A Review on Carbon Nanotubes as Novel Drug Carriers in Cancer Therapy

Dhyey M. Rajani, Frank Crasta, and Vijaya Kumar N. Kottur

Abstract Cancer causes one of the pre-eminent health problems all over the world currently. Chemotherapy is used as a conventional treatment, which uses one or more anti-cancer drugs as part of a standardized procedure. The idea of selective treatment to cure cancer is established by carbon nanotube (CNT). In this review paper, the advances in the application of carbon nanotubes as target carriers and drug delivery system for cancer therapies have been studied. CNTs due to their physicochemical and selective targeting abilities and shape act as drug delivery systems. Internal drug loading encompasses decoration utilizes capillarity, encapsulating anti-cancer drugs like Cisplatin. The external loading takes place by linkers. The biocompatible drug targeting mechanisms like active and passive lead to targeted delivery. Hence, eliminating any damage to healthy tissues resulting in negligible side effects. The functionalization of CNTs being crucial in penetrating and increasing hydrophilicity entails non-covalent and covalent methods. This also helps them to penetrate through immunity barrier and ensure a targeted release.

Keywords Carbon nanotubes (CNTs) · Chemotherapy · Drug delivery systems · Cisplatin · Biocompatible

1 Introduction

Cancer is an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases metastasize (spread) leading to blood coagulation and decreasing immunal resistance of human body, leading to rapid mutations in cell behaviour and

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DNA sequences. When the cancer cells coagulate and create a gobbet, they comprise to form a tumour. A tumour is cancerous when it seeds and starts developing in vicinal tissues. The tumour cells can disperse away and start coagulating the blood and lymphatic vessels. Cells may become cancerous due to the existence of tumour microenvironments (TMEs) leading to accumulation of defects, or mutations, in their DNA. Tumour micro-environments (TME) present a unique challenge in tumour therapy due to their complex structures and multiple components, which serve as the basis for tumour development. The complex region of TME consists of immune cells, collagen (amino acids bounded in triple helix) type structures encapsulated within the fibrous tissue structures and twisted (tortuous) blood vessels or lymphatic vessels, in which the traditional therapy is left useless [1]. In cases employing nanomaterials (here CNT), TME plays a pivotal role in synchronizing the nanochemical distribution of the medicaments. Therefore for the interaction of nanochemotherapeutics with the affected cells in tumour milieu, it is essential that nanochemotherapeutics are gathered in the tumour through the vascular connections. Subsequently, this interaction with target cells should be advanced by specific extravasation from tumour vascular chains.

Certain transmutable genetic defects like BRCA1 and BRCA2 mutations can increase the risk of cancer. BRCA1 and 2 produce suppressor proteins, when either of these genes is mutated, such that its protein synthesis does not function correctly, DNA damage may not be repaired. Therefore, cells tend to develop new genetic alterations that can lead to cancer. Most of the time, cells are able to detect and repair DNA damage [2]. If a cell is severely damaged and cannot repair itself, it usually undergoes so-called programmed cell death or apoptosis [3].

In recent few years have seen astounding discoveries in cancer drug research and development leading to more of a therapeutic and clinical approach, but there has been a lack in the drug delivery and targeted supply of these drugs to the accurate centres of malignancy, i.e. the epicentres of mutations, without affecting the healthy adjacent tissues [4]. The inadequacies in the ability to administer therapeutic agents with high selectivity and minimum side effects largely account for the discrepancies. Many numbers of tests have been performed for strategic and selective drug loading and delivery, for example, liposome-induced encapsulation [5]. Systemic toxicity may develop at the same time due to the lack of selectivity of the drugs for cancer tissues and cells, which often leads to the failure of chemotherapies [6, 4]. Hence, considerable efforts are being directed to such a drug delivery system that selectively targets the cancerous tissue with minimal damage to adjoining tissue [7]. The development of advanced drug delivery system does not only involve biomarking of neoplastic regions but also has targeted and extremely selective supply and release system to the neoplastic regions hence rendering them enervated, also rendering the free-floating micro-focuses ineffective. The requirements for new drug delivery systems have led to a marked increase in pharmacological effects and considerable weakening of toxicological effects of the neoplastic cells [8].

