ejpmr, 2020,7(7), 249-255

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW ARTICLE ON SUPRAMOLECULAR CARBON NANOTUBES FOR DRUG LOADING AND DELIVERY

Abhanya Surendran*, Jasna K.[1], Dr. Shijikumar P. S.[2], Dr. Sirajudheen M. K.[1] and Dr. Nishad K. M.[1]

[1]Department of Pharmaceutics, Jamia Salafiya Pharmacy College Pulikkal, Malappuram, India-673637.
[2]Department of Pharmaceutical Analysis, Jamia Salafiya Pharmacy College Pulikkal, Malappuram, India-673637.

***Corresponding Author: Abhanya Surendran**

Department of Pharmaceutics, Jamia Salafiya Pharmacy College Pulikkal, Malappuram, India-673637.

Article Received on 26/04/2020 **Article Revised on 16/05/2020** **Article Accepted on 05/06/2020**

ABSTRACT

In nanomaterials, carbon nanotubes (CNTs) have significant role in transporting and translocating therapeutic molecule. They turn up as a new alternative and efficient tool for drug loading and delivery. The CNTs having extraordinary electrical conductivity, heat conductivity and mechanical properties. They have distinct and unified physicochemical properties such as orderd structure with high aspect ratio, high mechanical strength, high electrical conductivity, high thermal conductivity, metallic or semimetallic behaviour and high surface area. Hence they offer an alternative, efficient and promising platform for drug delivery system of many therapeutic active compounds ranging from anti-neoplastic agents, cardiovascular drugs, anti-infectives to anti-inflammatory molecules and genes. The CNTs are produced by various methods, which include flame synthesis, arc discharge, laser ablasion, chemical vapour deposition (CVD) systems.

KEYWORDS: carbon nanotubes, supramolecular carbon nanotubes, synthesis, functionalisation, newer trends.

INTRODUCTION

The purpose of this introductory chapter is to draw readers attention to the achievements made in the chemistry of carbon nanostructures and, especially in carbon nanotubes (CNTs) and the most recent graphenes. Since the discovery of fullerenes in 1985 and their additional preparation in multigram quantities, the chemistry and reactivity of these molecular carbon allotropes have been well established. This chemical reactivity has been used as a reference for future studies carried out on the next carbon nanotubes (single and multiple walls) and graphenes. Assuming that the fundamental chemistry of fullerenes is known and basically corresponds to that of typical electron-deficient alkenes, it focus mainly on the chemistry of fullerene-containing polymers. In this sense, the combination of exclusive fullerenes with highly versatile polymer chemistry has provided a new and interdisciplinary field in which the resulting architectures are capable of exhibiting unprecedented properties. The basic knowledge of this important topic of macromolecular chemistry of fullerenes greatly complements the following chapters, dedicated to their supramolecular chemistry.[1]

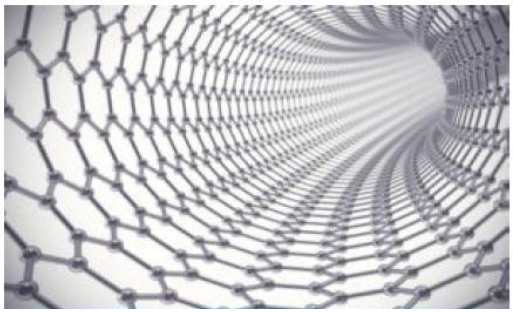
CARBON NANOTUBES

The extensive research carried out on CNTs in recent years has shown the unprecedented mechanical, electrical and thermal properties that these macromolecules exhibit. From the wide range of carbon nanostructures available, CNTs stand out as truly unique materials that have a notable impact on fields such as field-effect transistors (FETs), light-emitting diodes (LEDs), organic solar cells (OSCs), biochemists sensors, memory elements or additives in composite materials.

However, most CNT applications require manipulation, interaction or binding of CNTs to other materials, either in solution or in high viscosity matrices. These operations are often hampered by the chemical inertness of the CNT surface and the large aggregates that the tubes form due to stacking interactions. Some of these problems are overcome by chemical modifications of the CNT surface.

