

Application of Carbon Nanotubes as Drug Delivery System for Anticancer Therapy

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Abstract

Carbon nanotubes are one-dimensional allotrope of carbon having high aspect ratio, high surface area, and excellent material properties. It has applications in many fields such as catalyst, nano-electronics, field emission, nano medicine, solar cells, energy storage etc. Drug delivery is one of the important applications of carbon nanotubes because of its unique properties such as high drug loading capacity, thermal ablation, ease of cellular uptake. This article briefly overviews the different steps in drug delivery and anticancer therapy such as mechanism of drug loading, transportation, distribution, metabolism and finally excretion of drug.

Keywords: anticancer therapy, carbon nanotube, drug delivery.

Introduction

(a) General Introduction

Cancer ranks amongst the top three killers in modern society, next to the heart and cerebrovascular diseases. Cancer is a kind of disease that is very hard to cure, and most cancer patients die even when treated with highly developed modern medicinal techniques. Surgery can remove cancer affected area (focuses) but cannot do the same for the micro-focuses and neither can extinguish the free cancer cells that are often the origin of relapse. The chemo therapeutic agent used for the treatment of a range of cancers is always associated with severe, sometimes fatal toxicity due to a lack of target specificity (Alderton, 1992).

With the development of nanotechnology, few nanomaterial based products have shown promise in the treatment of cancers and many have been approved for clinical research, such as nanoparticles, liposomes, and polymer drug conjugates. Several attempts have been made to reduce this serious side effect, for example by liposomal encapsulation of doxorubicin. Ever since their discovery by Iijima, there has been intense interest in Carbon Nanotubes (CNTs) (Iijima, 1991) due to their unique physical and chemical properties, emerging as promising candidates for multimodal drug delivery systems. As a unique one-dimensional material, CNTs have been explored as novel drug delivery vehicles. CNTs can effectively shuttle various biomolecules into cells including drugs, peptide, proteins,

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plasmid DNA and small interfering RNA via endocytosis. The ultra-high surface area of these 1D poly-aromatic macromolecules allows for efficient loading of chemotherapeutic drugs. In addition, they interact with cellular membranes in a unique way: some types of CNTs have been reported to enter mammalian cells by an endocytosis-independent, “needle-like” penetration mechanism, which allows for direct cytoplasmic delivery of therapeutic payloads (Mu, 2009). Many studies have already reported successful delivery of anti-cancer drugs to human cancer cells using CNTs. In the medical field, three main attributes of CNTs have been exploited due to their small size, high surface area to volume ratio and their ability to contain chemicals. Carbon nanotubes can be produced small enough to pass through holes in tumors or to transport DNA (Singh & Pantarotto, 2005). The large surface to volume ratio provides a good platform for efficient transportation of chemicals and for the reactions needed for ultra-sensitive glucose detection.

(b) Carbon Nanotubes

Carbon is known to be the most versatile element that exists on the earth. It has many different properties which can be used in different ways depending on how the carbon atoms are arranged. Carbon nanotubes are rolled-up of graphene sheet into cylinders with diameters as small as one nanometer. They are created by heating ordinary carbon until it vaporizes, then allowing it to condense in a vacuum or an inert gas. The carbon condenses in a series of hexagons, like sheets (Fig. 1).

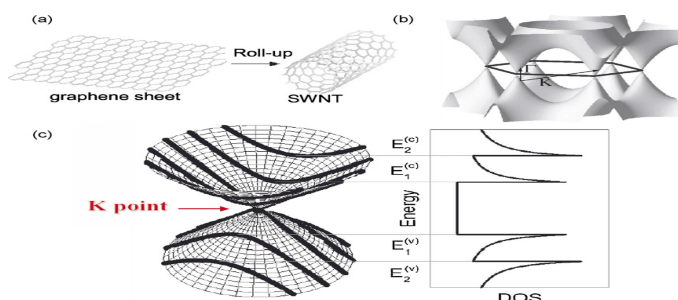


Fig. 1 Rolling of Graphene Sheet

The unique properties of the CNTs owing to the covalent sp^2 bonds in a honey comb arrangement (Tasis, 2006) and one dimensional structure with large length/diameter ratios renders them excellent candidates for many potential applications.

