CARBON NANOTUBES – A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT
Carbon nanotubes (CNTs) up to now are the most researched materials of the 21st century with an international intention of growing industrial quantities due to their superior properties for use in many applications either in medical or other potential applications. These compounds have become increasingly popular in various fields simply because of their small size and amazing optical, electric and magnetic properties when used alone or with additions of metals. These are often described as a graphene sheet rolled up into the shape of a cylinder. To be precise, they are graphene cylinders about 12 nm in diameter and capped with end-containing pentagonal rings. Carbon nanotubes have potential therapeutic applications in the field of drug delivery, diagnostics, and biosensing. Functionalised carbon nanotubes can also act as vaccine delivery systems. The basic concept is to link the antigen to carbon nanotubes while retaining its conformation, thereby, inducing antibody response with the right specificity. With the increasing interest shown by the nanotechnology research community in this field, it is expected that plenty of applications of CNTs will be explored in future.

INTRODUCTION
Since their discovery in 1991 by Sumio Iijima, carbon nanotubes have generated huge activity in most areas of science and engineering due to their remarkable physical and chemical properties. No previous materials have displayed the combination of superlative mechanical, thermal and electronic properties attributed to them. These properties make nanotubes ideal, not only for a wide range of applications but as a test bed for fundamental science. Researchers have envisaged taking advantage of their conductivity and high aspect ratio to produce conductive plastics with exceedingly low percolation thresholds. Carbon nanotubes tend to have impressive mechanical properties with Young’s modulus in the range 100-1000 GPa and strengths between 2.5 and 3.5 GPa. Nanotubes have diameter ranging from 1 to 100nm and lengths of up to millimeters. Their densities can be as low as ~1.3 g/cm3 and their Young’s moduli are superior to all carbon fibres with valves greater than 1 TPa. The highest measured strength for a carbon nanotube was 63 GPa and even the weakest of type of CNT has strength of several GPa.

CNTs have received much attention from scientific communities up to this date mainly because of their superior properties such as having a wide band gap, high melting point, high tensile strength and high thermal conductivity.
Its (CNTs) attractiveness comes from its unique physical, chemical, mechanical and thermal properties originating from the small size, cylindrical structure, and high aspect ratio of length to diameter. A single-walled carbon nanotube (SWCNT) consists of a single graphene sheet wrapped around to form a cylinder. A multi-walled carbon nanotube (MWCNT) is concentrically nested cylinders of graphene sheets. CNTs have extremely high tensile strength (~150 GPa, more than 100 times that of the stainless steel), high modulus (~1 TPa), large aspect ratio, low density (1100–1300 kg/m3, one-sixth of that of stainless steel), good chemical and environmental stability, high thermal conductivity (3000 W/m/K, comparable to diamond) and high electrical conductivity (comparable to copper). Carbon nanotubes have different potential applications, like electrodes for electrochemical double layer capacitors, field emitters, nano-electronic devices, and hydrogen storage, as functional polymers, etc. Researchers have also reported making of conductive, electromagnetic and microwave absorbing and high-strength composites, fibers, sensors, inks, energy storage and energy conversion devices, radiation sources and nanometer-sized semiconductor devices, probes, and interconnect using carbon nanotubes. Recently, strong and stretchable CNT fibers were spun from 0.65-mm-long CNT forests, which have the strength and Young’s modulus of 1.91 GPa and 330 GPa, respectively. SWCNT/PVA composite fibers are tougher than any natural or synthetic organic fiber described so far. Obviously the bulk production of carbon nanotubes in an economic way is the route for feasibility of these applications. CNTs are generally synthesized by electric arc discharge method, laser ablation method, catalytic chemical vapour deposition (CVD), flame synthesis, solar energy route, etc. The common feature of arc discharge and laser ablation methods is the need for high amount of energy, which is supplied by means of an arc discharge or laser to induce the reorganization of carbon atoms into CNTs. The temperature used is even higher than 3000 °C, which is beneficial for good crystallization of the CNTs, thus, the products are always produced with good graphite alignment. However, the basic requirements of these systems, including vacuum conditions and continuous graphite target replacement, pose difficulties to the large-scale production of CNTs. In contrast chemical vapour deposition (CVD) has been proven to be a preferred route for large-scale production of carbon nanotubes. Here the carbon is deposited from a hydrocarbon (or other carbon bearing source) in the presence of a catalyst at temperatures lower than 1200 °C. The CNT structure, such as its wall number, diameter, length, and alignment, can be well controlled during the CVD process. Thus, the CVD method has the advantages of mild operation, low cost, and controllable process, and is the most promising method for the mass production of CNTs. Various scalable processes have been reported with CVD methods, including “Carbon Multiwall Nanotubes” of Hyperion Company, “CoMoCATTM Process at SWCNT” of the University of Oklahoma, “HiPCO Process” of Rice university and “Nano Agglomerate Fluidized Bed” process of Tsinghua University. Though the fluidized bed technique is the most promising route for the mass production of carbon nanotubes, fluidization of nano-sized particles is itself a challenge. The published literature contains four good reviews on the present subject matter.