In general, the CNTs functionality can be divided into different categories.

1. The covalent fixation of functional entities in the CNT scaffold that can occur at the tube terminals and / or on the side walls.
2. The non-covalent interaction of organic and inorganic portions with the surface of the carbon nanotube through the use of varied interaction forces, such as Van der Waals, charge transfer and interactions, and the special case of endohedral filling of CNTs with atoms or small molecules.[2]



Properties of carbon nanotubes

- High thermal conductivity
- High electrical conductivity
- Proportion of CNTs
- They are very elastic
- Have very high tensile strength
- They are highly flexible - they can be folded considerably without damage.
- Have a low coefficient of thermal expansion.
- CNTs are good emitters of electron fields.[3]

Advantages of carbon nanotubes

- They are biocompatible, non-biodegradable and non-immunogenic nature.
- They are highly elastic nature and possibility of intracellular delivery.
- They exhibit minimal cytotoxicity.
- 96% excreted in the urine and the remaining 4% in the faeces.
- Ultra light weight and does not break during processing.
- CNTs has an open end on both sides, which makes the inner surface accessible and the subsequent incorporation of species into the nanotubes is particularly easy. The carbon nanotubes have a larger internal volume in relation to the diameter of the nanotubes for entrapment. CNTs are able to enter cells by spontaneous mechanism due to their tubular and nano-needle shape.
- It has different internal and external surfaces, which can be modified differently for chemical biochemical functionalization.

Types of carbon nanotubes (CNTs)

Two types of CNTs are there.

1) Single-walled carbon nanotubes (SWCNTs)
2) Multi-walled carbon nanotubes (MWCNTs)

Single-walled carbon nanotubes (SWCNTs): SWCNTs consist of a single cylindrical carbon layer with a diameter in the range of 0.4 to 2 nm, depending on the temperature at which they were synthesized. It was found that the higher the growth temperature, the larger the diameter of the CNTs. The structure of the SWCNTs can be arm chair, zigzag, chiral or helical. SWCNTs have an ultra high surface area of 1300 m^2 / g, which generates enough space for drug loading and bio conjugation. In drug administration, SWCNTs are known to be more efficient than MWCNTs. This is due to the reason that SWCNTs have an ultra high surface area and an efficient drug loading capacity. An anti-cancer drug complex SWCNT has been found to have a much longer blood circulation time than the anti-cancer drug alone. This leads to a more prolonged and sustained absorption of the drug by tumor cells through the enhanced effect of permeability and retention. Once the functionalized SWCNT releases the drug in a specific area, it is gradually excreted from the body via the bile duct and, finally, in the faeces. This suggested that SWCNTs are suitable candidates for drug administration and a promising nanoplate for cancer therapy.

Multi-walled carbon nanotubes (MWCNTs): MWCNTs consist of several coaxial cylinders, each made from a single sheet of grapheme that surrounds a hollow core. The outer diameter of the MWCNTs varies from 2-100 nm, while the inner diameter is in the range of 1-3 nm, and its length is one to several micrometers. The sp^2 hybridization is generated in MWCNTs, a cloud of electrons relocated along the wall, responsible for the interactions between adjacent cylindrical layers in the MWCNTs, resulting in less flexible and structural defects. MWCNT structures can be divided into two categories based on their graphite layer arrangements: one has a parchment-like structure, consisting of a sheet of graphene wrapped around it, and the other is known as a Russian doll model, where layers of graphene sheets within a concentric structure. The decoration of multi-walled carbon nanotubes (MWCNTs) consists of depositing nanoparticles on the walls or ends of the MWCNT, linked by physical interaction with possible applications in catalysis, biosensors, biomedical, magnetic data storage and electronic devices. The various methods used for this purpose include precipitation, high temperature hydrolysis or chemical decomposition of a metal precursor.[2]

