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Carbon Nanotubes in Pharmaceutical Nanotechnology Application to Future Drug Delivery System

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A B S T R A C T

The purpose of this review article was to study the application of carbon-nanotube in order to improved the drug delivery system. In nano materials carbon-nanotube have emerges the new alternative and efficient tool for transporting and translocating the therapeutic molecules. The technique has been developed to produce a multiple-walled carbon-nanotube and single wall carbo nanotube. The properties and characterization are still being research by various investigation which is able to pass through membranes, vaccine and nuclei acid deep into the target cells.

Keywords: Carbon-Nanotube, Target cells, cancer chemotherapy, cytostatic drugs, Nanotechnology

A R T I C L E I N F O

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1. Introduction

Drugs particles which is available in a nano size have the unique properties which can be able to enhance the performance in the variety of dosage forms. Nanoparticles in drug delivery by using carbon nano tube may be a single wall carbon nanotube (SWCNTs) or a multiple wall carbon nanotube (MWCNTs). This have many advantages over the conventional dosage forms, which included improved efficacy, reduced the toxicity and enhance bio-distribution with improved patient compliance. In nanotechnology the drug delivery system is being extent to all the therapeutics classes of pharmaceuticals, many of the therapeutics agent has not been use because of their limit ability of them reaching the target the tissue. In addition to this their also has been developed for delivery system for anti-cancer agents and vaccines. For example. In cancer chemotherapy, the cytostatic drugs damage both the malignant tumor and normal cells. So in order to improve, the carbon nanotube holds good for drug delivery system for treatment of cancer disease.

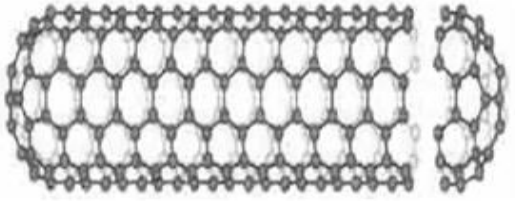

Figure 1: Structure of Carbon Nanotube (source A)

The carbon nanotube is consisting of a long hollow cylinder made up of grapheme, which may be a SWCNTs or a MWCNTs. The diameter of this tube lie in the range of 1-100nm , the tube is actually being cap with the half and full fullerene molecules at both the ends. These cylinder CNTs of one or co-axial graphite layer having an order of nano-meters. The CNTs (SW or MW) have the unique properties I,e Physical, chemical, and electrical properties. Its consist of 3A diameter. This carbon nanotube mainly show the application of drug delivery system.(Fig.1) (Smriti Khatri *et al, 2010*). Carbon nanotube can be produce by just rolling up the single layer of the sheet of graphene forming a single wall carbon nanotube (SWCNTs). However, by rolling up many layer scan form a concentric cylindrers which produced the multiple wall carbon nanotube (MWCNTs). Both the SW and MW carbon nanotube are commercially available with the different structure details and varie in degree of purity.

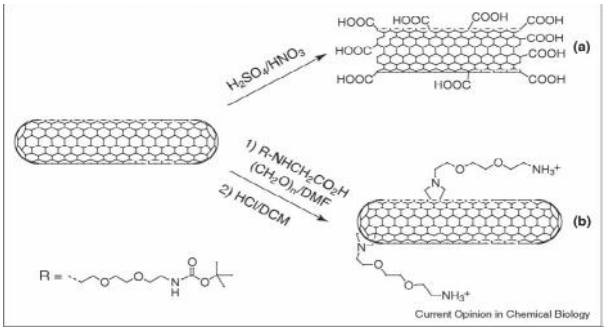

Figure 2: Organic functionalisation of carbon nanotubes.

Pristine single or multi-walled carbon nanotubes can be (a) treated with acids to purify them and generate carboxylic groups at the terminal parts, or (b) reacted with amino acid derivatives and aldehydes to add solubilising moieties around the external surface. (Source B). Carbon nanotube can be oxidized by using strong acids, resulting in the reduction of their length which generating the carboxylic group. This can lead into increase of their dispersibility. In aqueous solution in water, addition reaction of carbon nanotube and tips make them soluble in water.