Carbon nanotubes have the potential to carry drugs in the organism as they are hollow and much smaller than the blood cells. The methods were developed for attaching DNA and protein molecules to the inside and outside of the nanotubes. This gives one the ability to target and destroy individual cells that may be cancerous or infected by a virus. Nanotubes with attached enzymes might, in the long term, be used as enzymatic biosensors that could simultaneously detect and measure a variety of biological molecules.
TYPES OF CNTs
There are two types of Carbon nanotubes: Single walled carbon nanotubes (SWCNTs) and Multiwalled carbon nanotubes (MWCNTs).

<table>
<thead>
<tr>
<th>Differences between SWNT and MWNT</th>
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<tbody>
<tr>
<td>SWNT</td>
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<tr>
<td>Single layer graphene</td>
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<tr>
<td>Catalyst is required for synthesis</td>
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<tr>
<td>Bulk synthesis is difficult as it requires proper control over growth and atmospheric conditions.</td>
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<tr>
<td>Purity is poor</td>
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<tr>
<td>A chance of defect is more during functionalization</td>
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<tr>
<td>Less accumulation in body</td>
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<tr>
<td>Characterization and evaluation is easy</td>
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<td>It can be easily twisted &amp; are more liable</td>
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Method of preparation
There are three types of methods generally used:
- ARC Discharge method
- Laser Ablation method & CVD (chemical vapour deposition)

ARC Discharge method
This method is for preparations of large amounts. This method is used for producing C60 fullerence, it is the most common and the easiest way to produce carbon nanotubes. This technique produces a mixture of components and requires separating nanotubes from the soot and the catalytic metals present in the crude product. This is about ARC-vaporization of two carbon rods placed end to end, separated by approximately 1mm, in an enclosure filled with inert gas (helium or argon) at low pressures i.e. between 50 to 700 mbar. A direct current of 50 to 100A driven by approximately 20V creates a high temperature discharge between two electrodes. The discharge vaporizes one of the carbon rods and forms a small shaped deposit on the other rod. Depending on the exact technique it is possible to selectively grow SWCNTs or MWCNTs and the typical yield is up to 30 to 90%.

Laser Ablation method
This synthesis was first reported in 1995, by Smalley’s group at Rice University. A pulsed or continuous laser is used to vaporize a graphite target in an oven at 1200°C. The main difference between continuous and pulsed laser is that the pulsed laser demands a much higher light intensity (100KW/cm² compared with 12KW/cm²). The oven is filled with helium or argon gas in order to keep the pressure at 500 Tor. A very hot vapour plume forms then expands and cools rapidly. As the vaporized species cool, small carbon molecules and atoms quickly condense to form larger clusters, possibly including fullerences. The catalysts also begin to condense and attach to carbon clusters and prevent their closing into cage structure. (Catalysts may even open cage structures when they attach to them) and the typical yield is upto 70%.