SUPRAMOLECULAR CARBON NANOTUBES

Supramolecular interactions are generally short-range forces (close contact) between molecules, too weak to cause intermolecular changes or formation of bonds between particles. At the same time, its strength and range are sufficient to cause the self-assembly of the molecular units or certain elastic deformations of these building blocks. Due to the weakness of supramolecular interactions, the resulting organization is sensitive to external conditions and guarantees a certain ease of transformation in response to external fields. Well-

known is a fascinating class of liquid crystals, whose liquid appearance is exactly the result of a relatively small energy of intermolecular forces. Nanoparticles and especially nanotubes offer a type of building blocks that can be efficiently bonded by weak supramolecular forces in a self-assembly process. In the case of nanotubes, due to their hollow structure and large proportion, the same forces or interactions between them can cause flexion, torsion, flattened polygonization etc. In turn, the degree of this deformation can increases (as in the case of polygonization of nanotubes in the matrix bundles) supramolecular attraction or decrease it in other circumstances.

CHEMISTRY OF SUPRAMOLECULAR CARBON NANOTUBES

Linear elastic properties: Numerous theoretical calculations are dedicated to linear elastic properties when the displacements (stress) are proportional to the forces (stress).

Van Der Waals interactions: Supramolecular interactions between SWNTs are mainly due to van der Waals (VdW) forces, except in special situations where the local charge or covalently linked functional group introduces additional electrostatic fields. Van der Waals forces also play an important role in the interaction of nanotubes with substrates. The different shells of an MWNT (multi-walled nanotube) interact mainly by the forces of van der Waals; single wall tubes form strings for the same reason. Supramolecular morphological changes in the elastic shell model.

Supramolecular morphological changes in the elastic shell model: Almost any molecular structure can withstand very large deformations, compared to the common range in macroscopic mechanics. A less obvious property of CNTs is that the specific features of large nonlinear deformations can be understood and predicted in terms of continuous theories. One of the striking features of nanotubes are their hollow structure, constructed of densely packed atoms along a closed surface that defines the general shape. This also manifests itself in the dynamic properties of molecules, resembling both macroscopic objects of continuous elasticity known as shells. In nanomechanics, shell theory was applied for the first time in our initial buckling analysis and has since served as a useful guide. Its relevance to a covalent bond system with only a few atoms in diameter was far from obvious. Molecular dynamics simulations seem more suitable for small objects.

Thus, we can conclude that the mechanics of nanotubes has attracted great interest since their discovery and in the last decade. Due to qualitative differences, the mechanics of nanotubes can be subdivided into intramolecular, involving rearrangements of bonds and atomic removal or insertion in the carbon structure of the tube wall and supramolecular mechanics of interactions between the molecules in the tube. While supramolecular interactions play a central role in colloid chemistry, in numerous biochemical processes, and have been widely studied, in the case of nanotubes, certain special aspects stand out. The great strength of the carbon network makes it qualitatively different from most other molecules frequently involved in supramolecular processes: the lowest activation barrier for rearrangements of intratubular bonds is 7 to 9 eV high, which makes the bond covalent even with other species or between the tubes a small supramolecular disturbances. On the other hand, the same stiffness and smoothness of the surface of the tubes results in dramatic amplification or traditionally weak dispersion forces. Van der Waals interactions add up along the tube-to-tube contact and typically produce 1 eV per nanometer in length, that is, many volts of electrons for a typical side contact. This in turn makes the solubility or even the mechanical separation of the nanotube packages a very challenging task. These distinct characteristics of the supramolecular mechanics of nanotubes play a critical role in their assembly in sets of strings, nematic crystals, or in their distribution and coupling with solvents or matrix substances in composite materials.[4]

METHODS OF CARBON NANOTUBE SYNTHESIS

High temperature preparation techniques, such as arc discharge or laser ablasion were first used to prepare CNTs, but these methods have now been replaced by low temperature chemical vapour deposition (<800˚C) techniques (CVD).

Plasma based synthesis method or arc discharge evaporation method: The method uses higher temperatures (above 1700˚C) for CNT synthesis, which generally causes the growth of CNTs with less structural defects compared to other techniques. The electric arc method, used initially to produce fullerene $c_{60,}$ is the most common and perhaps the easiest way to produce CNTs. In this method, the electric arc created between two graphite electrodes leads to an extremely high temperature, sufficient to sublimate the carbon. MWCNTs or SWCNTs can be formed when carbon vapours cool and condense. Generally, MWCNTs are formed when there are no catalyst particles between two graphite electrodes; and SWCNTs are formed by adding Fe, Ni or Co as catalysts.

