Advances in Cancer Research & Therapy

www.advancejournals.org
Open Access Scientific Publisher

Review Article

CARBON NANOTUBES- THE HOLY GRAIL IN ANTICANCER THERAPY

Varsha Tripathi[1], Manoj Kumar Mishra[1], Pallavi Tiwari[1], Mayank Srivastava[1], Saurav Ghoshal [1]
[1]Shambhunath Institute of Pharmacy, Jhalwa, Allahabad (U.P.) India

Correspondence should be addressed to **Saurav Ghoshal**

Received September 07, 2015; Accepted September 13, 2015; Published September 22, 2015;

Cite This Article: Tripathi, V., Mishra, M., Tiwari, P., Srivastava, M., Ghoshal , S.(2015). Carbon nanotubes- the holy grail in anticancer therapy. Advances in Cancer Research & Therapy, 2(1)1-8.

ABSTRACT

Carbon nanotubes(CNT) are allotropes of carbon with cylindrical nanostructures. They can be visualized as a sheet of carbon atoms rolled up into a tube with a diameter of around tens of nanometers. They have electrical, optical, thermal, mechanical properties. There are two types of CNTs, single walled CNTs and multi walled CNTs. The multiwalled CNTs are formed by several concentric layers of rolled graphite. It has good adsorption properties which can detect some chemicals and biological agents. It is used to transport drug as well as proteins, DNA, RNA, into cells. The carbon network of shell is considered to be a result of the arrangement of carbon atoms in graphite sheets. Some properties of CNTs such as ease of cellular uptake, high drug loading, thermal ablation, among others, render them useful for cancer therapy. Cancer is one of the most challenging diseases of modern times because its therapy involves distinguishing normal healthy cells from affected cells. CNTs may prove to be the Holy Grail in cancer therapy because phenomena such as EPR, allow CNTs to distinguish normal cells from affected ones,. Considerable work has been done on CNTs as drug delivery systems over the last two decades. However, concerns over certain issues such as biocompatibility and toxicity have been raised and warrant extensive research in this field.

KEYWORDS: Carbon Nanotubes, Anticancer, SWCNT, MWCNT, Drug Delivery.

INTRODUCTION

The nanotubes contain one up to tens and hundreds of concentric shells of carbons with adjacent shells separated. The carbon network of the shells is considered closely related to the honeycomb arrangement of the carbon atoms in graphite sheets[1]. Carbon Nanotubes appear in many structures, differing in length, thickness, and in the type of helicity and number of layers[2]. Carbon nanotube which is made of carbon is a tube shaped material with nano-meter scale to measure diameter[3]. Carbon Nanotubes are emerging in today's scientific field due to their unique combination of stiffness, strength, and tenacity compared to other fiber materials which usually lack one or more of these properties and are also gaining importance as their thermal and electrical conductivity are very high, and comparable to other conductive materials, Depending on these structural variations carbon nano-tubes act either as metals or as semi-conductors. Carbon Nanotubes have diameters ranging from less than 1 nm up to 50 nm and lengths up to several microns[4-6].

HISTORY OF CNTS

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. For more than 6000 years carbon has been used for the reduction of metal oxides. Carbon in the form of graphite was discovered in 1779, and 10 years later

in the form of a diamond. It was then determined that both of these forms belong to a family of chemical elements. It was not until about 200 years later that the next advancements in carbon took place. In 1985, Kroto, Smalley, and Curl discovered fullerenes, recipients of 1996 Nobel Prize in Chemistry for the discovery of fullerenes. A few years later, CNT was discovered. The current huge interest in CNTs is a direct consequence of the synthesis of buckminsterfullerene C60, and other fullerenes, in 1985.[5]

The discovery that carbon could form stable, ordered structures other than graphite and diamond stimulated researchers worldwide to search for other new forms of carbon. The search was given new impetus when it was shown in 1990 that C60 could be produced in a simple arc evaporation apparatus readily available in all laboratories.

It was using such an evaporator that the Japanese scientist Sumio Iijima discovered fullerene-related CNTs in 1991 [6-7]The tubes contain at least two layers (multi-walled carbon nanotubes MWCNTs), often many more, and ranged in outer diameter from about 3 nm to 30 nm. They were invariably closed at both ends. A scanning of some MWCNT is shown in 1993; a new class of CNT was discovered, with just a single layer. These (single-walled carbon nanotubes SWCNTs) are generally narrower than the multi-walled tubes, with diameters typically in the range 1–2 nm, and tend to be curved rather than straight[8]

TYPES OF CNTS

The two main types of CNT are the single and multi-walled.