The SWCNTs formed in this case are bundled together by Van der walls forces.

Chemical vapour deposition (CVD)
It is achieved by putting a carbon source (methane, carbon monoxide and acetylene) in the gas phase and using an energy source, such as plasma or a resistively heated coil, to transfer energy to a gaseous carbon molecule. The energy source is used to crack the molecule into reactive atomic carbon. Then, the carbon diffuses towards the substrate, which is heated and coated with a catalyst (Ni, Fe & CO) where it will bind.

CVD synthesis is a two step process consisting of a catalyst preparation followed by the actual synthesis of CNT. The catalyst is generally prepared by sputtering a transition metal onto a substrate and then using either chemical etching or thermal annealing to induce catalyst particle nucleation. Thermal annealing results in cluster formation on the substrate, from which the nanotube will grow. Ammonia maybe used as the etchant. The temperature ranges maintained are 650 to 900°C and the typical yield is 20 to 100%.

Properties of carbon nanotubes
- Carbon nanotubes are cylindrical tubes of nanoscopic dimensions. There are two types of nanotubes: CNT-SW (single-walled nanotubes) and CNT-MW (multi-walled nanotubes).
- Typical diameters range from a few nanometers (approx. 5 - 30nm, and even...
shown that 70 percent of glucose is significantly prevalent in the body cells and organs.

The substructure of carbon nanotubes (“armchair”, “zigzag”) is derived from the type of process used during synthesis, and affects features such as the existence of semiconductor properties. The electric and thermal properties of the raw materials are greatly superior to those of conventional materials. In particular, correct insertion of the carbon nanotubes into a material matrix will cause a significant shift of the percolation curve towards reduced material concentrations. These promising properties are based on the emergence of a network that takes advantage of the high aspect ratio between the length and the diameter. The formation of networks also supports the improvement of mechanical properties within the matrices, particularly as the basic material has a tensile strength (11 - 63GPa) 20 times that of steel.

Another interesting property of carbon nanotubes is that their electrical resistance changes significantly when other molecules attach themselves to the carbon atoms.

Another property of nanotubes is that they can easily penetrate membranes such as cell walls. In fact, nanotubes long, narrow shape make them look like miniature needles, so it makes sense that they can function like a needle at the cellular level. Medical researchers are using this property by attaching molecules that are attracted to cancer cells to nanotubes to deliver drugs directly to diseased cells.

Filling up of nanotube
The Nanotube obtained in processes closes on both the ends. The ends can be opened by suitable chemistry. One of the methods used is acid treatment which oxidizes the ends and leaves behind the oxide containing functionalities. The common functional groups are –COOH and –OH.

Drug delivery
In general drug delivery system is designed to improve the physiological and therapeutic profile of a drug molecule. The large inner volume of CNTs allows encapsulation of both low as well as high molecules of drugs. It also permits encapsulation of both hydrophilic and lipophilic drugs. More than one drug can also be loaded in CNTs in the case of multi-drug therapy. Ligands and diagnostic materials can also be conjugated to surface of CNTs by fictionalization to target the drugs to specific sites.

The purpose of using nanotubes in the human body
Carbon nanotubes are very prevalent in today’s world of medical research and are being highly researched in the fields of efficient drug delivery and biosensing methods for disease treatment and health monitoring. CNT technology has shown to have the potential to alter drug delivery and biosensing methods for the better, and thus carbon nanotubes have recently garnered interest in the field of medicine.

The use of CNT’s in drug delivery and biosensing technology has the potential to revolutionize medicine. Fictionalization of SWNT’s has proven to enhance solubility and allow for efficient tumor targeting/drug delivery. It prevents SWNT’s from being cytotoxic and altering the function of immune cells.