In CNTs, the penetration and direct release of the payload are substantial. CNTs have an added advantage of tubular shape, which can be capped at the two ends for

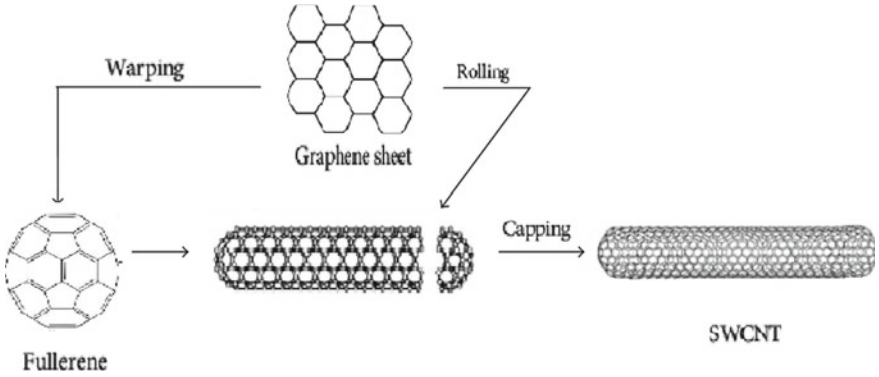

Fig. 1 Capped structure of SWCNT

drug holding, which can serve as an effective way to transcend the cellular restrictions and enter directly into the infected cytoplasmic cavity, allowing the drug to be jettisoned [9, 10]. Basic construction of CNT involves rolling of graphene sheet into single-walled carbon nanotube (SWCNT) or nesting of a number of single-walled nanotubes to form a multi-walled carbon nanotube (MWCNT). The secondary process of warping Graphene sheet into Fullerenes and then capping the nanotube to ultimately form an encapsulating carbon nanotube is as shown in Fig. 1.

2 Importance of CNT in Drug Delivery

CNTs are allotropic conformation of carbon. The nanostructure is of cylindrical nature. The structure of CNTs can be seen as cylindrical rolling up of nanothin graphene sheets consisting of sp^2 hybridized carbon atoms bonded to each other by covalent bonds [11]. There are two types of CNT, namely single-walled carbon nanotube (SWCNT) and multi-walled carbon nanotube (MWCNT). MWCNT consists of a more tubular and dense roll-up of graphene layers, i.e. more number of graphene layers roll up with an annular space of 0.34 nm in average [12]. In recent years, a wide range of different nanoscale therapeutic drug delivery mechanisms and loading systems have been evaluated, wherein, single-walled carbon nanotubes (SWCNTs) have attracted considerable interest, as they offer potential advantages of more stringent and target-oriented drug delivery system than other nanoparticle systems. SWCNTs have been loaded with antibody elements and low molecular weight targeting compounds, for nanotube integration into cells. Their advantages include their ability to carry a high cargo loading, intrinsic stability and structural elasticity, which can increase circulation time and hence the bioavailability of the drug molecules. An added advantage is, SWCNTs have been shown to enter mammalian cells and due to their reliable properties as of needle-shaped penetration mechanism [10]. SWCNT-based materials have already been found as potential delivery vehicles

for intracellular movement of immunity establishment nucleic acids and potential candidates for further functionalization and hence leading to a stealthy penetration and biocompatibility [9].