1. Single-walled

A single-walled carbon nanotubes (SWCNTs) can be considered to be formed by the rolling of a single layer of graphite (called a graphene layer) into a seamless cylinder (long wrapped graphene sheets). As stated before, CNTs generally have a length to diameter ratio of about 1000 and more so they can be considered as nearly one-dimensional structure. Most SWCNTs have a diameter of close to 1 nm. More detailed, a SWCNT consists of two separate regions with different physical and chemical properties. The first is the sidewall of the tube and the second is the end cap of the tube.[9-10]

2. Multi-walled

Multi-walled carbon nanotubes (MWCNTs) can be considered as a collection of concentric SWCNTs (consist of multiple layers of graphite rolled in on themselves to form a tube shape) with different diameters. The length and diameter of these structures differ a lot from those of SWCNTs and, of course, their properties are also very different. The interlayer distance in MWCNTs is close to the distance between graphene layers in graphite, approximately 3.3Å. The special case of MWCNTs (double-walled carbon nanotubes DWCNTs) must be emphasized here because they combine very similar morphology and properties as compared to SWCNT. DWCNT synthesis on the gram scale was first proposed in 2003 by the chemical vapour deposition (CVD) technique, from the selective reduction of oxides solid solutions in methane and hydrogen[11]

The Structural attributes of SWCNTs and MWCNTs are shown in Figure 1.

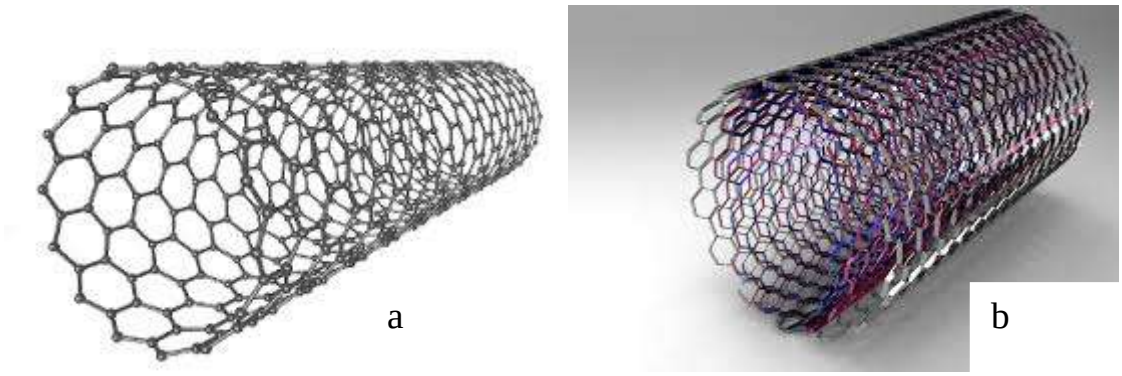

Figure 1:SWCNT (b) MWCNT

PROPERTIES OF CARBON NANOTUBES

A number of properties result from the regular formation of carbon atoms in graphene cylinders. Carbon nanotubes are a huge cylindrical large molecule consisting of a hexagonal arrangement of sp2 hybridized carbon atoms (C-C distance is about 1.4 Å). The wall of CNTs consists of single or multiple layers of graphene sheets, of which those formed by rolling up of single sheet are called single-walled carbon nanotubes (SWCNTs) and those formed by rolling up of more than one sheet are called multi-walled CNTs (MWCNTs). Both SWCNTs and MWCNTs are capped at both ends of the tubes in a hemispherical arrangement of carbon networks called fullerenes warped up by the graphene sheet. The interlayer separation of the graphene layers of MWCNTs measures approximately 0.34 nm on average, each forming an individual tube, with all the tubes having a larger outer diameter (2.5 to 100 nm) than SWCNTs (0.6 to 2.4 nm). SWCNTs have a better defined wall, whereas MWCNTs are more likely to have structural

defects, resulting in a less stable nanostructure. In the medical field, three main attributes of CNTs have been exploited:

Their small size.

Their high surface area to volume ratio.

Their ability to contain chemicals.