Cancer, a group of diseases in which cells grow and divide abnormally, is one of the primary diseases being looked at with regards to how it responds to CNT drug delivery. Current cancer therapy primarily involves surgery, radiation therapy, and chemotherapy. These methods of treatment are usually painful and kill normal cells in addition to producing adverse side effects. CNTs as drug delivery vehicles have shown potential in targeting specific cancer cells with a dosage lower than conventional drugs used that is just as effective in killing the cells, however does nto harm healthy cells and significantly reduces side effect. Current blood glucose monitoring methods by patients suffering from diabetics are normally invasive and often painful. For example, one method involves a continuous glucose sensor integrated into small needle which must be inserted under the skin to monitor glucose levels every few days. Another method involves glucose monitoring strips to which blood must be applied. These methods are not only invasive but they can also yield inaccurate results. It was shown that 70 percent of glucose readings obtained by continuous glucose sensors differed by 10 percent more and 7 percent differed by over 50 percent. The high electrochemically accessible surface area, high electrical conductivity and useful structural properties have demonstrated the potential use of single-walled nanotubes and multi-walled nanotubes in highly sensitive noninvasive glucose detectors.
CNTs in Drug Delivery and Cancer Therapy

Drug delivery is a rapidly growing area that is now taking advantage of nanotube technology. Systems being used currently for drug delivery include dendrimers, polymers, and liposomes, but carbon nanotubes present the opportunity to work with effective structures that have high drug loading capacities and good cell penetration qualities. These nanotubes function with a larger inner volume to be used as the drug container, large aspect ratios for numerous functionalization attachments, and the ability to be readily taken up by the cell. Because of their tube structure, carbon nanotubes can be made with or without end caps, meaning that without end caps the inside where the drug is held would be more accessible. Right now with carbon nanotube drug delivery systems, problems arise like the lack of solubility, clumping occurrences, and half-life. However, these are all issues that are currently being addressed and altered for further advancements in the field of Carbon nanotubes. The advantages of carbon nanotubes as nanovectors for drug delivery remain where cell uptake of these structures was demonstrated efficiently where the effects were prominent, showing the particular nanotubes can be less harmful as nanovehicles for drugs. Also, drug encapsulation has been shown to enhance water dispersibility, better bioavailability, and reduced toxicity. Encapsulation of molecules also provides a material storage application as well as protection and controlled release of loaded molecules. All of these result in a good drug delivery basis where further research and understanding could improve upon numerous other advancements, like increased water solubility, decreased toxicity, sustained half-life, increased cell penetration and uptake.

Selective cancer cell destruction

Carbon nanotubes can be used as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction. Biological systems are known to be highly transparent to 700-1,100-nm near-infrared (NIR) light. Researchers showed that the strong optical absorbance of single-walled carbon nanotubes (SWNTs) in this special spectral window, an intrinsic property of SWNTs, can be used for optical stimulation of nanotubes inside living cells to afford multifunctional nanotube biological transporters. They used oligonucleotides transported inside living Hela cells by nanotubes. The oligonucleotides translocated into the cell nucleus upon endosomal rupture triggered by NIR laser pulses. Continuous NIR radiation caused cell death because of excessive local heating of SWNT in vitro. Selective cancer cell destruction was achieved by functionalization of SWNT with a folate moiety, selective internalization of SWNTs inside cells labeled with folate receptor tumor markers, and NIR-triggered cell death, without harming receptor-free normal cells. Thus, the transporting capabilities of carbon nanotubes combined with suitable functionalization chemistry and their intrinsic optical properties can lead to new classes of novel nanomaterials for drug delivery and cancer therapy.

Mode of break down of CNTs in the body.

Carbon nanotubes were once considered biopersistent in that they did not break down in body tissue or in nature. In recent years, research has shown that laboratory animals exposed to carbon nanotubes via inhalation or through injection into the abdominal cavity develop severe inflammation. This and the tissue changes (fibrosis) that exposure causes lead to impaired lung function and perhaps even to cancer. For example, a year or two ago, alarming reports by other scientists suggested that carbon nanotubes are very similar to asbestos fibres, which are themselves biopersistent and which can cause lung cancer (mesothelioma) in humans a considerable time after exposure. A team of Swedish and American scientists has shown for the first time that carbon nanotubes can be broken down by an enzyme - Myeloperoxidase (MPO) -- found in white blood cells. Their discoveries are presented in Nature Nanotechnology and contradict what was previously believed, that carbon nanotubes are not broken down in the body or in nature. The scientists hope that this new understanding of how MPO converts carbon nanotubes into water and carbon dioxide can be of significance to medicine.
Medical applications