The functionalized carbon nanotube have emerge as a new tools in the field of nanoparticles and nano-medicine. The f-carbon nanotube can be linked to the wide variety of active molecules including the peptides, proteins, the nuclei acid and others therapeutics agent. It also help to improve the translocation of the drugs molecules into different types of mammalian cells. In order, to functionalized the external wall of CNTs , its depends on the 1,3-dipolar cycloaddition of azo-methine ylides. It can undergo the addition reaction when reacted with DMF in the presence of alpha-amino acid and aldehyde. This reaction is very important since it's produced a highly soluble in the wide range of solvents. CNTs is consisting of ammonium group and are very soluble in water and can be employed in the delivery of drugs or the other therapeutics molecule [2].

2. Fullerene

The fullerene molecules are the one which composed of carbon in the form of hollow sphere or ellipsoid or a tube. The spherical fullerenes are similar in the structure to graphite. The fullerene is actually form the basic parts of carbon nanotube. The first fullerene to be discovered was the family namesake Buck Minister fullerene C60 made in 1985 by Robert Kroto and Richard Smalley. The name was homage to Richard Buck Minister fuller, whose geodesic domes its resembles. Fullerens have since been found in nature [3].

3. Carbon Nanotube

Single wall carbon nanotube (SWCNTs)

The single wall carbon nanotube (SWCNTs) that has already mentioned that is made of the graphene being the same poly-aromatic monoatomic layer made of the hexagonal cells and the carbon exist as the sp2 hybridized. This graphene being rolled up into a cylinder along with the hexagonal ringsput in contact to join each other seamless. The wave on naonotube is build on graphene sheet which

does not have only on influence of diameter chirality of carbon nanotube but also for electronic appliances.

Multiple wall carbon nanotube (MWCNTs)

Multiple wall carbon nanotube (MWCNTs) as the name suggestis consist othe multipla wallof the graphene sheet rolled up in a concentric CNT, which is being filled each other inner cavities to end upwith nanotubes. The inner tube distance of CNTsis approximately that of the inter graphene distance in tubostratics poly-aromatic solid. Thus MWCNTs are stronger in their strength as compare to SWCNTs. Thus, SWCNTs with additional graphene tubes around the core of SWCNTs are called as multiple wall carbon nanotubes. **4** (**Smriti Khatri *et al***).

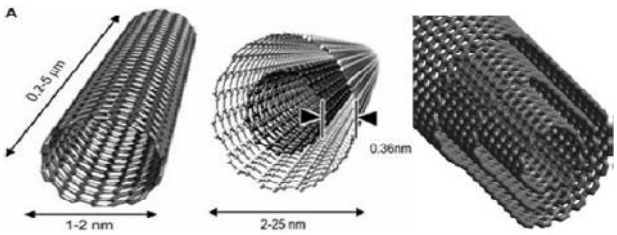

Figure 3: Conceptual diagram of SWCNT, DWNT & MWCN (source D)

4. Methods of Production

ARC Discharge Method

The arc discharge was the first one available method for the production of SWNTs and MWNTs. This method is base or creats a nanotubes through the arc vaporization of the two carbon rods placed end to end which is being separated each other by 1mmand is usually filled with the inert gas I (helium, argon) at low pressure (between 50 – 100 mbar). The recent investigation also shown that it is possible to creat a nanotube with this arc method in the presence of liquid nitrogen (Jug et al,1992). A direct current of 0.50 – 100 A driven by approximately 20V. Creats a high temperature discharge between the two electrodes . the discharge vaporize one of the carbon rods later forms a small shaped rod which is then deposit inti the other rod. Producing a nanotube in the high yield and depends on the uniformity of the plasma arc and the temperature of the deposits form on the carbon electrode (Ebbensen T W et. al, 1992). Depent on the exact technique, it is possible to select grow SWNTs or MWCNTs. Thus, this method can be performed into two different arc discharge apparatus. **7** (Kumar et al,2012)

5. Purification of CNTs

Nanotubes usually contain a large amount of impurities such as metal particles, amorphous carbon, and multishell. There are different steps in purification of nanotubes.

1. **Air oxidation**
   The carbon nanotube are the one which have less purity, the average purity is about 5-10. So the purification is needed before the attachment of drugs to the CNTs. The air oxidation is also very useful in reducing the amount of amorphous carbon and metal catalyst like particles (Ni, Y).the optimal oxidation condition is found tobe at 673K for 40mins.
2. **Acid Refluxing**
   When refluxing is done with the strong acid i.e sample leads to effective in reducing the amount of metal particles and the amorphous carbon. Different acid uses were hydrochloric acid (HCl), nitric acid (HNO3), sulphuric acid (H2SO4). However, HCl is mainly use because it was identified as the ideal refluxing acid.

