Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Issue 4, 2013

Review Article

CARBON NANOTUBES: IT'S ROLE IN MODERN HEALTH CARE

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Received: 26 May 2013, Revised and Accepted: 12 Aug 2013

ABSTRACT

Due to rapid evolution of complicated disease in our modern world, the existing methods of diagnosis, drug delivery and treatment are becoming less effective. Therefore, modern health care requires more sophisticated and effective carriers for the same. This review article provides information regarding Carbon Nanotubes (CNTs), its application in the diagnosis and effective treatment of several complicated diseases such as cancer. Currently available drug carriers including polymer based devices, liposomes, emulsions, microparticles, nanoparticles though effective, but posses certain limitations which could be overcome by the utilization of CNTs. The carriers also have impediments like incapability to penetrate cell membrane and to enter cytoplasm. Use of CNTs can easily overcome these limitations. This suggests the success of CNTs as effective tool in modern health care. The authors attempt to incorporate the findings from literature related with the applications of CNTs in relevant modern health care service and also discuss the hurdles of CNT dispersion with appropriate remedies under the purview of this review article.

Keywords: Carbon nano tube, Single walled carbon nanotubes, Multi walled carbon nanotubes, Drug delivery, Health care service.

INTRODUCTION

Noteworthy contributions of formulation scientists, pharmacy professionals and biomedical engineers have given new hopes in combating complicated diseases. Currently, polymer based carriers, liposomes, emulsions and microparticles all imparting substantial service in modern health care and are very popular in place. However, the delivery devices in many instances are associated with certain drawbacks such as readily activation by pH changes in surrounding environment; by means of rapidly oscillating magnetic field or by local application of heat. These carriers also have limitations like capacity to penetrate cell membrane, to enter cytoplasm, and to transport molecules of interest to the near vicinity of nucleus [1]. Rapid evolution of complicated diseases demands more sophisticated treatment strategies where the existing delivery devices fall short to cure effectively or to prevent the disease. However, literature enumerates many examples where 'nanotechnology' has established itself as competent technology to deal with such diseases. Carbon nanotubes has established a separate domain in the realm of nano-carriers and offer easy diagnosis or detection of diseases such as breast cancer, leukemia etc. Gradually the concept of nanotechnology and its materialization has flourished to a greater extent. Nanotechnology is the engineering of functional systems at molecular scale. This review article makes an attempt to discuss carbon nanotubes in detail including its relevant applications in biomedical field of interest. The article also incorporates the hurdles of CNTs dispersion in certain medium which in turn affect the therapeutic potency of the nano carrier.

CARBON NANOTUBES (CNTs)

Carbon nanotubes are seamless tubes of graphite sheets with nanosized diameter and includes, Single walled carbon nanotubes (SWNTs) and Multi walled carbon nanotubes (MWNTs). The terminal parts of some nanotubes are open; the others are closed with full fullerene caps. Carbon nanotubes are also named as 'King of Nanomaterials'. Depending on sheet direction and diameters, it may be either metallic or semi-conducting in nature. Carbon nanotubes have highest theoretical strength when compared with all kinds of natural materials. It is 100 times stronger than steel, although their specific gravity are only one sixth that of the latter. Carbon nanotubes enjoy special advantage in the field of absorbing electro-magnetic radiation, field emission, thermal conducting, hydrogen storing, adsorbing and catalyzing. Based on number of layer of graphite sheets, carbon nanotubes can be classified as SWNTs, Double Walled Carbon Nanotube (DWNTs) and MWNTs.

Characterization of SWNTs may be based on - Purity : >90%; Content: >60%; Diameter: <2nm; Length: 20 μM; amorphous carbon: 5%; ash (catalyst residue): <3%; Special surface area: >450m^2/g and thermal conductivity: ~4000W/m.K.

DWNTs may be characterized as- Purity : >50~80%; Diameter: <5nm; Length: 5-15 μM; amorphous carbon: <5%; ash: <2%; special surface area: 450-600 m^2/g and thermal conductivity: 3235 -4000 W/m.K.

Characterization of MWNTs may be based on - Purity: >95%; Diameter: 10-30 nm; Length: 5-15 μM; amorphous carbon: <3%; ash: <0.2%; special surface area: 40-300 m^2/g and thermal conductivity: ~2000Wm.K.