- Nanotubes bound to an antibody that is produced by chickens have been shown to be useful in lab tests to destroy breast cancer tumors. The antibody carrying nanotubes are attracted to proteins produced by a one type of breast cancer cell. Then the nanotubes absorb light from an infrared laser, incinerating the nanotube and the tumor they are attached to.32

- Using nanotubes as a cellular scale needle to deliver quantum dots and proteins into cancer cells. Improve the healing process for broken bones by providing a carbon nanotube scaffold for new bone material to grow on.32

- Combining carbon nanotubes with biological systems can significantly improve medical science — especially diagnostics and disease treatment. Nothing has been fully developed and finalized yet, but we see progress every day.

As an example, we’ll take anti-cancer treatment. When a patient goes through regular chemotherapy, he loses hair and has some other side effects for one reason — because chemotherapy doesn’t destroy “bad” cells only. Along with those tumor cells, it destroys healthy cells too. That’s why scientists are working so hard to avoid that. And carbon nanotubes could make that possible. Scientists from Stanford University have discovered that nanotubes, when exposed to infrared light, tend to heat up to 160°F (70°C) in just 120 seconds. If they are placed inside the cancer cells, they simply destroy them. Testings also showed that infrared has no effects on cell where no nanotubes are placed. This could lead to development of a cancer-killer. Gene therapy could also be improved by using carbon nanotubes. Let’s say that a damaged or missing gene could be replaced with another one from outside. But that’s complicated — because DNA can’t pass through the cell membrane. What is needed is a transporter, and modified carbon nanotubes play their role here.32

- Another application of carbon nanotubes in medicine is for sensing the molecules or species. Many studies on the electrochemical reactivity of carbon nanotubes showed that carbon nanotubes can enhance the biomolecules and promote the electron transfer in proteins. It has been found that carbon nanotubes promote electron transfer in heme containing proteins. In heme containing proteins carbon nanotubes are able to access the heme centre of biomolecules that is generally not sensed by the glass electrodes.

- Carbon nanotubes can also be used as blood vessels in order to deliver drugs to their target. When the drug delivery is done that way, the drug dosage can be lowered (and it’s cheaper for the pharmaceutical companies). There are two methods, both equally effective — a) the drug can be attached to the side or behind, b) or the drug can actually be placed inside the nanotube.43

- Synthetic muscles — due to their high contraration/extension ratio given an electric current CNTs are ideal for synthetic muscle.44

- Artificial muscles- CNTs have sufficient contractility to make them candidates to replace muscle tissue.45

- As the nanotubes function like a needle at the cellular level. This property is used in attaching molecules that are attracted to cancer cells to nanotubes to deliver drugs directly to diseased cells.

- The attachment of ethylene glycol molecules to nanoparticles of nanotubes stops WBCs from recognizing the nanoparticles as foreign materials, allowing them to circulate in the blood streams long enough to attach to cancer tumor therapy.

- Used to stimulate an immune response to fight respiratory viruses when inhaled.

- To promote blood cell maturation in bone marrow transplant recipients.

- Magnetic fields drive drug loaded nanoparticles to reduce blood vessel blockages in an animal study.

- Functionalized carbon nanotube as emerging nanovectors for the delivery of therapeutics.

- Carbon nanotubes as nanomedicines: from toxicology to pharmacology.

- Compressive mechanical properties of carbon nanotubes encapsulating helical copper nanowires.

- CNTs are being highly used in the fields of efficient drug delivery and biosensing methods for disease treatment and health monitoring.32

- Functionalization of SWCNTs enhances solubility and allow for efficient tumor targeting drug delivery. It prevents SWNTs
from being cytotoxic and altering the function of immune cells.