Syntesis of SWNTs

If the SWNTs are preferable the anode should has to be doped with metal. Catalyst such as Fe, Co, Ni, Y or Mo. A lot of elements and mixture of the element has been tested by various authors (Journet et al,1998) and its noted that the result vary a lot,even though using the same element. The quantity and quality of nanotubes obtained mainly depends on the various paramaters such as concentration of metal, inert gas pressure, kinds of gases, current and system geometry. The diameter is range from 1.2 to 1.4nm. A few ways to improve the process of the arc discharge are:-

(a) Inert gas
(b) Optical plasma control
(c) Catalyst
(d) Improvement of oxidation resistance
(e) Open air synthesis with welding arc torch

Synthesis of MWNTs

If both the electrodes which are using in the graphite, the main product will be MWNTs . But during the formation a side product are formed such as fullerenes, amorphous carbon and same graphite sheet. When purify the MWNTs it means loss of structure and disorder of the wall. However many of the sciencetist is developing ways to gain a pure MWNts in a large scale process without purification. The size of MWNTs is about 1-3nm diameter and outer diameter approximately 10nm. Because catalyst involves in this process, there is no need for acidic purification step. Thus MWNTs can be synthesis with the low amount of defects.

(a) Syntesis in liquid Nitrogen
(b) Magnetic field synthesis
(c) Plasme rotating arc discharge. **[8]**

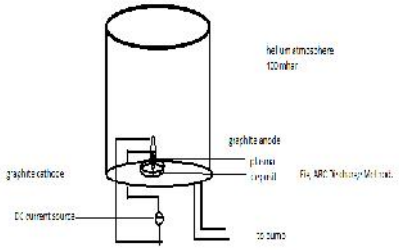

Figure 4: ARC Discharge Method (source E)

3. **Surfactant Aided Sonication, Filtration And Annealing**

After the acid refluxing, the CNTs were undergo Purer, but the tube was entangled together, trapping most of the impurities such as carbon particles and catalyst particles which were difficult to remove with filtration. So surfactant aided sonication was carried out Sodium dodecyl benzene sulphonate (SDBS) aided sonication with ethanol or methanol as the organic agent. This is used because it takes a long time to settle down. The sample is then filter by ultrafiltration unit and annealed at 1273K in Nitrogen for 4hours. The annealing is effective in optimizing the CNTs structure. It was proved that the surfactant aided the sonication is effect the CNTs . Nanotube can also be done the purification by different method.**9**

Dimensional Properties

Due to the nano-scale dimensions, electron transport in CNTs will take place by quantum effects and will be able to propagate along the axis of the tube. These electrical and structural properties best serve CNTs as far as bio-sensing is concern because current in CNTs changes can signify the specific biological entities that they are desing to detect. The fact that the CNTs are small is that allows them to deliver smaller doses of drugs to specific diseases cells in the body. Thus by reducing the side effect and harm to healthy cells unlike the other conventional drugs.

Chemical Properties

It has been observed that CNTs enhance the solubility when funtionalized with lipids which would make their movement through the human body very easy and would also reduce the resist of blockage of the important body organ pathway. CNTs exhibit a strong optical absorbance in certain spectral windows such as NIR (near infrared light).[**10]**

6. Applications

Delivery of Small Molecules By Carbon Nano-tube

Drug delivery is one of the most extensively explored applications of CNTs in bio-medicine. In recent years it has been developed by various group to load small molecules such as chemotherapeutics cancer drugs on CNTs via either covalently conjugation or non- covalent conjugation or non-covalent adsorbtion. This theoretical modeling has also been guide the design of CNTs –base drug carriers. The conjugated drug molecules are linked to the functional group on the CNTs surface or the polymer coating of CNTs via a cleavage bond.

The anti-cancer or anti-fungal drugs are maily linked by 1,3-dipolar cycloaddition of functionalized carbon nanotube via amide bonds in case of drug delivery system. In this case of a non-covalently PEGlygated transport of a Pt (4) complex, which has to reduced to cytoxic Pt (II) after endocytosis for cancer cells destruction. Beside the covalent linkage, aromatic molecules with a flat structure can be adsorbed on the surface of CNT through non-covalent $\pi - \pi$ stacking. In 2007, the discovered of doxorubicin, a commonly used cancer theraphy drug, could be stacked on the surface of PEglygated SWCNTs with a remarkably high loading capacity of up to 4 gms of drug per 1gm of nanotubes to the ultra high surface area **[11].**