Carbon nanotubes can be produced small enough to pass through holes in tumours or to transport DNA 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.[12]

CNTS AS CARRIERS OF ANTICANCER MOLECULES

It is well known that cancer cells overexpress folic acid (FA) receptors, and several research groups have designed nanocarriers with engineered surfaces to which FA derivatives can be attached. Moreover, nonspherical nanocarriers (e.g., CNTs) have been reported to be retained in the lymph nodes for longer periods of time compared to spherical nanocarriers[13] (e.g., liposomes). Thus, CNTs might be used for targeting lymph node cancers as shown by various investigators.In these studies, magnetic nanoparticles containing the anticancer cisplatin were entrapped into folic-acid-functionalized MWNTs. An external magnet was employed to drag the nanotubes to the lymph nodes where the drug was shown to be released over several days and the tumor to be selectively inhibited. In a recent study[17] loaded the anticancer molecule gemcitabine into magnetic MWNTs and, using mice, they reported high activity against lymph node metastasis when the formulation was injected subcutaneously[17]In another study, the poorly water-soluble anticancer camptothecin has been loaded into polyvinyl alcohol-functionalized MWNTs and reported to be potentially effective in treatment of breast and skin cancers.[18]

FUNCTIONALISATION

Functionalisation helps in making CNTs more soluble than the impurities by attaching other groups to the tubes and this will make it easy to separate from insoluble impurities, such as metal, this is usually done using filtration. [19-20]Functionalisation technique also leaves the CNT structure intact and makes them soluble for chromatographic size separation. For recovery of the purified CNTs, the functional groups can be simply removed by thermal treatment, such as annealing[21]

METHODS FOR OPENING, FILLING AND CAPPING CARBON NANOTUBES

As mentioned previously, carbon nanotubes are end-capped and thus for drug loading there are essentially two approaches which include the filling of carbon nanotubes during synthesis or after synthesis. Adding the contents of the nanotubes *in-situ* tends to be a less efficient approach, producing a yield of around 10% whereas the post-synthesis process can be better controlled and yields of 50-100% are achievable.[22] The appropriate method depends on the material that is to be inserted into the CNT. The criteria include melting temperature, reactiveness, surface tension and sensitivity of the material.

Post-synthesis production of CNTs implies that the ends must be opened, This can be accomplished by passing electric currents through the CNT, through attacking the CNT with acid which corrodes the angled parts of the tube the most (i.e. the ends), or by oxidization using carbon dioxide.[23-24]There are two ways to include foreign particles in CNTs. One category is decoration, which is the process of bonding a functional group to CNTs[25]This is difficult as carbon is rather inert, so oxidization is used to produce a more reactive attachment surface. The functional group is either bonded to the inside or outside of the walls. The most common mechanism for filling CNTs is capillarity. The limiting factor in capillarity is the diameter of the CNT and the surface tension of the material (the threshold material surface tension is approximately 200mN/m). However, hydrophobic and Van der Waals forces also play a role in aqueous solutions. For chemicals with higher surface tensions it is possible to lower this tension by creating a suitable composite, which can be chemically reduced to the original substance once the CNT has been filled. The CNTs are washed using a solution which has been chosen to offer only limited solubility to the impregnating fluid and thus can dissolve only deposits left outside the CNT. After filling, the CNTs are capped by passing a current which fuses the ends closed. [26] The loading of CNTs remains an area requiring further research and more frequently mathematical methods are used rather than laboratory experiments due to the comparatively lower cost.[27]

PASSIVE AND ACTIVE TARGETING

Previous attempts at antibody-mediated drug delivery have been largely unsuccessful due to the loss of specificity of the antibodies on binding with drug molecules. It was found that using nanotubes to support antibodies did not change their properties and so did not inhibit their targeting abilities. Targeting methods such as active or passive targeting are a direct result of functionalisation. Passive targeting is a result of inertness and physical size of the macromolecule, “hiding” it from the immune system. CNTs must be nanosized to prevent cellular opsonisation (the susceptibility of the macromolecule to ingestion by phagocytes resulting in its destruction) by the innate immune system but also functionalised with molecules/polymer chains such as PEG which do not promote an adaptive immune response. The CNT must also be of sufficient size to utilise the EPR effects and so a trade-off is required. PEG is useful in determining the degree of optimal functionalisation as it is an easily controllable variable. This passive targeting can cause problems; microspheres can lead to chemoembolism-type problems in the lymphatic nodes. For such cases, functionalisation with nanomagnetic particles (e.g. iron oxide) and placing of a magnet at the desired location for extended periods of time allows for drug release over an extended period. Active targeting requires functionalisation with tumour-specific binding sites to selectively bind to tumour cells. Many cells of various cancers are known to overexpress certain receptors, such as brain tumours showing typically 100 k to 900 k LDL (low density

lipoprotein) receptors. Functionalising CNTs with LDL not only increases uptake dramatically in the cancer cells, but reduces uptake in other cells that have far fewer LDL receptors.