3 Drug Loading

Carbon nanotubes are end-capped by many nanomechanical processes the facilitate encapsulation of therapeutic drugs. This inclusion takes place either during or after synthesis of formatted nanotubes. The most important of the two methods is the post-synthesis method which is marked by a remarkably 70–100% yield, also including different criteria of sensitivity, melting point, etc. [13]. Now the post-synthesis involves melting of end caps to load the drug particles, and the loading is carried out by decoration. Decoration is establishing the bonding between the nanotube's wall with functional groups, and here, the only problem faced is that the carbon atoms in a chain being extremely inert do not allow any kind of bond formation [14]. Also, another drawback is being the small diameter of CNT for capillarity action, for filling CNT. In order to overcome this oxidation of carbon takes place in order to obtain desired efficacy of bonding, this bonding can be done inside or outside the nanotube wall [15]. The capillarity action can be changed by altering surface tension of the solution. Due to the tubular structure, capillarity is possible depending upon factors like the tube diameter and surface tension of the nanomaterial. The chemicals used if they have higher surface tension, it can be reduced by forming a suitable composite with the carbon nanotube which under the influence of other chemicals can be reduced to pristine chemicals without changing the wall properties [15, 16]. After filling the CNTs, the ends can be capped again by passing high electric currents to CNTs as a result encapsulating the drug for uninterrupted delivery [16].

4 Attachment of Drugs (External)

The external attachment of drugs takes place by attaching the drug molecules by amide or disulphide bonds. These attachments serve the function of covalent bonds between the drug and the wall of nanotube, known as linker. The nanotubes injected either subcutaneously or intravenously are administered to follow different routes to the effective site of relevance by means of blood circulation or lymphatic circulation [17]. The folic acid content when increases beyond a certain limit the cancer cells is active in folic acid content. This folic acid affinity can be used in nanotubes to guide them to the cancerous cells, once the sulphide links come into this cancerous environment there is a decrease in reduction potential leading to the release of the drug to the pre-planned region. This marks the importance of linkers [18].

5 Drug Targeting

The traditional cancer treatments involve plenty of after-effects; this is due to the toxic effects of anti-cancer drugs on vicinal healthy cells. In order to avoid this, biocompatible therapeutic drugs along with efficient targeting of nanotubes are pertinent [19]. The ability of CNTs to target the tumour-affected area establishes them as carriers to deliver therapeutic medicament. There are two major types of targeting involved, namely passive and active targeting.

1. Passive targeting: this is mainly dependent on nanoparticle sizing and their proliferation. A tumour cell, when it grows and spreads, requires oxygen and proteins, and for this, it links to a number of blood vessels, by angiogenesis [19]. Drugs that are being delivered intravenously distribute evenly throughout the body. Now, the cancer cells due to their irregulated particle screening have a high intake of a particular type of particles. This tumour cells act as parasites on the blood supply for their nourishment, this property can be exploited and nanotubes can be used as foreign particles in the blood stream to get deposited into tumour cells; this is due to the abnormal lymphatic drainage and positioning of tumour cells [20–22]. All of these factors lead to abnormal molecular and fluid transport dynamics. This mechanism is known as "Enhanced Permeability and Retention (EPR) effect" in solid tumours. The EPR effect is usually employed to describe nanoparticle and liposome delivery to cancer tissue. One of many examples is the work regarding thermal ablation with gold nanoparticles.
2. Active targeting: another path selective process of drug target delivery is active targeting, involving the assimilation of ligands and immune globulins (antigens). These are target-oriented molecules with coordination complexes with proteins. This incorporation of ligands is extremely peculiar and discrete to the types of cells throughout the body. These ligands completely react with target sites, being electron donors, hence safeguard nanotubes from enzyme influence and desolation. The coordination ligands increase the uptake selectivity of nanotubes to which they are bounded. Efficient approaches in identifying the cancer cell receptor are also considered like the "in vivo phage screening" which involves F3 galactosidase to have a strong binding ability with nucleolin [23, 24], which is a major nucleolar protein found on tumour cell surfaces. This mechanism also involves a drawback, i.e. ligands may lead nanotubes to become marginally toxic because of non-specific binding, and also the positive charged ligand particles may decrease drug delivery and reduces the efficiency once inside of cells [25, 26]. Active targeting is pertinent in overcoming multi-drug aversion in tumour cells [27].