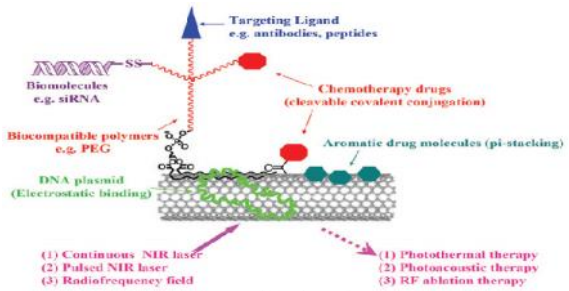

Figure 5: A schematic drawing showing various approaches for CNT-based drug delivery and cancer therapies (source F)

Carbon nanotube in drug delivery system

The drug delivery of carbon nanotube is designed generally to improved the pharmacological and profile of drug molecules. The ability of the f-carbon nanotube to penetrate in to the cells offer the potential by using f-CNT as the vehicle for delivery of the anti-cancer, antibacterial, or anti-viral agents has no yet been fully ascertained. The development of the delivery system are able to carry one or more therapeutic agents with the recognize capacity, signal optical for imaging and specific targeting. For example in case of cancer treatment and many infectious disease for the MWCNTs with the different types of molecules. The functional CNTs (f-CNTs) were emerging as a new tool in the field of nano-medicine. The f-CNTs have been show that it can be deliver the proteins, nuclei acids, drugs, antibodies and the other therapeutics. In order to get the CNTs in the field of drug delivery. This is because it can be easily manipulated and modified by taking along with bio-polymers or by covalent linking to solobulising group to the external walls and tips. The formation of f-CNTs in the biological system has open a new way to the exploration of application in biology and medicinal chemistry. Within the different field of application (i.e. biosensors, composite materials, molecular electronics). The carbon nanotube can be use as the carrier for drug delivery and various therapeutics molecules. Amidst The Myraid of drug delivery system able to enhance the delivery, absortion and intracellular uptake of the bioactive molecules. While protecting it from deactivation. CNTs are considered potentials materials in biomedical because of their flexibility structure and prosperity for chemical funtionalization. The pharmaceuticals excipients have been regarded as invert non-active components dosage forms. The application of CNTs in biological system depends on their compatability with hydrophilic environment. The carbon nanotubes are able to reduce the unwanted toxicity of the drug when administered alone. Ammonium f-CNTs can also be considered as the very promising vectors for the gene en-coding nuclei acids. In the comparison to the DNA alone the one that can form a stable complex is between the

cationic CNTs and plasmid DNA. The unique property of CNTs is thst the ability to pass or cross the membrane of many different types of cells following the translocation mechanism thet has been term as nanotube mechanism. In this way, CNTs has open a great opportunities in drug discovery base on intracellular targets. More over f-CNTs can be eliminated from the body following systematic administration offering further encouragement for their development. CNTs safely profile and consequently any further pharmaceutical development.**12** (**Smriti Khatri *et al***)

Functionalized Carbon Nanotube

The functionalized carbon nanotube contain the additional fundtional group on their surface that is why we called a functionalized carbon nanotube . when CNTs are treated with the with the mixture of concentrated sulphuric acid and nitric acid. Its result into the formation of carboxylic group and hydroxyl group of their surface. These activated the CNTs are able to react with the other funcyional group forming a coupling to the different compounds (Ruiz-Hitzky et al,2008). The SWCNTs are funtionalized using the molten urea as a solvent and disperse with azenediazodium salt in less than 15 minutes. (Codell et al, 2007)

Cancer Targeting

Towards the drug delivery and cancer treatment carbon nanotubes is a good candidates in the field of cancer treatment. For examples the dispersion of SWCNTs by the use of ultrs sonic with phospholipids glycol (PEG) fragments it, this can be able to interfere with the ability to block non-specific uptake of the cells. However when there is an unfragmented (PC-PEG) this can be able to promoted the specific cellular uptake of targeted SWCNTs to two distinct classes of receptors expressed by cancer cells. Chemically f-CNTs have show promises in tumor targeted accumulation in mice and exhibit biocompatibility excertion, and little toxicity. Here we shoe In vivo SWCNTs in drug delivery for tumor suprresion in mice. The widely used chemotherapy PTX I.e paclitaxel in widely used to the branced Peg chains in the SWCNTSs via a cleavable ester bond to obtained a water soluble SWCNTs – PTX conjugate. SWCNTs –PTX can be able to afford higher efficacy in suppressing the growth of tumor than the clinical Taxolin a murine 4TI breast cancer model, owing to prolonged blood. Circulation and 10-fold higher tumor PTX uptake by SWCNTs delivery through the permeability and retention. Drug molecules carried into the reticuloen dothelial system and are also being release from SWCNTs and being excreted out through biliary pathway without causing toxicity effects to the normal organs. Thus, CNTs in drug delivery in promising for high treatment efficacy and minimum side effects for future cancer therapy with low drugs doses. [**11]**

