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Review Article

A Review of Carbon Nano Tubes Synthesis and Its Application as Potent Carriers in Cancer Therapy

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ABSTRACT

In 2017, about 252, 710 new cases have been diagnoses of breast cancer are expected in women, and around about 40,610 women are being likely to die from breast cancer. As of now there are many therapies for cancer treatment among them these carbon nano tubes are gaining a lot of intrest from the researchers side as an unique and a novel delivery system. These are chemically derived as the allotropes of the carbon molecules, hence due to their nano structures and their novel structural properties they are gaining a lot of scope in the nano technology, as that held a extensive scope in the pharmacy field. There are many methods for producing the nano tubes, to alter them structurally they have to be functionalized to have a good physio-biological properties to perform as a good delivery system for many drugs. The purity of the tubes can be enhanced by various purification techniques. Extensive and an in depth research work is being carried out in this field to make them a potent delivery system.

Keywords: carbon nano tube, purification, functionalization, toxicity.

HISTORY

Earlier in 1952 Radushkevich & Lukyanovich[1] has published clear images of a size about 50nano meters carbon nano tubes. Later in 1976 Koyama & oberlinendo showed clear hallow fibers of carbon with nano meter scale they used vapor growth technique[2] to produce these fibers. John Abrahamson[3] in 1979 presented evidence of carbon nano tubes. In 1981 a group of Soviet scientists published the results of chemical and structural characterization of carbon nanoparticles produced by a thermo catalytical disproportionation of carbon monoxide. Using TEM images and XRD patterns, the authors suggested that their "Carbon multi-layer tubular crystals" were formed by rolling graphene layers into cylinders. The attribute of discovery of CNT'S is given to Iijima[4]. These are also known as tubular fullerenes they are sp^2 hybridized carbon atoms with cylindrical grapheme sheets.

INTRODUCTION

Cancer is a disease which involves the abnormal growth of cells which has potential even spread to other parts of the body. Generally the abnormal growth of cells is referred as "tumor". We can not conclude that all the tumors are cancerous. There are various types of cancer like lung, breast, colon, bone, brain etc. The rate of survival after the attack of cancer has increased from past few decades due to the advancement in the cancer therapies.

In 2016 a figure of about 1,685,210 new cases of cancer & about 59,690 deaths are caused due to cancer. Of all the cancers 25-32% of cancers accounts to breast cancer in India. It is including all age groups of women[5].

Over the past few years of cancer research we have observed a lot of innovative discoveries& development in the research area. Most of the cancer research is concentrated in the nano scale. These nano materials are derived either from organic or inorganic materials. As we came across larger sorts of nano materials & novel nano formulations. Carbon nano tubes are one such innovative products. Basically these carbon nano tubes are the allotropes of carbon. They are mostly made from the graphite powder as it acts as major source for carbon. They tubular, hallow inside structurally. Due their unique properties these

CNT'S are also used in the field of nanotechnoly. Because of their novel structural properties they have a broad range of applications in various fields. As of their unique surface area, strength, structure, shapes & resilience have brought them into the field of pharmacy[6].

Types of nano tubes

Depending up on the structure and diameter they can be classified in to single walled, double walled, multi walled carbon nano tubes[7].

Single walled carbon nano tubes

These were first discovered in 1993 the diameter range differs around 0.4-30nm. They consists of a single layer of graphene. They do not require any catalyst for the synthesis of single walled carbon nano tubes but the synthesis cannot be carried out in bulk as we need special attention over the growth & the atmospheric conditions can penetrate in to the cell easily and the accumulation is less in the body can be evaluated easily. The bonds present between them are of vanderwaals forces[8,9].

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Double walled carbon nano tubes

In the double walled carbon nano tubes diameter ranges from 1-3nm. Double walled carbon nano tubes can be obtained by a mixture of single walled carbon nano tubes and multi walled carbon nano tubes. They contain similar morphology, properties. They need to be further functionalized for any special properties. Posses a great flexibility, stability than that of single walled carbon.

Multi walled carbon nano tubes

Diameter ranges from 1-3nm width ranges from 2-100nm catalyst may be or may not be used for synthesis. When compared to SWCNT the accumulation rate of these tubes is more in the body.

Preparation of carbon nano tubes

While coming to the synthesis of carbon nano tubes they involve a vast methods of production which includes Arc discharge, Laser ablation, Flame synthesis, Chemical vapour deposition, High pressure carbon monoxide pyrolysis, Electrolysis, etc.

All the above processes can be certainly further classified in to 3 types of major categories which can mainly grouped as follow

Physical Process

This process makes use of physical principles for the synthesis of nano tubes. Carbon is used for the synthesis of nano tubes. This process is mostly used for the synthesis. Physical process includes techniques like Laser ablation, Arc discharge.