Laser ablasion method: The laser ablasion method uses a pulsed, continuous laser to vapourize a graphite target in an oven, which is filled with helium or argon gas to maintain pressure. SWCNTs were prepared by laser ablasion of continuous wave carbon dioxide without applying additional heat to the target.

Thermal synthesis process: In thermal synthesis, only thermal energy is relied on and the hot reaction zone never exceeds 1200˚C, including the case of CVD with increased plasma.

Chemical vapour deposition (CVD): Catalytic synthesis of CVD is achieved by placing a carbon source in the gas phase and using plasma or a resistently heated coil to heat the carbon-containing gas molecules. Heat is used to break the molecule into reactive atomic carbon. The most frequently used catalysts are transition metals, mainly Fe, Co or Ni.

Plasma enhanced CVD (PECVD): PECVD systems have been used to produce SWCNTs and MWCNTs. PECVD is a general term, covering several different methods of synthesis. In general, PECVD can be direct or motor. Direct PECVD systems can be used for the production of MWCNT field emitting towers and some SWCNTs. A remote PECVD can also be used to produce MWCNTs and SWCNTs.[2]

PURIFICATION OF CARBON NANOTUBES

Removal of carbonaceous and the catalyst particles involved in the purification process. The purification includes one or more processes including dispersion, dry-oxidation, wet oxidation, chemical treatment, filtration (including the chromatographic methods) and annealing.[5] The techniques such as ultrasonication is mainly used for dispersion. Even after dispersion, direct acid treatment is less effective for removing the catalyst particles due to the carbon coating on them, wet oxidation is combined with dry oxidaion to break these coatings and expose catalyst particles with acid. This step is carried out with strict control over the oxidation temperature, because the metal particles catalyze the discriminatory oxidation of carbon and destroy the CNTs.[6] Microwave heating has also been used to achieve metallic acid treatment that leads to other purification processes, ie dry oxidation, wet oxidation, filtration and annealing etc. The purity of the CNTs can be assessed in the sense of qualitative and quantitative analysis, usually scanning electron microscopy (SEM), transmission electron microscopy (TEM) and scanning tunnel microscopy (STM) are used for the evaluation of purity. Other techniques like thermal gravimetric analysis (TGA), Raman spectroscopy, near-infrared spectroscopy (NIR) were introduced for quantitative analysis.[7]

APPLICATIONS

Therapeutic applications: The functionalization of CNTs makes them useful in a variety of different applications. Applications of CNTs are investigated in four main areas: drug administration, biomedical imaging, biosensors and scaffolding in tissue engineering.

Drug delivery: They are an effective drug delivery system for cancer therapy, as they show the targeted delivery of therapeutic agents. For example, the delivery of anticancer drugs, such as doxorubicin and platinum-based anticancer drugs, has already been demonstrated.

Gene therapy: Gene therapy is an efficient way to activate biological functions and signal the destruction of cancer cells. Early investigations using carbon nanostructures suggest that they are promising non-viral vector platforms for transfection in gene therapy. The first demonstration was the nanotube with amine functionality, which served to condense the plasmid DNA to form supramolecular complexes (CNT-DNA).

Imaging applications: In diagnostics, they can be used as contrast agents in magnetic resonance imaging (MRI), NIR fluorescence, Raman spectroscopy, photoacoustic tomography and even radionuclide-based images.[8]

Blood cancer: Taghdisi et al., developed a tertiary complex of Sgc8c aptamer (this aptamer targets biomarker protein tyrosine kinase-7), daunorubicin and SWCNT, called Dau-aptamer SWCNTs. Flow cytometric analysis observed that the tertiary complex was effectively internalized in human T-cell leukemia cells (MOLT-4 cells), but not in U266 myeloma cells.