Nanotubes are only a few nanometers (billionths of a meter) in diameter. When made exclusively from carbon molecules, they are chemically inert, about 100 times stronger than steel, and offer a full range of electrical and thermal conductivity possibilities. Three different types of carbon nanotubes are there depending upon the number of walls. Those are: single walled (a), doubled walled (b) and multi-walled carbon nanotubes(c) as shown in Fig. 2.

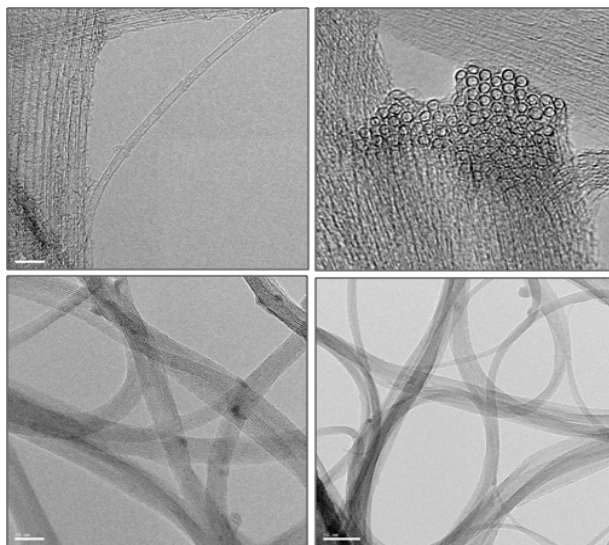


Fig. 2 (a) Single walled, (b) Doubled walled, (c) Multiwallcarbon nanotubes

There are different steps for drug delivery by carbon nanotubes.

(c) Functionalization of CNTs and Loading of Drug

As drug carriers, the solubility of CNTs in aqueous solvent is a prerequisite for gastrointestinal absorption, blood transportation, secretion, and biocompatibility and so on. Again, it is important that such dispersions of CNTs should be uniform and stable. In this context, the solubilization of pristine CNTs in aqueous solvents is one of the key obstacles in the way for them to be developed as practical drug carriers. Several methods are reported for dispersion of CNTs such as acidic and non acidic treatment, aerial oxidation etc.

The important step is the loading of drug that can be done by π - π interaction/non-covalent functionalization and covalent functionalization.

Many small, as well as large, polymeric anticancer agents can be adsorbed non-covalently onto the surface of pristine CNTs. Forces for such adsorption are the hydrophobic and π - π stacking (Fig.3) interactions between the chains of the adsorbed molecules and the surface of CNTs. Since many anticancer drugs are hydrophobic in nature or have hydrophobic moieties, the hydrophobic forces are the main driving forces for the loading of such drugs into or onto CNTs. The presence of charge on the surface of nanotube which was formed due to chemical treatment can enable the adsorption of the charged molecules through ionic interactions (Jia, 2007).

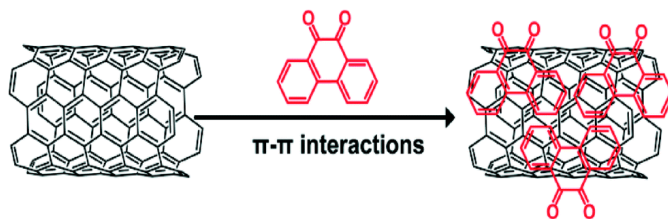


Fig. 3 Non-covalent functionalization

Covalent functionalization (Fig. 4) gives the more secure conjunction of functional molecules. CNTs can be oxidized, giving CNTs hydrophilic groups as OH, COOH, and so on. Strong acid solution treatment can create defects in the side walls of CNTs, and the carboxylic acid groups are generated at the defect point, predominantly on the open ends. The functional groups on the oxidized CNTs can further react with anticancer agent and other compounds (Prato, 2008).