DRUG LOADING

The location of the drug to be delivered by the CNT can be internal or external. Internalisation or encapsulation relies on Van der Waals forces for insertion into the CNT and is best used for drugs that are sensitive to external environments and easily broken down. [28]

DRUG TRANSPORT AT THE BLOOD-BRAIN BARRIER

The physiological function of the BBB is to maintain brain homeostasis by selectively transporting nutrients and beneficial endogenous substances into the brain and excluding toxic metabolite or xenobiotics from the brain. The pivotal component of the BBB is a monolayer of brain capillary endothelial cells fused by tight junctions. Other components of the BBB including the astrocytic foot process, pericytes and perivascular macrophages within a basal lamina regulate and further strengthen the BBB.[29-30] In addition to tight junctions, the absence of fenestrations also contributes to the barrier property of brain endothelial cells. Furthermore, in contrast to vascular endothelial cells in other tissues, the low activity of pinocytosis and vesicular traffic further limits non-specific trans-endothelial transport with the exception of small lipid-soluble molecules[31]Transport mechanisms at the BBB can be divided into two categories: passive diffusion and endogenous carrier-mediated transport. Passive diffusion is a process whereby drugs or endogenous substances travel across the BBB dependent upon along a concentration gradient from blood to brain, and the physicochemical properties of the drug. Qualitatively, drugs that passively diffuse through the BBB are generally lipophilic, often related to the octanol/water partition coefficient, and have a molecular weight of less than 400-500 Da. Numerous quantitative relationships have been cast to correlate BBB penetration to lipophilicity and molecular weight as well as other chemical structural features.[31-32]

DRUG DELIVERY TARGETED TO LYMPHATIC SYSTEM

Many cancers metastasize through the lymphatic canal. Drug delivery systems targeted to the lymphatic system can block the metastasis of cancers effectively. Using radical polymerization, polyacrylic acid (PAA) can be appended onto CNTs, making them highly hydrophilic. Through coprecipitation, Fe3O4-based magnetic nanoparticles can be adsorbed on the PAA-CNT surface. Through the interaction with COOH groups of grafted PAA, the nanoparticles can be stabilized from clustering. By stirring the solution containing PAA-CNT, Fe3O4-based magnetic nanoparticles, and gemcitabine for 24 h, gemcitabine was loaded into the nanosystem with a loading efficiency of 62%. It was found that CNTs were seen only in the local lymphatic nodes and were absent in the major organs, such as liver, kidney, heart, spleen, and lungs, after 3 h of subcutaneous injection. Without the help of such nanostructures gemcitabine cannot preferentially distribute in the lymphatic system.[33]

NONCOVALENT DRUG ATTACHMENT TO CNTS

In addition to covalent attachment, anticancer drugs can also attach to the surface of the CNT by noncovalent bonding. This involves physical conjugation of the drug to CNT via π–π stacking, hydrophobic interaction, or electrostatic adsorption. Although covalent attachment is a very feasible procedure, it has been suggested that this may cause chemical changes in anticancer drugs, implying that their efficacy can potentially be altered[34]However, one of the disadvantages of noncovalent bonding is the lack of efficient attachment, potentially resulting in release of the drug before it reaches its site of action[35-36]An example of noncovalent attachment of an anticancer drug in this context is the attachment of doxorubicin to MWCNTs. In one experiment, MWCNTs were dispersed in 1% Pluronic® F127 solution until a final MWCNT concentration of 1 mg/mL was formed. The solution was then bath-sonicated for 30 minutes. Increasing concentrations of Pluronic-MWCNT (10, 20, and 40 μg/mL) were then reacted with doxorubicin 20 μg/mL. The interaction between the MWCNTs and doxorubicin was studied using luminescence spectrometry. The results showed that the fluorescence intensity of doxorubicin decreased with increasing concentrations of MWCNT. This suggests that as the concentration of the MWCNT increases, more platforms become available for noncovalent interaction of doxorubicin with the surface of the MWCNT.In another experiment, pegylated CNTs were reacted with doxorubicin, resulting in doxorubicin becoming loaded onto the PEG that was covering the surfaces of the CNTs. It was suggested that, due to the aromatic nature of doxorubicin, noncovalent binding of this molecule onto the surface of the CNT was most likely because of π–π stacking and hydrophobic interactions[37]

KINETICS OF CNTS

As drug carriers, the administration, absorption, and transportation of CNTs must be considered for obtaining the desired treatment effects. The studied routes of CNT administration include oral and injections such as subcutaneous injection, abdominal injection, and intravenous injection. There are different ways of absorption and transportation when CNTs are administered by different routes. The absorbed CNTs are transported from the administration sites to the effect-relevant sites by blood or lymphatic circulation. After administration, absorption is the first key step for drug carriers to complete their drug-delivering mission. Studies have suggested that CNTs themselves are capable of being absorbed. It has also been established that physically shortened CNTs that are orally administered can be absorbed through the columnar cells of intestinal mucous membrane, where this was confirmed by transmission electron microscopy[38]