- CNTs functionalized with lipids are highly water soluble which would make their movement through the human body easier and would also reduce the risk of blockage of vital body organ pathways thus making them more attractive as drug delivery vehicles.\textsuperscript{32} CNTs as drug delivery vehicles have shown potential in targeting specific cancer cells with a dosage lower than conventional drugs used (does not harm healthy cells and significantly reduces side effects)\textsuperscript{32}

- CNTs can be used as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction.

- An aligned CNT with ultra sensitive biosensor for DNA detection was developed.\textsuperscript{32}

Non Medical Applications

Contents

1. Structural
2. Electromagnetic
3. Electroacoustic
4. Chemical
5. Mechanical

1. Structural
They are used for various purposes

- Textiles – with the help of CNT we can make waterproof and tear resistant fabrics

- Body armor – using CNT fibres MIT was able to stop bullets and monitor the condition of the wearer.\textsuperscript{37}

- Concrete – CNTs in concrete increase the tensile strength and stops the crack propagation.\textsuperscript{40}

- Sports equipment – Stronger and lighter tennis rackets, bicycle parts, golf balls, golf clubs and baseball bats can be made.

- Bridges – CNT may be able to replace steel in suspension.

- Fire protection – Thin layers of buckypaper can significantly improve fire resistance due to the efficient reflection of heat by the dense, compact layers of CNT or carbon fibers.\textsuperscript{49}

- Aircraft using carbon nanotubes to increase strength and flexibility in highly stressed components.\textsuperscript{32}

2. Electromagnetic

- Optical ignition – A layer of 29% iron enriched single-walled nanotubes (SWNT) is placed on top of a layer of explosive material such as PETN, and can be ignited with a regular camera flash.\textsuperscript{50}

- Superconductor – Nanotubes have been shown to be superconducting at low temperatures.\textsuperscript{51}

- Ultra capacitor - MIT is researching the use of nanotubes bound to the charge plates of capacitors in order to dramatically increases the surface area and energy storage ability.\textsuperscript{52}

- Electromagnetic antenna – CNTs can act as antennas for radios and other electromagnetic devices.\textsuperscript{53}

3. Electro acoustic

- Loudspeaker – In November 2008 Tsinghua-Foxconn Nanotechnology Research Centre in Beijing announced that it had created loudspeakers from sheets of parallel CNT, generating sound similar to how lightening produces thunder. Near term commercial uses include replacing piezoelectric speakers in greeting cards.\textsuperscript{54}

4. Chemical

- Desalination – water molecules can be separated from salt by forcing them through networks of carbon nanotubes, which require far lower pressures than conventional reverse osmosis methods.\textsuperscript{55}

- Air pollution filter – CNT membranes can filter carbon dioxide from power plant emissions.

- Hydrogen storage – CNTs have the potential to store between 4.2 and 65% hydrogen by weight. If they can be mass produced economically, 13.2 liters (2.9 imp gal; 3.5 US gal) of CNT could contain the same amount of energy as a 50 liters (11 imp gal; 13 US gal) gasoline tank.

5. Mechanical

- Oscillator- Oscillators based on CNT have achieved higher speeds than other technologies (> 50 GHz).

- Infrared detector – The reflectivity of the buckypaper produced with “super growth” chemical vapour deposition method is 0.03 or less, potentially enabling performance gains for pyroelectric infrared detector.\textsuperscript{56-57}

- Thermal radiation – For thermal emission in space such as space satellites.

CONCLUSION

As Carbon nanotubes work beyond our expectations and their simple mechanism with long lasting life makes it more reliable to use. Using it in cancer treatment can guarantee 85% of the cure which other treatments cannot afford and having 100% site target with its body friendly nature adds to its advantage. The versatile properties of CNTs have made them...
stand high in all fields, especially in medicine it has become a boon to mankind but the lack of technology for mass production and the costs of the production is what is holding them back. Until now the accumulation of Carbon nanotubes and its harmfulness has taken pave back.

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