Cancer cells is express of folic acid receptors, from which various research its was concluded the nano-carriers which was engineer surfacely to which folic acid can be attached for cancer targeting . moreover CNTs has reported that it has retaining capacity to accumulate in the lymph nodes for the long duration of time as compare to the other nano carriers. Hence can be used for targeting cancer cells as shown by the various investigator. Such a cisplatin anticancer this drug has been formulated into magnetic raw particles loaded into yhe MWCNTs and functionalized with folic acid. With the help of external magnetic, CNTs were targeted to lymph nodes and release the drug for longer period in order to inhibit the tumor growth . Yang et al revealed the anti-cancer drug gemcitabine was loaded into magnetic MWCNTs . then which was study with mice module show the high activity against lymph node metasteses when formation was injected.**14** Further (N Gsahoo et al) reported that camphothecin poorly water soluble drug loaded into PVA functionalized MWCNTs was very effective for treatment of skin and breast cancer. In vitro, study LIP and co-worker (2011) developed dual targeting drug nano-carrier by conjugating the iron nanoparticles along with folate molecules, which was loaded with doxorubicin and showed that there were superior deliver of drugs to HeLa cells. When compared to to free doxorubicin.**15** The bio adhesive such as Chitosan and sodium alginate act as the enhancers to the aqueous dispersability of the nanotubes and folic acid was use to improve targeting properties.

Lymph

By controlling the size of nanoparticles can be effectively taken into a lymphatics. In this case the various nanoparticles have been investigated for the transporter of chemotherapy pharmaceuticals but only a few retained in the draining lymph note. In this case , we can use technology of magnetic CNTs (MNTs) delivery system which is more effectively. Chemotherapeutic were incorporated into the pores of f-CNTs which has been synthesized with the layer of magnetic nanoparticles on the inner surface of nanotubes. In order to improve the drug delivery to cancer cells is the lymph node, indivualised MNTs were non-covalently functional by folic acid. By using an externally placed magnet to guide the drug matrix to the regional targeted lymph nodes, the MNTs can be retained in the draining targeted lymph nodes for several days and continuously release chemotherapeutic drugs. Selective killing of tumor cells over expressing the folate receptors (FRs) in the lymph nodes can be achieved, as FR is over expressed across a broad spectrum of human tumors.**17** The lack of solubility, nonbiodegradability, circulation half-life of 3-3.5 hours, biocompatibility, and immunogenicity are some limitations of CNTs which produce the challenges associated with the. These limitations indicate the need for modifications in order to explore the feasibility of CNTs as delivery vehicles. Lymph metasis occur in cancer which may be result in frequent tumor re-occurrence even after the lymph dissection. In order to overcome this issue, Yang et al use magnetic MWCNTs which can delivered the gemcitabine to lymph node under the guidance of magnetic field. By using, this method various chemotherapeutic agents can be delivered to lymph node. (yang et al)

Other Applications

Besides the cancer treatment advances of carbon nanotube shows their extraordinary of physical and chemical

properties. CNTs reveal a promising potential as bio-medical agent for heating temperature, sensoring of drug delivery the cellular level**.** Pathogenic bacteria from liquid medium can be trapped by using surface engineered CNT. Also, CNT itself had anti microbial effect which adsorbs the micro organism into engineered surface. Nanotube induced oxidation of intercellular antioxidant glutathione, resulting in increased oxidative stress on bacterial cell and cause death. Binaco et al. reported the antifungal activity of amphotercin B which was transported into mammalian cell through CNTs which reduced the antifungal toxicity when compared to the free drug. About 40% of cells were killed by using free drug, where as no cells were killed in CNT formulation. Antibiotic, Doxorubicin given with nanotubes is reported for enhanced intracellular penetration. The gelatin CNT mixture (hydro-gel) has been used as potential carrier system for biomedicals. They can be used as lubricants or glidants in tablet manufacturing due to nanosize and sliding nature of graphite layers bound with van der waals forces. Normally body shows rejection reaction for implants with the post administration pain. **23** But, miniature sized nanotubes and nanohorns get attached with other proteins and amino acids avoiding rejection. Also, they can be used as implants in the form of artificial joints without host rejection reaction. Moreover, due to their high tensile strength, carbon nanotubes filled with calcium and arranged/grouped in the structure of bone can act as bone substitute. Carbon nanotubes and nanohorns are antioxidant in nature. Hence, they are used to preserve drugs formulations prone to oxidation. Their antioxidant property is used in antiaging cosmetics and with zinc oxide as sunscreen dermatological to prevent oxidation of important skin components. [**11]**