Distribution indicates the sites or places the absorbed CNTs can arrive and exist, of great importance in clinical pharmacology and toxicology of CNTs as drug carriers. There have been experiments to investigate *in vivo* and *ex vivo* biodistributions, as well as tumor targeting ability of radiolabeled SWCNTs (diameter, approximately 1 to 5 nm;

length, approximately 100 to 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 biodistribution and circulation of CNTs.

The nonbiodegradability in the body and non-eliminability from the body raise questions on the possibility of their successful use in clinical practice, factors which have always been a concern. Functionalized SWCNTs seem to be metabolizable in the animal body. For example, SWCNTs with carboxylated surfaces have demonstrated their unique ability to undergo 90-day degradation in a phagolysosomal simulant, resulting in shortening of length and accumulation of ultrafine solid carbonaceous debris. Unmodified, ozonolyzed, aryl-sulfonated 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, modifiable COOH groups onto CNT surfaces, also induces collateral damage to the tubular graphenic backbone in the form of neighboring active sites that provide points of attack for further oxidative degradation[39]

BIOCOMPATIBILITY OF CNTS AND ITS ENHANCEMENT

An ideal non-covalent functionalisation coating should have the following properties[40]

- Coating should be nontoxic and biocompatible·
- Coating should be sufficiently stable to resist de-tachment from nanotube surface under biological conditions
- Amphiphilic coating molecules should have a low critical micelle concentration so CNT is stable once removed from solution
- Coating should have functional groups which are available for bioconjugation with antibodies or other molecules to create various CNT conjugates for various applications.

Producing biocompatible CNT requires low levels of toxicity and to ease-of-processing by the body. Addition of polyethylene glycol (PEG) by attachment via phospholipids allows for this, as both constituents are easily removed from the body over time. The toxicity is greatly reduced by functionalisation[41]

APPLICATION

The tiny structures find their way in different applications that touch nearly every field of technology, including aerospace, electronics, medicine, defense, automotive, energy, construction, and even fashion. Indeed, NASA is developing materials using these carbon nanotubes for space applications, by taking advantage of their tremendous stiffness and strength[42]

- It can be used to sniff bombs, search for toxins in the air and water and can be used to test whether someone has skin cancer by checking for a chemical called dimethyl-sulfone.
- They are strong, elastic, and possess amazing electrical properties due to which researchers created a carbon nanotube aerogel that expands and contracts as it converts electricity into chemical energy.
- Carbon nanotubes are suitable as artificial muscles since they retain their shape after being compressed thousands of times, in similar way as that of soft tissue.[43]
- Geckos climb up smooth surfaces with the help of tiny hairs on their feet exploiting the electrostatic force between themselves and the wall. Carbon nanotubes used in agecko-inspired tape sticks to dry smooth surfaces when pressed against them which make climbing up of smooth surfaces easier.
- Carbon nanotubes application can increase viewing pleasure and portability of flat screens, LEDs, flexible displays as these use tiny pipes of carbon which make excellent field emitters or conductive surfaces[44]
- Studies proved that carbon nanotubes are perfect for allowing damaged bone to restructure itself as they are strong, lightweight, and can be modified for compatibility with any part of the body.
- Carbon nanotubes may also help to reduce inflammation in broken bone.
- In medicine, modified carbon nanotubes find their use as they can enter cells to deliver drugs or knock out unwanted genes.
- Use of carbon nanotubes as electrodes in capacitors provides more current and better electrical and mechanical stability when compared to other leading materials.[45]
- Storage of solar energy in molecules that change state in response to light could be entirely transformed by carbon nanotubes.
- Medical researchers are demonstrating carbon nanotubes as potential needles for injecting drugs or genes into sick cells. Nanotube probes may be used to test for certain substances and test certain processes beyond cell membranes[46]

Some of the recent works in which nanotubes have been successfully used as drug carriers are summarized in table1

Table 1: Summary of past work done on CNTs as drug carriers for anticancer molecules