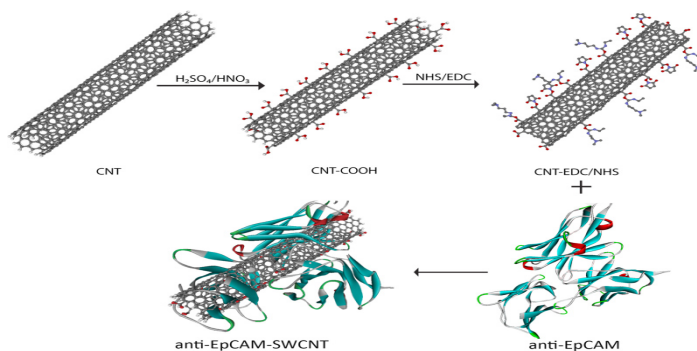


Fig. 4 Covalent functionalization

Steps in Drug Delivery and Anticancer Therapy

(a) Administration, Absorption, and Transportation

After loading of drug on CNTs, it must be absorbed from the administration site into the body. There are few ways for the administration of drugs, such as oral, vein injection, muscle injection, subcutaneous injection and local injection. Then absorbed CNTs must be transported from the administration sites to the affected, such as cancer focuses, infection focuses, ischemia focuses etc. For the excretion, CNTs must be transported from everywhere in the body to the excretion organs such as kidney, liver.

After administration, absorption is the first key step for drug carriers to complete their drug-delivering mission. Yukako studied the absorption of erythropoietin (EPO) loaded in CNTs from rat small intestine and they study the effect of fiber length(Ito, 2007). Erythropoietin-

loaded carbon nanotubes (CNTs) with surfactant as an absorption enhancer were prepared for the oral delivery of EPO using two types of CNTs, long and short fiber length CNTs. These results suggest that CNTs themselves are capable of being absorbed and that the short fiber length CNTs deliver more both EPO and absorption enhancer to the absorptive cells of the rat small intestine and the aggregation of CNTs is not the critical factor for the oral delivery of EPO. Another study showed that the physically shortened CNTs orally administered can be absorbed through the columnar cells of intestinal mucous membrane. When subcutaneously and abdominally administered, a part of CNTs exist persistently in the local tissues while some of them may be absorbed through lymphatic canal. If anticancer drugs are loaded into CNTs, they will be delivered into lymph system, where the drugs will be released to kill metastatic cancer cells. Ji et al successfully delivered gemcitabine to lymph nodes with high efficiency by using lymphatic targeted drug delivery system based on magnetic MWCNTs under the magnetic field guidance (Ji, 2010). When administered through veins, CNTs can directly get into blood circulation and distribute in many internal organs, such as liver, spleen, heart and kidney.

(b) Distribution

Distribution indicates the sites or places the absorbed CNTs can arrive and exist there, which are of great importance in clinical pharmacology and toxicology of CNTs as drug carriers. It was shown that Polyethylene glycolylation (PEG) is believed to be one of the most important strategies to prolong the circulation time of CNTs in blood (Schipper, 2008).

The experiment was carried out to investigate *in vivo* and *in vivo* bio distributions, as well as tumor targeting ability of SWCNTs having diameter, 1 - 5 nm and length, approximately 100-300 nm noncovalently functionalized with phospholipids(PL)-PEG in mice using positron emission tomography and Raman spectroscopy, respectively. It was interesting to note that the PEG chain lengths determine the bio distribution and circulation of CNTs. PEG-5400-modified SWCNTs have a circulation time (2 h) much longer than that of PEG-2000-modified counterpart (0.5 h),

