dimensions, strength and the remarkable physical properties of these structures make them a very unique material with a whole range of promising applications. These cylindrical carbon molecules have novel properties that make them potentially useful in many applications in nanotechnology.

Keywords: Nanomedicines, Carbon nanotubes, Buckytubes, Cylindrical

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1. Introduction

The bonding in carbon nanotubes is sp^2, with each atom joined to three neighbors, as in graphite. The tubes can therefore be considered as rolled-up graphene sheets (graphene is an individual graphite layer)[1]. This bonding

structure, which is stronger than the sp3 bonds found in diamond, provides the molecules with their unique strength. Under high pressure, nanotubes can merge together, trading some sp^2 bonds for sp^3 bonds, giving the possibility of producing strong, unlimited length wires through high-pressure nanotube linking. Structure of nanotubes is as shown in (Fig 1)[2].

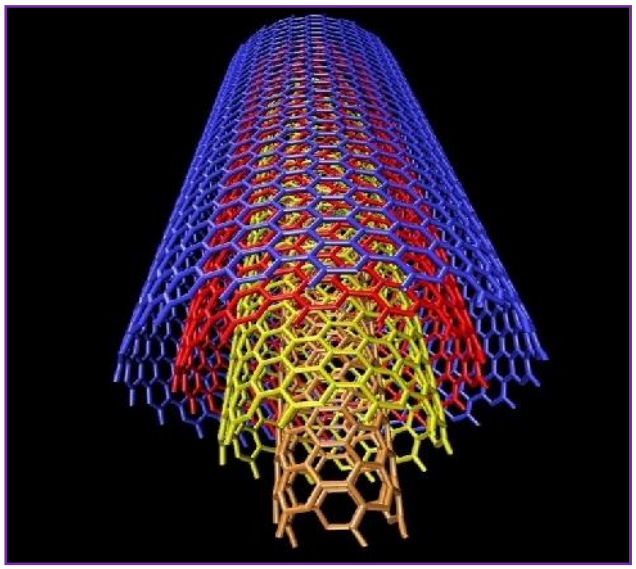

Figure 1. Structure of carbon nanotube

Classification of Carbon Nanotubes

Carbon nanotubes are classified in following two types

1. Multiple walled carbon nanotubes (MWNTs)
2. Single walled carbon nanotubes (SWNTs)

Functionalisation of Carbon Nanotubes

For biological and biomedical applications, the lack of solubility of carbon nanotubes in aqueous media has been a major technical barrier. To overcome this problem the modification of the surface of CNT i.e. functionalisation is done[4, 5]. With different molecules it is achieved by adsorption, electrostatic interaction or covalent bonding of different molecules and chemistries that render them more hydrophilic. Through such modifications, the water solubility of CNT is improved and their biocompatibility profile is completely transformed. Moreover, the bundling/aggregation of individual tubes through vander Waals forces are also reduced by the functionalisation of their surface[4, 6]. The recent expansion in methods to chemically modify and functionalize carbon nanotubes has made it possible to solubilize and disperse carbon nanotubes in water, thus opening the path for their facile manipulation and processing in physiological environments. Equally important is the recent demonstration that biological and bioactive species such as proteins, carbohydrates, and nucleic acids can be conjugated with carbon nanotubes. These nanotube bioconjugates will play a significant role in the research effort toward bioapplications of carbon nanotubes. One focal point has been the development of nanoscale bioelectronics systems based on carbon nanotubes, which has been driven by the experimental evidence that biological species such as proteins and DNA can be immobilized either with the hollow cavity of or on the surface of carbon nanotubes[5]. Concerning the intrinsic toxicity of CNT, in vitro studies had indicated that SWNT functionalised by a covalent method with phenyl-SO3H or phenyl- (COOH)2 groups produced less cytotoxic effects than aqueous dispersions of pristine SWNT stabilised with a surfactant— 1% of Pluronic F108 . Moreover, in the same study, the cytotoxicity of covalently modified SWNT has been reported to be further decreased with the increase in the degree of sidewall fictionalization[7].

2. Pharmacology of Carbon Nanotubes

The biodistribution and pharmacokinetics of nanoparticles rely to a large extent on their physicochemical characteristics such as size, shape, aggregation, chemical composition, surface functionalisation and solubility[8, 9]. Two studies have been reported so far concerning the biodistribution of CNT. Both studies were performed with water soluble CNT, which are biocompatible with the body fluids. None of the studies report toxic side effects or mortality. Wang et al. have used 125Iodinelabeled multiple hydroxylated SWNT (125I-SWNT-OH), functionalized by oxidation of the nanotubes, and radiotraced their distribution in mice after administration by, primarily, intraperitoneal (i.p.) administration. Other routes of administration were compared to i.p. such as subcutaneous, oral (by stomach intubation) and intravenous. This study reported that the CNT biodistribution was not significantly influenced by the administration route and that the 125ISWNT- OH distribute quickly throughout the whole body.

The preferred organs for accumulation were the stomach, kidneys and bone. Most importantly from the safety point of view, 94% of the nanotubes were excreted into the urine and 6% in the feces as observed in this study. No tissue damage or distress was reported. Second study, focusing on the intravenous route of administration and using functionalised SWNT and MWNT following a different surface chemistry (i.e. via the 1, 3-dipolar cycloaddition reaction) compared to the SWNT used in the study by Wang et al., was performed[10].