S. No.	Drug	Functionalization	SWCNT/ MWCNT	Advanatge	Reference
1	Doxorubicin	PEG conjugation	SWCNT	Reduced toxicity	47,48
2	Mitoxantrone	PEG conjugation	SWCNT	Increased circulation period	47
3	Paclitaxel	PEG conjugation	SWCNT	Increased circulation period	49
4	Cisplatin	Non functionalised	SWCNT	Decreased toxicity	50
5	Carboplatin		SWCNT		51
6	Doxorubicin	Conjugated with folate	MWCNT	Active Targetting	52
7	6 Mercaptopurine	Carboxy Functionalized	MWCNT	Increased Absorption	53, 54
8	Paclitaxel	Conjugated with folate	MWCNT	Increased circulation period	49
9	Methotrexate	PEGlyated	MWCNT	Increased circulation period	55
10	Quercitin	PEGlyated	SWCNT	Controlled toxicity	56
11	Folic Acid	-	MWCNT	Active targeting, longer circulation period	57

CONCLUSION

The small dimensions, strength and the remarkable physical properties of carbon nano tubes make them a very unique material. The rapid research development and industrial application has made it necessary to summarize the current status about these carbon nano tube structures. In this review article, we have made efforts to emphasize on the structural characterization, preparation, purification, optical characteristics, mechanical aspects, thermal properties and electrochemical properties as these tiny structures find their way in different applications that touch nearly every field of technology, including aerospace, electronics, medicine, defense, automotive, energy, construction, and even fashion. We have also discussed the use of these tube structures in pharmaceutical and medical fields as drug delivery equipments because of their site targeting capacity and as biosensors in glucose level and DNA hybridization determination due to their electric resistance property. The ability of these tiny particles to effectively target the cancer cells may revolutionize our approaches in treating this dreaded disease and bring us near the Holy Grail.

REFERENCES

[1] Bethune CH, Kiang MS. Cobalt-Catalysed Growth Of Carbon Nanotubes With Single-Atomic-Layerwalls. *Nature* 1993;363: 605-607.

[2] Iijima S, Ichihashi T. Single-Shell Carbon Nanotubes of 1-nm Diameter. *Nature* 1993; 363: 603-605.

[3] Ebbesen TW, Ajayan PM. Large-scale synthesis of carbon nanotubes. *Nature* 1992;358: 220–222.

[4] Tans MH. Individual single-wall carbon nanotubes as quantum wires. *Nature* 1997;386: 474-477.

[5] Bockrath DH, Cobden PL. Single-electron transport in ropes of carbon nanotubes. *Science* 2001;275: 1997-2008.

[6] Grimes CA, Dickey EC, Mungle C. Effect of purification of the electrical conductivity and complex permittivity of multiwall carbon nanotubes. *J. Appl. Phys* 2001;90: 4134–4137.

[7] .Kroto HW, Heath JR, O'Brien SC, Curl RF, Smalley RE. *Nature* 1985; 318: 162.

[8] Iijima S. *Nature (London)* 1991; 354: 56.

[9] Iijima S, Ichihashi T. *Nature (London)* 1991; 363: 603-634.

[10] Iijima S, Ichihashi T. *Nature (London)* 1993; 363: 609-619.

[11] Flahaut E, Bacsa R, Peigney A, Laurent C. *Chem Commun* 1985; 12: 1442-1468.

[12] Muguruma, Hitoshi M, Yasunori, Shibayama. Carbon Nanotube Plasma Polymer-Based Amperometric Biosensors: Enzyme-Friendly Platform for Ultrasensitive Glucose Detection. *Japanese Journal of Applied Physics* 2007;46(9A): 6078–6082.

[13] Liu Z, Chen K, Davis C. Drug delivery with carbon nanotubes for in vivo cancer treatment. *Cancer Research* 2008; 68(16): 6652–6660.

[14] Lay CL, Liu HQ, Tan HR, Liu Y. Delivery of paclitaxel by physically loading onto poly(ethylene glycol) (PEG)-graftcarbon nanotubes for potent cancer therapeutics. *Nanotechnology* 2010; 21(6): 214-256.

[15] Chan JYW, Chu ACY, Fung KP. Inhibition of P-glycoprotein expression and reversal of drug resistance of human hepatoma HepG2 cells by multidrug resistance gene (mdr1) antisense RNA. *Life Sciences* 200; 67(17), 2117–2124.

[16] Suri SS, Fenniri H, Singh B. Nanotechnology-based drug delivery systems. *J Occupational Medicine and Toxicology* 2007; 2(1), 256-268.

[17] Cheng J, Meziani MJ, Sun YP, Cheng SH. Poly(ethylene glycol)-conjugated multi-walled carbon nanotubes as an efficient drug carrier for overcoming multidrug resistance. *Toxicology and Applied Pharmacology* 2011; 250(2): 184–193.