Electric arc discharge technique

One of the oldest methods used for the production of carbon nanotubes production. In 1991 at NEC's Fundamental Research Laboratory to produce new type of finite carbon structures consisting of needle-like tubes. The tubes were synthesized by using an arc discharge evaporation method similarly to that used for the production of fullerene. The size of carbon needles, varies from 4 to 30 nm in width and up to 1 mm in length, and were developed on the negative end of the carbon electrode used for the direct current (DC) arc-discharge evaporation of carbon. Throughout the process Iijima has used pressurized chamber filled with a gas mixture of 40 Torr argon and 10 Torr methane. Two vertical thin electrodes were fitted in the center of the chamber. The lower electrode (cathode) contained a small piece of iron in a shallow dip made purposefully to grip iron. The arc was produced by running a DC current of 200A at 20 V between the electrodes. The three main components, namely argon, iron and methane was critical for the production of SWNT. Carbon soot formed as result of arc-discharge settled and nanotubes grew on the iron catalysts contained in negative cathode. The nano-tubes had diameters of 1nm with a broad diameter varying in between 0.7 and 1.65 nm. In a similar process Bethune *et al*. used thin electrodes with bored holes as anodes, which were packed with a mixture of pure powdered metals (Fe, Ni or Co) (catalysts) and graphite. The vaporization of electrodes with a current of 95 -105 A in 100-500 Torr of Helium. SWNT were also synthesized by the variant of arc-technique by Journet *et al*. as well. In his alternate, the arc was produced between two graphite electrodes in a reaction chamber under helium atmosphere (660 mbar). This method also gave a larger yield of carbon nanotubes[10,11].

Laser ablation

By using this technique we can get an yield of about (>70%). Diameter ranges from 10-20 nm. The principle of this process is by laser ablation of graphite rods with small amounts of Ni&CO at 1200°c. In this process two step laser ablation of graphite rods are used. This two step processes reduces the amount of carbon deposition. This process is mainly used for the synthesis of swcnt which contains narrow size. Various parameters will affect the cnt properties synthesized by this this method. Properties which are affected are structural and chemical composition of the target material, the laser properties chemical composition, the distance between the target and the substrates, and ambient temperature This technique has a added potential for producing SWNTs with high purity and high quality. The principle and mechanisms of this laser ablation is similar to that of arc-discharge technique, but in this method, the energy is provided by a laser which hit a pure graphite pellet holding catalyst materials[12,13]. The diameter and length of the tubes can be varied by changing the process parameters and catalyst materials.The advantage of this method is it gives a very low metallic impurities and a high yield is obtained.The disadvantage of this process is the tubes formed will be branced instead of straight tubes.

Chemical Process

Chemical vapor deposition

Tubes produced by this technique has a greater advantage we can get the tubes at lesser temperature. The tubes produced thought this technique can have a well organized structure. We can monitor the growth. This technique has various types such as plasma enhanced oxygen assisted CVD, catalytic chemical vapor deposition. Compared to all other techniques catalytic CVD is currently one of the standard technique used for the production of carbon nano tubes. In this a reaction chamber is made and a blend of hydro carbon gases (methane, ethylene) and process gas (nitrogen, ammonia) are made to react in the chamber at about 700-900°c at normal atmospheric pressure it results in the formation of tubes on the substrate[14,15,16].

High pressure carbon monoxide reaction

In the year 1999 at university of RICE this unique technique is suitable for large scale production. This process of nano tube production is free from catalytic backings the advantage of this process is we can run the process continuously. We normally use CO gas the hydrocarbon gas and is made to react with iron penta carbonyl with leads to the formation of the single walled carbon nanotubes[17].

Miscellaneous Process

Helium arc discharge method

This method was developed in 2000 by the NASA's scientists. The helium arc discharge method is used for the synthesis of swcnt & this is a economical process. Technique of this process is helium arc welding process. The obtained cnt's by this process will be in bundle ropes. The other positive effect for this process is no catalyst is

required in the process. This process is not yet commercialized[18].

flame synthesis

This is a commercial method for the manufacturing of CNT in a large scale. In this process the heat is released out from the exothermic chemical reaction taken place in the process. The intiation of this process starts by the hydrocarbon flames which results ultimately the CNT growth. The sources which acts as carbon many gases can supply gases but the gases like CO,C2H2,C2H4 are use in this process as the carbon source for the synthesis of CNT[19].