Carbon nanotube is a member of fullerene structural family having cylindrical configuration. It also includes buckyballs which are spherical and cylindrical in shape. The nanotube is cylindrical with at least one end typically capped with a hemispherical configuration. The name nanotube is derived from their size, since the diameter of the tube is in the order of few nanometers (approximately about 50,000 times smaller than the width of human hair) while they may have a length of several millimeters.

Manufacture of nanotube is dependant on applied quantum chemistry, specifically, orbital hybridization. Nanotubes are composed of entirely Sp^2 bonds, similar to those of graphite. This bond is stronger than Sp^3 bonds found in diamond and provides the molecules with their unique strength. Nanotubes naturally aligned themselves into 'ropes' held together by Vander Waal`s forces. Under high pressure, nanotubes can merge together, trading some Sp^2 bonds for Sp^3 bonds, giving great possibility for producing strong, unlimited length wires through high pressure nanotubes.

Carbon nanotubes are also described as large molecules of carbon atoms. The atoms are arranged in hexagons and look alike 'chicken wires' and the similar arrangement are also found in graphite. Conceptually, SWNTs may be formed by the rolling of single graphite layer (also called graphene layer) into a seamless cylinder. MWNTs formation may be attributed to the coaxial assembly of SWNTs cylinders and the separation between tubes are equal and similar to that exists between the layers of natural graphite.

Carbon nanotube was discovered in the year 1991 by Sumio Iijima and resembles rolled graphite. A graphene sheet can be rolled more than one way, producing different types of carbon nanotubes. Carbon nanotubes are molecular tubes of graphite carbon with outstanding properties. They are among the stiffest and strongest fibers known and have remarkable electronic properties and other unique characteristics. Hence the carbon nanotubes has gained considerable attention and studied for different applications.

Synthesis of Carbon nanotubes

There are four different methods for the synthesis of carbon nanotubes

1) Arc discharge (Arc evaporation)

2) Laser ablation

3) High pressure carbon monoxide (HiPCO)

4) Chemical vapor deposition (CVD)

Properties of Carbon nanotubes

There are four different physical properties associated with carbon nano tubes. Unique properties of CNTs are attributed to these properties. The section below attempts to discuss these properties reasonably.

1) Strength of nanotubes

Carbon nanotubes are one of the strongest materials (in terms of tensile strength and elastic modulus) known to man. This strength results from the covalent Sp^2 bonds formed between the individual carbon atoms. In the year 2000, MWNTs was studied to determine the tensile strength in comparison to high-carbon steel. Tensile strength value for MWNT was found to be 63 GPa which is significantly higher than steel of 1.2 GPa. Carbon nanotubes also have very high elastic modulus of 1TPa (Tera Pascal). Under the applied strain, tubes undergo plastic deformation and at a point of maximum strain, tubes undergo fracture by releasing energy.

2) Kinetic property

MWNTs, multiple concentric nanotubes precisely nested within one another, exhibit a striking telescoping property whereby an inner nanotube core may slide, almost without friction, within its outer nanotube shell thus creating an automatically perfect linear or rational bearing. This property has already been utilized to create the world's smallest motor and a nanorheostat.

3) Electrical property

Because of symmetry and unique electronic structure of graphene, the structure of nanotube strongly affects its electrical properties. Theoretically metallic nanotubes can have an electrical current density 1,000 times greater than metals like silver and copper.

4) Thermal property

Nanotubes are expected to behave as good thermal conductors along the tube axis, a property known as 'ballistic conducting', but at the same time a good insulator, lateral to the tube axis.

Applications of carbon nanotubes in modern health care

1) CNTs in the delivery of drugs

Nanotubes posses the unique feature of being able to enter the living cell without causing its death or without inflicting other damage. Apparently they behave like miniature needles and pass through the cell membrane through a spontaneous and still unclear mechanism. According to computer simulation, first the functionalized-CNTs are absorbed and accommodated onto the membrane surface with axis parallel to the plane of the membrane. Functionalized CNTs enter various cell lines like human promyelocytic leukemia cells (HL-60) and human T-cells. This is the fact why the CNTs may be used to deliver small organic drugs molecules and various peptides, proteins and nucleic acids into cells. Therapeutic and diagnostic agents can be encapsulated, covalently attached or absorbed on the surface of CNTs. The use of CNTs in drug delivery requires the attachment of different functional groups onto the external surface of nanotubes. Such modified CNTs are used for the delivery of antibiotics to different types of cells by selective transport through the membrane. For example, CNTs were employed in the administration of Amphotericin-B, a very powerful antibiotic, most effective in the treatment of chronic fungal infections. The incorporation of Amphotericin-B on CNTs could also allow reduction in the administered dose of the drug [2]. It was also observed that antibiotic potency increases resulting into high anti-fungal activity, when conjugated with CNTs.