6 Functionalization of CNTs

Carbon nanotubes when in the pristine state are highly hydrophobic in nature, i.e. they are highly non-polar and the atoms making the molecule do not establish a static electric field with respect to each other. This is where functionalization is used. The functionalization of nanotubes is defined as a process to enhance the surface characteristics hence making them biocompatible. The meaning establishes that the functionalization of carbon nanotubes involves the linking of organic or inorganic functional groups to their respective tubular structure [26]. Through the functionalization of carbon nanotubes, it is possible to regulate the physicochemical functions, reduce cytotoxicity, gives an opportunity to append molecules of drugs or proteins for delivery system build-up [27]. Majorly, the different methods of functionalization of CNTs include:

1. Non-covalent Functionalization: non-covalent bonding is a better method used in functionalization. This method enhances the biocompatibility along with validity in biological functions. This can be carried out by the creation of molecular dispersed liquid colloidal type structures with amphiphilic molecules studded and dispersed uniformly according to the topological distribution on the walls of CNTs. Another efficient method is piling up of pyrene molecules on the surface area of the CNT as a result establishing π–π bonds with CNT surface. This type of non-covalent π–π attachments preserves the sanctity of aromatic base structure and hence the electronic characteristics. Due to weak π–π bonding, this method is not suitable for the target release of drugs [28].
2. Covalent Functionalization: the attachment of biocompatible functional groups to the surface is a more stringent target delivery method, wherein a stronger arena is needed [29]. CNT functionalization process involves oxidation of the walls of CNT using concentrated acids of sulphuric acid (H_2SO_4) or nitric acid (HNO_3). The solution is then heated and agitated by means of soniferous methods of sound agitation. This process results in side wall of CNT forming covalent bonding with carboxylic acid, which makes CNT water soluble, as shown in Fig. 2. The carboxylic group is having a high negative charge, which leads to an increased amount of hydrophilicity. [29, 30]. The CNT can also be coated with polyethylene glycol as a part of maintaining bio-metastability [31]. This

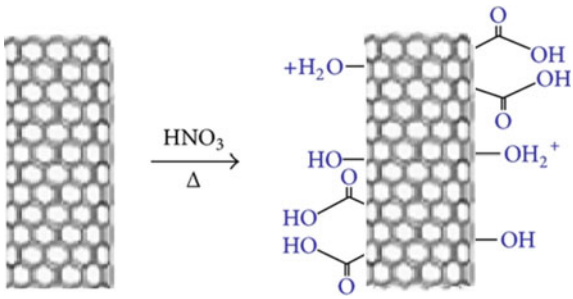

Fig. 2 Covalent functionalization (oxidation) reaction

covalent functionalization leads to a stronger bond formation between the drug and CNT. The only drawback is being the wear out of walls of CNT resulting in transmuting certain features of CNTs [28].

7 Conclusion

This paper reviews a major application of carbon nanotubes (CNTs) as novel drug carriers and selective anticancer treatment vehicles which can be used for drug targeting and delivery. The paper also explains about the prime method of loading and encapsulating the drug within the carbon nanotube (CNT). An effective and substantial substitution of chemotherapy, which is the most traditional and one-handed way to deal and treat the cancer-causing elements, is nanotechnology. Since nanoparticles (nanotubes, in this case) are highly efficient carriers in high pH levels and highly selective in targeting the tumour micro-environment (TME), which goes unabated in case of direct chemotherapy. Before CNTs are loaded with drugs, they need to undergo in vivo and in vitro clinical testing and preliminary checking for their toxicity to healthy tissues. Also, the hydrophobic nature needs to be overcome in order to enhance biocompatibility while penetrating inside the cell and overcoming the immunity barriers, by functionalization and manipulation of surface chemistry using either covalent or non-covalent functionalization. The drug targeting plays a major role in this technology to undergo selective analysis and positioning on nanocarrier to the target cells. There are two types of targeting, namely passive and active, such that passive involves the concept of ERP and active circumscribing around the mechanism of targeting by ligands. The drawbacks which need involved are regarding the toxicology effect of the CNTs without any attenuation in pharmacological efficacies, lack of reliable attachments of drugs externally and risk of releasing the drug before the target site.

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