[18] Liu X, Tao H, Yang K, Zhang S, Lee ST, Liu Z. Optimization of surface chemistry on single-walled carbon nanotubes for in vivo photothermal ablation of tumors. *Biomaterials* 2011; 32(1): 144–151.

[19] Zhao B, Hu H, Niyogi S, Itkis ME, Hamon MA, Bhowmik P, Meier MS, Haddon, RC. Chromatographic purification of soluble single-walled carbon nanotubes. *J Am Chem Soc* 2001; 123 (47):

[20] Georgakilas, V., Voulgaris, D., Va´ zquez, E., Prato, M., Guldi, M.D. , Kukovecz, A., Kuzmany, H., 2002. J. Am. Chem. Soc. 124 (48), 14318. 11673.

[21] Monthioux M. Filling single-wall carbon nanotubes. *Carbon* 2002; 40(10): 1809-1823.

[22] Tsang SC, Chen YK, Harris PJF, Green MLH. A simple chemical method of opening and filling carbon nanotubes. *Nature* 1994; 372(6502) 159-162.

[23] Ajayan PM, Ebbesen TW, Ichihashi T, Iijima S, Tanigaki K, Hiura H. Opening carbon nanotubes with oxygen and implications for filling. *Nature* 1993; 362(6420): 522-525.

[24] Ebbesen TW. Wetting, filling and decorating carbon nanotubes. *J Phys Chem Solids* 1996; 57 (6-8): 951-955.

[25] Gao YK, Dx C, Cs O. Spontaneous insertion of DNA oligonucleotides into carbon nanotubes. *Nano Letters* 2003;3(4): 471-473.

[26] Dejonge N, Doytcheva M, Allioux M, Kaiser M, Mentink S, Teo K, Lacerda R, Milne W. Cap closing of thin carbon nanotubes. *Adv Mater* 2005; 17(4): 451-455.

[27] Heister E, Neves V, Tolmaciu C, Lipert K, Sanz Beltrõn V, Coley H. Triple functionalisation of single-walled carbon nanotubes with doxorubicin, a monoclonal antibody, and a fluorescent marker for targeted cancer therapy. *Carbon* 2009; 47(9): 2152-2160.

[28] Hillebrenner H, Buyukserin F, Kang M, Mota MO, Stewart JD, Martin CR. Corking nano test tubes by chemical self-assembly. *J Am Chem Soc* 2006;128(13): 4236-4237.

[29] Abbott NJ, Ronnback L, Hansson E. Astrocyte-endothelial interactions at the blood brain barrier. *Nat Rev Neurosci* 2006; 7(1): 41–53.

[30] Lai CH, Kuo KH. The critical component to establish in vitro BBB model: Pericyte. *Brain Res Rev* 2005; 50(2): 258–265.

[31] Reese TS, Karnovsky MJ. Fine structural localization of a blood-brain barrier to exogenous peroxidase. *J Cell Biol* 1967; 34(1): 207–217.

[32] Levin VA, Patlak CS, Landahl HD. Heuristic modeling of drug delivery to malignant brain tumors. *J PharmacokinetBiopharm* 1980; 8(3): 257–96.

[33] Di L, Kerns EH, Bezar IF. Comparison of blood-brain barrier permeability assays: in situ brain perfusion, MDR1-MDCKII and PAMPA-BBB. *J Pharm Sci* 2009; 98(6): 1980–91.

[34] Yang Z, Zhang Y, Yang Y, Sun L, Han D, Hong LI, Wang C. Pharmacological and toxicological target organelles and safe use of single-walled carbon nanotubes as drug carriers in treating Alzheimer disease. *Nanomedicine* 2010; 6(3) 427-441.

[35] Liu Z, Sun X, Nakayama-Ratchford N, Dai H. Supramolecular chemistry on water-soluble carbon nanotubes for drug loading and delivery. *ACS Nano* 2007; 1: 50–56.

[36] Shi Kam NW, Jessop TC, Wender PA, Dai H. Nanotube molecular transporters: Internalization of carbon nanotube-protein conjugates into mammalian cells. *J Am Chem Soc* 2004; 126: 6850–6851.

[37] Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: Role of ATP-dependent transporters. *Nat Rev Cancer* 2002; 2: 48–58.

[38] Ali-Boucetta H, Al-Jamal KT, McCarthy D, Prato M, Bianco A, Kostarelos K. Multiwalled carbon nanotube-doxorubicin supramolecular complexes for cancer therapeutics. *ChemCommun (Camb)* 2008; 4: 459–461.