Breast cancer: Liu et al., Studied the SWNT delivery of paclitaxel (PTX) in xenograft tumors in mice with greater tumor suppression efficacy than the formulation of the clinical drug Taxol. PTX conjugated to PEGylated SWNTs showed high solubility in water and maintains toxicity similar to cancer cells such as Taxol in vitro. SWNT-PTX provides a much longer blood circulation time than Taxol and PTX using PEG, leading to a high tumor uptake of the drug by the EPR effect.

Liver cancer: The polyamidoamine dendrimer modified CNTs (dMWCNTs) were manufactured for the efficient delivery of antisense c-myc oligonucleotide (asODN) in the HepG2 cells of the liver cancer cell line. The ODN-dMWCNTs composites were incubated with HepG2 cells and confirmed to enter tumor cells within 15 minutes by confocal laser microscopy. These composites inhibited cell growth.

Brain cancer: Xing et al., Functionalized SWCNTs of phospholipid-bearing polyethylene glycol (PL-PEG) conjugated to protein A, which was additionally coupled to the fluorescein-labeled integrin monoclonal antibody to form the monoclonal antibody SWCNTintegrin (SWCNT-PEGmAb). Confocal microscopy revealed that SWNT-PEG-mAb showed a much higher fluorescence signal in U87MG positive integrin cells and showed a high targeting efficiency with low cell toxicity.

Lymph node metastasis: Yang et al., Compared the potential therapeutic effect in vitro and in vivo of magnetic MWCNTs loaded with gemcitabine (GEM) (mMWCNTs) with that of magnetic carbon particles (mACs) loaded with gemcitabine. The result reflects that mACs and mMWNTs effectively increased GEM cytotoxicity in vivo and inhibited lymph node metastases, especially when using high-dose agents and / or applying magnets implanted in vivo. The systems

offer the possibility of improving the therapeutic effects and reducing the side effects associated with chemotherapeutic agents, using the synergistic effects of magnetic targeting and lymphatic chemotherapy.

Cervical cancer: Wu et al., developed a new approach to the use of natural biocompatible polymer of chitosan for imaging tumor cells. In this assay, SWCNTs were modified by chitosan (CHIT), fluorescein and othyocyanate (FITC). Combining the intrinsic properties of CNTs, the versatility of chitosan and folic acid, FITC-CHIT-SWCNT-FA can be used as a potential device to target the drug to tumor cells and also for imaging.

Immune therapy: Xu et al., Studied that MWNTs conjugated to tumor lysed protein will increase the effectiveness of an anti-tumor immunotherapy that employs tumor cell vaccine (TCV) in a mouse model with H22 liver cancer. The study showed that MWNTs conjugated to the tumor lysed protein increased the specific antitumor immune response and cancer cure rate of a TCV immunotherapy in mice.

Biomedical imaging: SWNTs have a strong optical absorption from the ultraviolet (UV) to the near infrared (NIR) regions and are useful in several different imaging techniques. This includes photoacoustic images, Raman images, fluorescence images and, with the functionalization of CNTs, positron emission tomography (PET) and magnetic resonance (MR) images.

Biosensors: Biosensors are used to mention biological processes or to recognize biomolecules and differ from other sensors in that they have a sensor element made up of a biological material, such as proteins, oligo or polynucleotides or microorganism. Electrochemical biosensors are popular for detecting biomolecules in solutions due to their simplicity and relative ease of calibrations.

Tissue engineering: CNTs are also useful for improving tissue matrices. The matrix, or scaffolding, played an important role in tissue engineering, as this is what provides the structural support for the new tissue.[2]