Table 1: Comparison between SWNT and MWNT

1	Single layer of graphene.	Multiple layer of grapheme
2	Catalyst is required for synthesis.	Can be produced without catalyst.
3	Bulk synthesis is difficult as it requires proper control over growth and atmospheric condition	Bulk synthesis is easy.
4	Purity is poor.	Purity is high.
5	A chance of defect is more during Functionalization	A chance of defect is less but once occurred it's difficult to improve.
6	Less accumulation in body.	More accumulation in body.
7	Characterization and evaluation is easy	It has very complex structure.
8	It can be easily twisted and are more pliable.	It cannot be easily twisted.

7. Conclusion

CNTs are used as a prospective carrier in drug delivery, due to their unique properties they can be used as a carrier for drugs and bio molecule and genes. Due to their novelty and potential applications they can be used in treatment diagnosis and to adsorb pathogenic micro organisms. The major challenge and limitation of the CNTs is the toxicity. Although many reports had suggested that well functionalized carbon tubes is safe. More pre clinical and clinical studies are needed before carbon nano-tubes based drug delivery. More specific drugs are being developed to use the specificity and potency of these drugs, new drug delivery systems must be implemented. Optimistically, carbon nano tube technology is also a one of such potential technique to deliver the most specific and potential drugs to treat acute as well as chronic diseases. Carbon nano tubes delivery are promising candidates that will enable efficient and targeted delivery of novel drug compounds.

8. References

1. Sushma Drabu; Smriti Khatri, Sheveta Babu, Roshan Kumar Sahu. Carbon Nanotubes in Pharmaceutical Nanotechnology: An introduction to Future Drug Delivery System. *J. Chem. Pharm. Res.*, **2010**, 2(1): 444-457
2. S Sandeep Kumar, D prathibha, N L Gowri Shankar, R parthibarajan, L Mastyagiri, and M Shankar. Pharmacueticalapplication of Carbon nanotube-Mediated Drug Delivery System. International of journal and Pharmaceutical Science and Nanotechnology**,** **2012**, 5(2).
3. F. Yang, D.L. Fu, J. JLong, Q.X. Ni, Magnetic lymphatic targeting drug delivery system using carbon nanotubes, Med. Hypotheses. **2007**, 70.
4. N.G. Sahoo, H. Bao, Y. Pan, M. Pal, M. Kakran, H.K. Cheng, L. Li, L.P. Tan, Functionalized carbon nanomaterials as nanocarriers for loading and delivery of a poorly water-soluble anticancer

drug: a comparative study, Chem. Commun. (Camb). **2011**, 47.
5. R. Li, R. Wu, L. Zhao, Z. Hu, S. Guo, X. Pan, H. Zou, Folate and iron difunctionalized multiwall carbon nanotubes as dual-targeted drug nanocarriers to cancer cells, Carbon. **2011**, 49.
6. Schipper ML, Nakayama-Ratchford N, Davis CR, Kam NW, Chu P, Liu Z, Sun X, Dai H,
7. Gambhir SS. *Nat Nanotechnol*.**2008**, 3(4).
8. F. Yang, D.L. Fu, J. JLong, Q.X. Ni, Magnetic lymphatic targeting drug delivery system using carbon nanotubes, Med. Hypotheses. **2007**, 70.
9. W. Wu, S. Wieckowski, G. Pastorin, M. Benincasa, C. Klumpp, J.P. Briand, R. Gennaro, M. Prato, A. Bianco, Targeted delivery of amphotericin B to cells by using functionalized carbon nanotubes, Angew Chem. Int. Ed. **2005**, 44.
10. A. Bianco, K. Kostarelos, C. Partidos, M. Prato. Biomedical applications of functionalised carbon nanotubes, Chem. Commun. **2005**, 5.
11. Pai P, Nair K, Jamade S, Shah R, Ekshinge V, Jadhav N. Pharmaceutical applications of carbon tubes and nanohorns. Current Pharma research Journal, **2006**, 1: 11-15.