[39] Liu X, Tao H, Yang K, Zhang S, Lee ST, Liu Z. Optimization of surface chemistry on single-walled carbon nanotubes for in vivo photothermal ablation of tumors. *Biomaterials* 2011; 32(1): 144-151.

[40] Raffa V, Ciofani G, Vittorio O, Riggio C, Cuschieri A. Physicochemical properties affecting cellular uptake of carbon nanotubes. *Nanomedicine* 2010;5(1): 89-97.

[41] Liu Z, Tabakman S, Welsher K, Dai H. Carbon nanotubes in biology and medicine: in vitro and in vivo detection, imaging and drug delivery. *Nano Res* 2009; 2(2): 85-120.

[42] Bianco A, Kostarelos K, Prato M. Applications of carbon nanotubes in drug delivery. *Curr Opin Chem Biol* 2005;9(6): 674-679.

[43] Berber S, Kwon YK, Tomanek D. Unusually high thermal conductivity of carbon nanotubes. *Phys Rev* 2000; 84: 4613–4616.

[44] Hone J, Llaguno MC, Nemes NM, Johnson AT, Fischer JE, Walters DA, Casavant MJ, Schmidt J, Smalley RE. Electrical and thermal transport properties of magnetically aligned single wall carbon nanotube films. *Appl Phys* 2000; 77: 666–668.

[45] Hone J, Whitney M, Piskoti C, Zettl A. Thermal conductivity of single-walled carbon nanotubes. *Phys Rev* 1999; 59: 2514–2516.

[46] Hone J, Llaguno MC, Biercuk MJ, Johnson AT, Batlogg B, Benes Z, Fischer JE. Thermal properties of carbon nanotubes and nanotube-based materials. *Appl. Phys A Mater* 2002; 74: 339– 343

[47] Biercuk MJ, Llaguno MC, Radosavljevic M, Hyun JK, Johnson AT, Fischer JE. Carbon nanotube composites for thermal management. .*Appl. Phys* 2002;80: 2767–2769.

[48] Heister E, Neves V. Drug loading, dispersion stability, and therapeutic efficacy in targeted drug delivery with carbon nanotubes. *Carbon* 2006; 128(2): 10568-10571.

[49] Xiaoke Z, Lingjie M. Targeted delivery and controlled release of doxorubicin to cancer cells using modified single wall carbon nanotubes. *Biomaterials* 2009; 30(30): 6041-6047.

[50] Liu Z, Sun X M, Nakayama-Ratchford N, DaiH J. Supramolecular chemistry on water soluble carbon nanotubes for drug loading and delivery. *ACS Nano* 2007; 1(1): 50-56.

[51] Liu Z, Davis C, Cai W B, He L, Chen X Y, Dai H J. Circulationand long-term fate of functionalized, biocompatible single-walled carbon nanotubes in mice probed by Raman spectroscopy. *Proc Natl Acad Sci* 2008; 105(5), 1410-1415.

[52] Hampel S, Kunze D, Haase D. Carbon nanotubes filled with a chemotherapeutic agent: a nanocarrier mediates inhibition of tumor cell growth. *Nanomedicine* 2008; 3(2): 175-182.

[53] Li R, Wu R, Zhao L. Folate and iron difunctionalized multiwall carbon nanotubes as dual-targeted drug nano-carrier to cancer cells. *Carbon* 2011; 49(5): 1797-1805.

[54] Ghoshal S, Kushwaha SKS, Tiwari P, Srivastava M. Loading and Release of 6- Mercaptopurine from functionalized multiwalled carbon nanotubes using fusion method. *BMR CancerRes* 2014; 1(1) :1-10.

[55] Ghoshal S, Kushwaha SKS, Srivastava M, Tiwari P. Drug Loading and Release from functionalized multiwalled carbon nanotube loaded with 6-Mercaptopurine using incipient wetness impregnation method. *Am J Adv Drug Del* 2014; 2(2): 213-223.

[56] Modi C D, Patel S J, Desai A B, Murthy RSR. Functionalization and evaluation of PEGylated carbon nanotubes as novel drug delivery for methotrexate. *J Appl Pharm Sci* 2011; 1(5): 103-108

[57] Dolatabadi JEN, Jamali A A, Hasanzadeh M. Quercetin delivery into cancer cells with single walled carbon nanotubes. *Int J Biosci Biochem Bioinforma* 2011; 1(1): 21-25.

[58] Reddy S T, Rehor A, Schmoekel H G, Hubbell J A, Swartz M A. In vivo targeting of dendritic cells in

lymph nodes with poly(propylene sulfide) nanoparticles. *J Control Release* 2006; 112(1): 26-34.