CARBON NANOTUBES IN DRUG DELIVERY RECENT TRENDS AND FUTURE ASPECTS

Functionalized carbon nanotubes (f-CNTs) are emerged as new tool in the field of nanomedicine and nanobiotechnology. f-CNTs has been shown to deliver proteins, nucleic acids, drugs, antibodies and other therapeutics. The CNTs can be easily manipulated and modified by encapsulation with biopolymers or by covalently binding solubilising groups to outer walls and tips. Hence emerging developments in this field directed to the successful use of CNTs in drug delivery. The possibility of incorporating f-CNTs in biological systems has opened the way to the exploration of its potential applications in biology and medicinal chemistry.[9] The CNTs emerged as a promising and recent option, especially in drug delivery and cancer therapy. This is because of their unique properties, which makes them extremely versatile by incorporating several functional groups and targeting molecules at the same time, while their natural forms allows them to selectively penetrate through biological barriers in a non-invasive manner.[10] Carbon nanotubes are considered as potential biomedical materials due to their flexible structure. Pharmaceutical excipients has also been considered as inert or non-active components of the pharmaceutical preparations. The applications of CNTs in biological systems depends on its compatibility with hydrophilic environments; hence, the solubilization of CNTs in pharmaceutical solvents is essential.[11] The CNTs have a potential application in nanomedicine as biocompatible and support substrates, and as pharmaceutical excipients to create versatile drug delivery systems.[12] SWCNTs are presently under evaluation in biomedical applications, which include in vivo delivery of drugs, proteins, peptides and nucleic acids for gene transfer or gene silencing, in vivo tumor imaging and tumor targeting of SWCNTs as an anti-cancer treatment.

The versatile physicochemical features of CNTs allow the covalent and noncovalent introduction of a number of pharmaceutically relevant entities and allow for rational design of nove nanoscale candidate constructs for drug development. The f- CNTs deliver several moieties for targeting, imaging and for therapy. In which most interesting example, which carrying a fluorescein prob along with amphotericin B (antifungal drug) or fluorescein and methotrexate(antitumor agent). The biological activity is improved or retained, while the CNTs are capable to mitigate the unwanted toxicity of the drug administered alone. Ammonium functinalized CNTs can also be considered as a vector for gene-encoding nucleic acids. The CNTs conjugated antigenic peptides can also be grown as a new and effective system for synthetic vaccine applications. The CNTs have an ability to passively cross the membranes of many different type of cells following a translocation, called nanoneedle mechanism. Recently, the CNTs opened numerous possibilities for future drug discovery based on intracellular targets. In addition, properly functionalized CNTs can be rapidly removed from the body after systemic administration, which offers a greater stimulus for its development. The rates of excretion and accumulation of CNTs in the organs and any reactivity with the immune system, determine the safety profile of CNTs and, consequently, any additional pharmaceutical development. Caution is advised on the need for long-term systematic data on nano-objects in correlation with the type of CNT material used.[13]

The CNTs made an excellent progress in the drug delivery. However, there is still a challenge in delivering clinically optimal levels of therapeutic molecules. Advances in nanotechnology and nanomedicine have announced the occurrence of several innovative

nanomaterials that will revolutionize the field of drug delivery.[14]

The CNTs are very good candidate in cancer treatment. One example is the dispersion of SWCNTs by ultrasonication with phospholipids-polyethylene glycol (PL-PEG) fragments, which interferes with its ability to block non-specific absorption by cells. It will promote the cellular uptake of targeted SWCNTs to two different classes of receptors expressed by cancer cells.[15]

To determine the efficacy of drug delivery system, they were designed, synthesized, characterized and subjected three fluorescent and fluorogenic molecular probes to the analysis of receptor mediated endocytosis and drug release inside the tumor cells by using confocal fluorescene microscopy. Chemically functionalized SWCNTs have shown promise in tumor-targeted accumulation in mice and exhibits biocompatibility, excretion and poor toxicity. In this, in vivo SWCNTs drug delivery for cancer suppression in mice are shown. Drug molecules delivered into the reticuloendothelial system are released from SWCNTs and excreted via biliary pathway without causing any toxic effects to normal organs. Thus the drug delivery using carbon nanotubes are promising for high efficacy and minimum side effects for future cancer therapy with low drug doses.[16] Hampel prescribed CNTs as feasible carriers of carboplasin, a therapeutic agent for the treatment of cancer. The drug was introduced into the CNTs to demonstrate that they are suitable as nanocontainers and nanocarriers and that they can release the medication to initialize their medical virtue. The filling was done by a wet chemical approach after the CNTs was opened. The effect on cell proliferation and cytotoxicity of carboplatin-filled CNTs was investigated through the use of viability assays. Using various analysis methods, such as electron energy loss spectroscopy and X-ray photoelectron spectroscopy, it was found that the structure of the carboplatin incorporated in the CNTs was retained.[17]