The CNT were functionalised with the chelating molecule diethylene triaminepentaacetate(DTPA) and radiolabeled with 111Indium ([111In] DTPA-CNT). In this study, the effect on biodistribution and blood circulation halflives of different degrees of surface functionalisation with DTPA was also studied, using 100% and 60% surface functionalisation with DTPA (the remaining 40% functional group were amino functions). The biodistribution profiles obtained were found very similar for both types of functionalised [111In] DTPA-SWNT which showed an affinity for kidneys, muscle, skin, bone and blood 30 min after administration. However, all types of nanotubes were found to be rapidly cleared from all tissues and a maximum blood circulation half life of 3.5 h was determined. The excretion of DTPACNT, both SWNT and MWNT functionalised with 100% DTPA were found to be excreted through the renal route into the bladder and urine following intravenous administration. Moreover, both types of DTPA-CNT were observed intact in the excreted urine by transmission electron microscopy[4].

Toxicity of Carbon Nanotubes

Generally, the harmful effects of nanoparticles arise from the combination of various factors, two of which are particularly important: (a) the high surface area and (b) the intrinsic toxicity of the surface[9]. In contrast with conventional particles of larger mean diameter, nanoparticles under 100 nm can potentially be more toxic to the lung (portal of entry), can redistribute from their site of deposition, can escape from the normal phagocytic defenses and can modify the structure of proteins. Therefore, nanoparticles can activate inflammatory and immunological responses and may affect the normal tissue function[11]. CNT, in the context of toxicology, can be classified as 'nanoparticles' due to their nanoscale dimensions, therefore unexpected toxicological effects upon contact with biological systems may be induced. The nanometer-scale dimensions of CNT make quantities of milligrams possess a large number of cylindrical, fiber-like particles, with a concurrent very high total surface area.

This total surface area will also depend on their degree of bundling and aggregation of nanotubes in solution. The intrinsic toxicity of CNT depends on the degree of surface functionalisation and the different toxicity of functional groups. Batches of pristine CNT (non-purified and/or nonfunctionalised) readily after synthesis contain impurities such as amorphous carbon and metallic nanoparticles (catalysts: Co, Fe, Ni and Mo), which can also be the source of severe toxic effects[6, 7]. Donaldson et al. have shown that the structural characteristics of nanomaterials, such as the fibre shape, the length and the aggregation status of the CNT, can also influence their local deposition in the lungs and the immunological response following exposure to CNT[11]. Another important factor is the bioavailability of CNT in the body. The mechanism of CNT metabolism, degradation or dissolution, clearance and bioaccumulation requires attention and study in order to obtain a clearer idea of the limitations of such nanomaterials as components of pharmaceuticals. So far the vast majority of reports published on the administration of CNT are primarily concerned with the toxicology of CNT, addressing the possible negative side effects of this nanomaterial on human health and environment, and particularly from the point of view of public health and safety for CNT production plant workers. As large-scale manufacturing gradually becomes routine for the production of CNT, handling and exposure (dermal and pulmonary) of workers to CNT brings exposure-risk issues to the surface[5]. Maynard et al. have studied the release of particles from unrefined SWNT material into the air and the potential routes of exposure of the workers in a small-scale production facility. They have found that handling of unrefined material produces airborne particle concentrations of 53 $\mu g/m^3$ and glove deposits of 0.2–6 mg per hand[12].

3. Applications of Carbon Nanotubes

Various applications of CNTs are as follows:

1. Carrier for Drug delivery: Carbon nanohorns (CNHs) are the spherical aggregates of CNTs with irregular horn like shape. Research studies have proved CNTs and CNHs as a potential carrier for drug delivery system.
2. Functionalised carbon nanotubes are reported for targeting Amphotericin B to Cells.
3. Cisplatin incorporated oxidized SWNHs have showed slow release of Cisplatin in aqueous environment. The released Cisplatin had been effective in terminating the growth of human lung cancer cells, while the SWNHs alone did not show anticancer activity.
4. Anticancer drug Polyphosphazene platinum given with nanotubes had enhanced permeability, distribution and retention in the brain due to controlled lipophilicity of nanotubes.
5. Antibiotic, Doxorubicin given with nanotubes is reported for enhanced intracellular penetration.
6. The gelatin CNT mixture (hydro-gel) has been used as potential carrier system for biomedicals.

7. CNT-based carrier system can offer a successful oral alternative administration of Erythropoietin (EPO), which has not been possible so far because of the denaturation of EPO by the gastric environment conditions and enzymes.
8. They can be used as lubricants or glidants in tablet manufacturing due to nanosize and sliding nature of graphite layers bound with van der waals forces.

Limitations of Carbon Nanotubes [4,7]

1. Lack of solubility in most solvents compatible with the biological milieu (aqueous based).
2. The production of structurally and chemically reproducible batches of CNTs with identical characteristics.
3. Difficulty in maintaining high quality and minimal impurities.

4. Conclusion

The properties and characteristics of CNTs are still being researched heavily and scientists have barely begun to tap the potential of these structures. They can pass through membranes, carrying therapeutic drugs, vaccines and nucleic acids deep into the cell to targets previously unreachable. With the prospect of gene therapy, cancer treatments, and innovative new answers for life-threatening diseases on the horizon, the science of nanomedicine has become an ever-growing field that has an incredible ability to bypass barriers. Overall, recent studies regarding CNTs have shown a very promising glimpse of what lies ahead in the future of medicines.

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