Saline solution method

We can produce carbon nano tubes even using saline solution of metal. In this technique we use a carbon paper or a stainless steel mesh. These are to be immersed in to a saline solution which is of metal catalyst. Generally preferred catalysts are Co and Ni, these are taken in a ratio of 1:1, then a gas containing carbon is used as carbon source. This gas is passed through the metal catalyst and substrate mixture, eventually the substrate was heated with the help of an electrical source which leads for the reaction with in the catalyst and gas which result in the yield of carbon nano tubes[20].

Purification Process of Carbon Nano Tubes[21,22]

We need to purify the synthesized nano tubes as they contains a larger number of impurities which may be from amorphous carbon and the metal ions used in the process. The process of nano tubes purification can be carried in various steps

acid reflux

Strong acids are used for the purification of the nano tubes. As these acids are considered to be show a good action in reducing the amorphous carbon and metal ion particles. Various acids used for acid refux are Sulphuric Acid(H2SO4), Nitric Acid(HNO3), Hydrochloric Acid(HCL). Out of these HCL is considerd as most effective acid for the process.

air oxidation

Before loading the drugs on to the carbon nano tubes they need to be purified as they have a lot of impurities. In this process we oxidize the nano tubes to purify them and make them free from impurities the average purity range is of 5-10%. Here we maintain a condition of 673 K for about 40 mins to oxidize the tubes and set them free from the catalyst particles.

sonication

In this process of separation of the tubes is caused due to the ultra sonic vibrations. The process of separation of the tubes will be dependent on the reagents, solvents, nature of the surfactant used in the preparation process. Acids can also be used in the process, but if they are set for longer duration sometimes they may damage the tubes.

Characterisation of carbon nano tubes

Scanning electron microscopy is used to study the structural appearance of the nano tubes. Transmission electron microscopy will be help full in characterizing the detailed study of the structure. For screening the carbon nano tubes RAMAN spectroscopy is a very reliable source. Thermo gravimetric analysis is used to get the details about the produced nano tubes, catalyst materials and other carbon particles.

Functionlization of carbon nano tubes[23]

Due to the solubility issue of the nano tubes in the biological system and its poor aqueous solubility this is a major disadvantage for nano tubes as a delivery system, to overcome this hurdle we need to further modify their structure, so that the problem can be resolved.

Functionalization is done in order to enhance their water solubility for this process we do covalent bonding, electro static interactions or may be absorption. The process of functionalization also helps in reducing the aggregation of the tubes as we are chemically changing their surface.

Non Covalent Functionalization of Carbon Nano Tubes

This process of non covalent functionalization will help to preserve the structure and also their properties. The advantage of non-covalent functionalization is that it does not destroy the conjugated system of the CNTs sidewalls, and therefore it does not affect the final structural properties of the material. The non-covalent functionalization is an alternative method for tuning the interfacial properties of nanotubes. The CNTs are functionalized non-covalently by aromatic compounds, surfactants, and polymers, employing π-π stacking or hydrophobic interactions for the most part. In these approaches, the non-covalent modifications of CNTs can do much to preserve their desired properties, while improving their solubility's quite remarkably. It will summarize as followed: aromatic small molecule absorption, polymer wrapping, surfactants, biopolymers and endohedral method[24,25].

Alternative Ways for Functionalizing Carbon Nanotubes

The two main routes; namely covalent and non-covalent functionalization generally provided. As discussed earlier, both methods had their own merits depending on the platform. Additionally, the traditional covalent functionalization strategy of CNT is most frequently initiated by chemical acid oxidation acid treatment. However, dramatic amounts of induced defects during functionalization hinder the intrinsic mobility of carriers along CNTs, which is not preferred in any case. This method not only functionalizes the nano tube surfaces with carboxylic acid groups but leaves behind detrimental structures, hence hampering their potential for practical applications and can also compromise the mechanical properties of the nano tubes. Therefore, as a common rule, and a now widespread approach to alleviate these problems is to find alternative routes such as an effective functionalization method that can not only introduce high density and homogenous surface functional groups, which enhance the compatibility between CNTs and the foreign matrix, but allow direct grafting and has little or no structural damage to the CNTs, thus, optimizing their properties for various applications. To overcome this challenge, Baek et al have reported an efficient route to covalently functionalize CNTs via direct Friedel-Crafts acylation technique. This kind of covalent grafting of the nano tubes is a promising strategy to not only improve nano tube dispersion but also provide a means for creating microscopic interlinks. On the whole, this kind of surface