(c) Metabolism and Excretion

Another important step is the metabolism and excretion. The non-biodegradability in the body and non-eliminability from the body interrogate on the possibility of their successful use in clinical practice, which has been always concerned about. Functionalized SWCNTs seem to be metabolizable in animal body. For example, SWCNTs with carboxylated surfaces have demonstrated their unique ability to undergo 90-day degradation in a phagolysosomal stimulant, resulting in shortening of length and accumulation of ultrafine solid carbonaceous debris. Unmodified,

SWCNTs exhibit no degradation under similar conditions. The observed metabolism phenomenon may be accredited to the unique chemistry of acid carboxylation, which, in addition to introducing the reactive, -COOH groups on CNT surfaces, also induces a collateral damage to the tubular grapheme backbone in the form of neighboring active sites that provide points of attack for further oxidative degradation (Kolosnjaj, 2010). Some experiments showed that CNTs persisted inside cells for up to 5 months after administration. Short (< 300 nm) and well-dispersed SWCNTs effectively managed to escape the RES and finally were excreted through the kidneys and bile ducts. A very recent investigation reveals that the biodegradation of SWCNTs can be catalyzed by hypochlorite and reactive radical intermediates of the human neutrophil enzyme myeloperoxidase in neutrophils. The biodegradation of CNTs is the important step for it as a drug carrier.

Carbon Nanotubes and Drugs

Most of the anticancer agents are small molecules and can be loaded into or onto CNTs by physical adsorption through π - π stacking interactions between pseudo aromatic double bonds of the graphene sheet and the drug molecules, and covalent immobilization of the interest drug molecules onto the reactive functional groups present on the sidewalls of CNTs. The examples of small molecules which can be loaded in or on CNTs are cis-platin (Tripisciano, 2009), doxorubicin (Ali,2008), many antioxidants(Lucente, 2009) etc. CNTs not only can deliver drugs of small molecules but also can deliver proteins (Weng, 2009). Similarly the application of CNTs as gene carriers in gene delivery has been considered quite promising. Gene therapy (El, (2004)involves not only the gene-based treatment for cancers but also that for the infectious diseases by introducing genetic materials. It is generally believed that the tumor formation is the results of the gene alterations and gene therapy aims to correct them.

Drug Delivery: in Vivo Studies

As drug carriers, they will be finally used in living animals and human. Although the results of the in vitro experiments have provided a lot of useful information about the application of CNTs as drug carriers, only the *in vivo* experiments can give corroboration for the usefulness of CNTs in practical gene delivery for cancer therapies. There different target for drug delivery.

Drug delivery targeted to lymphatic system: Many cancers metastasize through lymphatic canal. The drug delivery systems targeted to the lymphatic system can block the metastasis of cancers effectively.

Drug delivery targeted to tumor: To deliver anticancer drugs into cancer focus is the prerequisite for the drugs to develop their effects.

Drug delivery targeted to central nervous system: To deliver drugs to central nervous system is still a serious challenge in anticancer drug delivery system for the treatment of the tumors in the central nervous system because of the blood-brain barrier.

Conclusions

The treatment efficacy of CNTs based drug delivery vehicles could be further improved by optimization of the surface chemistry and size of nanotubes as well as the positioning of drug molecules for desired pharmacokinetics. Targeting ligands on nanotubes for tumor targeted drug delivery is also expected to further enhance treatment efficacy. Again for successful practical use of CNTs as drug carriers, mechanisms for their pharmacological and toxicological effects should be clear. The weighing of the advantage and disadvantage in the treatment of a special disease is also very important because CNT-based drug delivery system also has its indication and contraindication just like any other drugs. Important achievements have been achieved on the application of CNTs as drug carriers for the treatment of cancers. Some key obstacles in the way to practical use have been overcome. Although there is still a long way to go for the practical use, it may be predicted that, on one day in the future, CNTs will become an important class of drug carriers for treatment of cancer. This is an extremely promising application of nano-technology in the field of medical science.

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