2. Vaccine delivery via CNTs

Peptide functionalized CNTs are capable of penetrating mammalian cell membrane and translocating to the nucleus. The basic concept for vaccine delivery by CNTs is to link an antigen to CNTs while retaining its conformation and inducing an antibody response with right specificity. CNTs can also bind to enzyme-linked immunosorbent assay plates, overcoming potential problems that may be encountered with the direct coating of peptide onto a solid support [3, 4].

3) CNTs as protein carriers

CNTs can transport various types of proteins into the cells. The proteins must have a molecular weight less than 80 KDa, and may be covalently or non-covalently bound to nanotube sidewalls. Proteins bound to SWNTs transported inside the cell by endocytosis. Streptavidin, Fibrinogen, Protein-A, Bovine Serum Albumin, Erythroprotien and Apolipoprotien transported inside the cell by CNTs following the said mechanism [5, 6].

4) CNTs as vectors in gene delivery

CNTs have considerably been used as a vector in gene delivery. A nanotube for its small size, cells don't recognize them as harmful intruders. The most common gene therapy today involves modified viruses as the vector for gene delivery. The virus vector is associated with limitations like immune response which however not the case with CNTs [7].

5) Nanoscale transport offers controlled drug delivery

CNTs have been tried to deliver anti-cancer drugs to human cancer cells. Anticancer molecule like methotrexate was studied where a fluorescent probe was attached to MWNTs. The fluorescent probe allowed the monitoring of nanotubes uptake in human cancer cells *in-vitro*. It was found that fluorescent signal from the cells was proportional to the nanotube dose [8].

6) Binding and condensation of plasmid DNA into functionalized CNTs

Functionalized-CNTs are being extensively explored in advanced biotechnological applications ranging from molecular biosensors to cellular growth substrates. According to one recent report, the capability of ammonium- functionalized SWNTs to penetrate human and murine cells has facilitated the delivery of plasmid DNA leading to the expression of marker genes. Nanotube-DNA complexes were analyzed by scanning electron microscopy, surface plasmon resonance, Pico-Green dye exclusion and agarose gel shift assay. The interactions of three types of functionalized CNTs namely, ammonium-functionalized single-walled and multiwall carbon nanotubes (SWNT-NH_3^+; MWNT-NH_3^+) and lysine functionalized single-walled carbon nanotubes (SWNT-Lys-NH_3^+), with plasmid DNA were studied and the results indicate that all three types of cationic carbon nanotubes are able to condense DNA to varying degrees, indicating that both nanotubes surface area and charge density are critical parameters that determine the interaction and electrostatic complex formation between functionalized CNTs with DNA [9].

7) Carbon nanotubes in the treatment of broken bones

The success of bone grafting depends on the ability of the scaffold which assists the natural healing process. The scaffolds are made from a wide variety of materials, such as polymers or peptide fibers which however, associated with few drawbacks like low strength and many times may experience body rejection. Bone tissue is a natural composite of collagen fibers and hydroxyapatite crystals. Study unveils that the nanotubes can mimic the role of collagen as the scaffold formation material for growth of hydroxyapatite into bone [10].

8) Blood compatible heparin-CNTs biomaterials as artificial kidney

Heparin composites or coatings on CNTs and/or membranes having nano-sized pores are shown to demonstrate high compatibility with blood. Heparin is a common therapeutic used to prevent clotting and maintain blood flow. The results demonstrate that the heparin composite membrane with nano-pores, could work efficiently as an artificial kidney or dialyzer, by filtering the blood and maintaining its flow. The presence of this blood compatible heparin-CNTs dialyzer thus potentially eliminates the need of systemic administration of heparin during dialysis [11].