In addition, the cancer treatment advances of CNTs explore their excellent physical and chemical properties of CNTs disclose promising potential as biomedical agents for heating, temperature sensoring and drug delivery on the cellular level. By filling the CNTs with tailored materials, nanoscale containers are made in which the active content is encapsulated by a protective carbon shell. The filling of CNTs with magnetic materials offers the potential for hyperthermia applications while the introduction of NMR active substance allows the use as markers and sensors. The potential of CNTs for biomedical applications is point out by hyperthermia studies which show their applicability for local in situ heating. In addition, a non-invasive temperature control is possible under a nanoscale carbon-wrapped thermometer and the filling of anti-cancer drugs.[18]

SUMMARY

Carbon nanotubes are a new emerging system in the field of biomedical engineering, nanobiotechnology and nanomedicine, due to their distinct and unified physicochemical properties. CNTs are produced by various methods, in which the chemical vapour deposition (CVD) method is the most popular. Various studies show that carbon nanotubes have emerged as a promising area for the multimodal drug delivery system. They are equipped with target molecules that help in their various applications. Carbon nanotubes have a unique combination of physical and chemical properties. The special properties and possible applications of carbon nanotubes make them materials for the future and the unique properties of carbon nanotubes lead to the manufacture of different devices.

REFERENCES

1. Francesco Giacalone, M Angeles Herranz, and Nazario Martin, Carbon nanostructures: covalent and macromolecular chemistry, Supramolecular chemistry of fullerenes and carbon nanotubes, first edition, 2012; 1-11.
2. Parijat Pandey, Mandeep Dahiya, Carbon nanotubes: Types, methods of preparation and applications, International journal of pharmaceutical science and research, 2016; 15-19.
3. R. Saito et al, Physical properties of carbon nanotubes, 1998.
4. Boris. I, Luise. S, Carbon Nanotubes: Supramolecular Mechanics, 2006; 587: 589-599.
5. Jeong, T.; Kim, W.Y. & Hahn, Y.B. Chem.. Phys. Lett, 2001; 344: 18.
6. Fei, B.; Lu, H.; Hu, Z. & Xin, J.H. Nanotechnology, 2006; 17: 1589-93.
7. Sushma Drabu, Smriti Khatri, Sheveta Babu, Roshan Kumar Sahu, Carbon Nanotubes in Pharmaceutical Nanotechnology: An introduction to Future Drug Delivery System, 2010; 444-454.
8. Rafael G .Mendes, Alicja Bachmatiuk, Bernd Buchner, Gianaurelio Cuniberti, Mark H. Rummeli, Carbon nanotubes as multi-functional drug delivery platforms, 2012; 402: 409-416.
9. Foldvari M, Bagonluri M, Nanomedicine, 2008; 4(3): 183-200.
10. Prato M, Kostarelos K, Bianco A, Acc Chem Res, 2008; 41(1): 60-8.
11. Prakash S, Kulamarva AG, Recent Pat Drug Deliv Formul, 2007; 1(3): 214-21.
12. Zeineldin R, Al-Haik M, Hudson LG, Nano Lett, 2009 Jan 16.
13. Chen J, Chen S, Zhao X, Kuznetsova LV, Wong SS, Ojima I. J, Am. Chem. Soc, 2008 Nov 14.
14. Liu Z, Chen K, Davis C, Sherlock S, Cao Q, Chen X, Dai H, Treatment.Cancer Res, 2008 Aug 15; 68(16): 6652-60.
15. Murakami T, Sawada H, Tamura G, Yudasaka M, Iijima S, Tsuchida K, Nanomed, 2008 Aug; 3(4): 453-63.

16. Jia N, Lian Q, Shen H, Wang C, Li X, Yang Z, Nano Lett, 2007 Oct; 7(10): 2976-80.
17. Armentano I, Dottori M, Puglia D, Kenny JM, J Mater Sci Mater Med, 2008 Jun; 19(6): 2377-87.
18. Yang F, Fu De L, Long J, Ni QX, Med Hypotheses, 2008; 70(4): 765-7.