9) DNA-wrapped nanotubes as biosensors

Researchers have wrapped SWNTs with double stranded DNA in a way reminiscent of wrapping a pencil with electric wire. This novel bio-nanostructure acts as biosensor and allows the intracellular detection of contaminants [12].

10) CNTs in osteoporosis

Currently, most of the bone building drugs are either not well absorbed or toxic. CNTs might offer a non-toxic molecular ship to deliver the drugs safely to fragile bones [10].

11) CNTs based blood test in early breast cancer detection

Detection of breast cancer at an early stage is going to be a reality very soon. Research is on the way to develop a new blood test that would be capable of detecting the said cancer. The test could be particularly beneficial for the younger women whose current mammography scans are less effective. Currently the diagnosis relies on three tests namely breast examination, mammography and biopsy. Accurate blood testing using CNTs could reduce the need for open biopsy [13].

12) Carbon nanotubes in laser mediated killing of cancer cells

Scientists are working to develop nanotechnology based laser treatment strategies that could destroy cancer cells without damaging healthy tissues. Scientists placed the solution of CNTs, synthetic rods that are only half the width of DNA molecules, under infrared laser beam. The beam was capable of heating CNT solution above 158^0 F within 2 minutes. When the nanotubes placed inside the cells and radiated by laser beam, the cells were quickly destroyed by the heat. However, cells without nanotubes were not affected by the laser beam. This behavior of CNTs is attributed to the fact that they absorb near infrared which are slightly longer waves than the visible rays of light and pass harmlessly through the cells [14].

13) Carbon nanotube x-ray for *in-vivo* imaging

CNT-based field emission x-ray source has been experimented. It has come out with the potentiality to overcome the limitations like effectiveness which is associated with currently used x-ray technology. This technology may open a new horizon in imaging modalities *in-vivo* [15].

14) Electrochemical antitumor drug sensitivity test for leukemia K562 cells at a CNT- modified electrode

The change in electrochemical behaviour of tumor cells induced by antitumor drugs was detected by MWNTs- modified glass carbon electrode (GCE). Based on the changes observed, a simple *in-vitro* electrochemical antitumor drug sensitivity test was developed. MWNTs promoted electron transfer between electroactive centers of cells and the electrode. Leukemia K562 cells exhibited a well defined anodic peak of guanine at +0.823V at 50mVs-1. HPLC assay with ultra-violet detection was used to elucidate the reactant responsible for the electrochemical response of the tumor cells. The method proposed could be developed as convenient means to study the sensitivity of tumor cells to antitumor drugs [16].

15) Nanotubes in tumor therapy

CNTs have a role in targeting drugs to tumor cells. One of the longstanding problems in medicine is how to cure cancer without harming normal body tissue. Functionalized nanotubes with folate moiety acts on cancer cells utilizing folate receptor present on their surface. Normal cells remain unaffected by this therapy and a suitable alternative in tumor treatment.

Unlike other molecules that are used to encapsulate drugs, fullerene resist breakdown by the body. The structural robustness is especially important for holding compounds that are prone to cause harm if released in healthy cells, e.g. radioactive metal ions. Literature holds hope that the nanotubes would be one useful basis in cancer treatment, gene therapies and in vaccines delivery [17, 18].

16) Tissue distribution and clearance of intravenously administered CNT radiotracers

SWNTs had been functionalized with chelating molecule diethylentriaminepentaacetic and labeled by indium (111In) for imaging purposes. Intravenous administration of this f-SWNT followed by radioactivity tracing using gamma scintigraphy indicated that f-SWNT are not retained in any of the reticuloendothelial organs (liver or spleen) and are rapidly cleared from systemic blood circulation through the renal excretion route. The observed rapid blood clearance and half life (3hrs) of f-SWNT has major implications for all potential clinical uses of CNT and reveal that it excreted as intact nanotubes. This work signifies the pharmacokinetic parameters after IV administration of f-CNT relevant to many therapeutic and diagnostic applications [19].

HURDLES OF CARBON NANOTUBES DISPERSION

Working with carbon nano tubes researchers often experienced notable hurdles in the dispersion of CNTs. The following section takes into account these hurdles along with appropriate remedies.

Dispersion: a common hurdle

One of the major and recurring hurdles encountered by researchers during the investigation of CNTs, toxicity and biocompatibility is its tendency to aggregate in large bundles and ropes. This may be attributed to their high molecular weights and strong intertubular forces (both Vander Waals and electrostatic) [20]. This is especially true when the CNTs are studied in presence of saline media or serum commonly used in toxicology. Aggregating nature of CNTs in different media results into discrepant data's of toxicity and biocompatibility. The dispersion media is very significant as it ultimately dictates the introduction of CNTs inside the cell. CNTs are applied in biomedical or other relevant field and should be dispersible in variety of solvents. Though successful dispersion remains a big question; however not without any appreciable remedy like: sonication, stabilization with the help of surfactant and covalent functionalization.

Sonication is a common physical method used for homogeneous dispersion of CNTs aggregates in solution. There are two main methods of sonication, the ultrasonic bath and the ultrasonic probe, both of which utilize a bubble nucleation and collapse mechanism. The frequency of ultrasound determines the maximum bubble size. With the increase in frequency bubble size reduces [21]. Ultrasonic baths typically have higher operating frequencies (40-50 kHz) and no defined cavitations zone, while ultrasonic probes operate at frequencies around 25 kHz with a conical bubble nucleation zone extending from the probe tip. Highly polar organic solvent such as N, N-dimethylformamide, when used in conjunction with ultrasonic baths or probes, have been shown to produce stable dispersions of individual pristine CNT [22-24]. Sonication being the most common method of dispersion used today, many toxicological findings still consists CNT aggregates [25-26].

Incorporation of surfactants to improve CNT solubility in aqueous solutions is another widely used alternative. It is of low cost, commercially available and relatively simple experimental procedures can be adopted. Sodium dodecyl sulfate and Triton ™ X-100 are two of most popular surfactants [27], though the application of Pluronic ™ surfactant is also very common [28]. Biomolecules such as DNA [29, 30], carbohydrates [31-32] and peptides [33] are also commonly studied as surfactants to solubilize CNT in aqueous solution. Wide variety of synthetic and biological surfactants remains as an attractive alternative for tailoring solubility profile of CNTs towards particular application. Utilization of surfactants though well executed the dispersion and stabilization of CNTs; few reports of surfactant dissociation from CNT surface are also available, which may lead to poor dispersion and stability of the formulation [34].

Chemical functionalization of CNT is another commonly employed technique for improving solubility [16]. Typically, this involves covalently attaching appropriate molecules such as peptides [35-

37], acids, amines, polymers [38, 39] and poly-L-lysine [32] to the side-walls of CNT. This is most commonly achieved either by amidation or esterification of the -COOH groups present after CNT purification [37, 38] or by 1, 3-dipolar cyclo-addition [41, 35, 36]. By their reactive nature, many of these methods are associated with uneven surface coverage, or inter CNT coupling. In the context of biomedical applications, chemical functionalization of CNT or adsorption of biomolecules, unveiled its suitability as most promising dispersion technique. In this technique no CNT specific cytotoxicity was observed during the delivery of drugs or vaccine [42, 43]. Unfortunate enough that till date, no long term stability reports are available upon the application of chemically functionalized CNT.

CONCLUSION

Carbon nanotubes are one of the strongest materials known to man. They are about 100 times stronger than steel in terms of tensile strength and elastic modulus. They have the diameter range 2 nm to 50 nm which is about 10,000 to 50,000 times smaller than the diameter of human hair. Hollow core of CNT are able to draw the interest of chemist because it permits encapsulation of molecules. Because of the above properties, carbon nanotubes are named as 'King of nanomaterials'. Available drug carriers including liposomes, polymers, niosomes, microparticles and nanoparticles none of them are without limitations. On the contrary, CNTs are experimented in wide capacities to evaluate its different instrumental uses in modern health care. CNTs with its extraordinary properties have the ability to overcome many limitations and can be used as an effective drug carrier also. They can easily penetrate living cell without causing death or inflicting other damage. Carbon nanotubes can also be used in the diagnosis and treatment of complicated diseases like cancer in a better way. Hence, conclusion may be made that carbon nanotubes holds hope for better diagnosis and treatment of various diseases, thus serving modern health care in a better way.

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