Table 1: Comparison between SWCNT and MWCNT's

Single walled carbon nano tubes	Multi walled carbon nano tubes
In this only a single layer of grapheme is used	In this multiple layers of grapheme is used
Bulk synthesis of tubes is difficult as it requires proper control over growth	In this bulk synthesis is not as difficult this process is easy
We need catalyst in this process for the synthesis of tubes	Catalyst may not be required
Purity of tubes produced by this process is very poor	We get tubes with high purity
Functionalization may leads to defect in the tubes	May not lead to defects but if affected it is very difficult to recover them
Accumulation is very less in the body	More accumulation is seen in body
Evaluation an characterization of tubes is easy	Characterization and evaluation is very complex

functionalization not only enhances the reactivity, but also improves the specificity and provides an avenue for further chemical modification of CNTs. Considerable achievements have been made in enhancing the various functionalities of CNT-polymer nano composites, generally not achievable for each of the components individually. The approach is conceptualized on the basis of our foray into the CNT chemistry using 'direct' Friedel-Crafts acylation technique which has superior operational simplicity. Not only a mild and an alternative route to functionalize CNTs, this strategy was previously shown to be a less-destructive and/or nondestructive reaction condition for the efficient dispersion and functionalization of carbon nano materials. As a result, CNT damage from severe chemical treatments including oxidation and sonication can be avoided to a larger extent. Thus, maximum enhanced properties can be expected from improved dispersion stability as well as chemical affinity with matrices.

Toxicity of Carbon Nano Tubes

Carbon nanotubes are high- profile, nano-scale technology. This nanotubes are important to know the impact on biological systems because they can be used before the mainstream drug delivery.

Properties

Larger surface area, High reactivity, High aspect ratio, Small size.

There are many mechanisms of causing cell damage but the main way is due to DNA damage[26]. When experiments were conducted in mice CNT's exhibit behaviour similar to asbestos fibers. Main drawback of asbestosis includes their light weight and nano scale so they may be easily become airborne and carried into the lungs which causes PULMONARY FIBROSIS.This leads to reduce the area in lungs and difficult for transfer of oxygen into the blood. MWCNT's in high doses don't affect the cells in lungs as the way asbestosis fibers do.

Factors that which affect the carbon nano tubes[27]

Long term exposure to pristine MWCNT's at low concentration will not cause any adverse effects.

CNT toxicity may be due to

Length of the tubes.
Concentration or dose of CNTs.
SWCNTs or MWCNTs
Degree of aggregation.
Oxidation.
Functionalization.

In the above points 2 seems to have the concurrent results concentration and functionalisation. 2 parameters used for this test are incubation period and concentration of dose. This test has be experimented on rat erythrocytes at 2 different concentrations 25g/ml where no adverse effects were observed. 50 g/ml erythrocyte haemolysis was increased. Observation can be explained as on increasing the MWCNTs agglomerate which accelerates the haemolysis[28] process. Several papers agree that prolonged incubation period and high dose concentration both increases the induced toxicity and decreases the cell viability mainly in human bronchial epithelial[29] cells. The incubation time and concentration of a dose is a small area in nanotechnology in the treatment of cancer which requires study because it is used for the treatment of eradication of cancerous growth and minimise body exposure to the drug. This is one of the likely area of research were active and passive targeting which are directly related to degree and type of functionalization of CNT. It hs been demonstrates that Cytotoxicity will be decreased by increasing the degree of functionalization of a SWCNT.

Applications of carbon nano tubes

Carbon nano tubes are having a vast and wider range of application in the nano technology field, and its applications are also being expanded to various other fields even. Due to the different physical and structural properties they are growing very rapidly in the nano technology field. These are being considered as a special type of drug carriers for specific site targeting to cancer. The process of functionalization of these carbon nano tubes can enhance the ability of the carbon nano tubes. This process of functionalization can over come the main draw backs like toxicity and pharmacological affects. The novel applications of the carbon nano tubes were hooked in to diverse fields other than medicine like, electronics and energy and energy storage, material sciences, manufacturing, construction.

Bio medical applications of CNT'S

Bianco et al.[30] has prepared nano tubes which are soluble and he linked them with biologically active peptides. This is used for foot mouth disease virus it shows immunogenicity and antibody response to over come this chemotherapy is further carried out in which the nano tubes directly attack on virus cells and destroy them completely.

Table 2: Comparision of synthesis processes

Method	ARC discharge	Laser ablation	Chemical Vapour Deposition
Condition	Low pressure inert gas	Argon or nitrogen gas	High temperature with in 500-1000°c
Typical yield	30-90%	Up to 70%	20-100%
Source of carbon	Only graphite	Graphite	Hydro carbons
Cost	High	High	Low
Diameter	0.6-1.4nm	1-2nm	0.6-4nm
Desing	Difficult	Difficult	Designed as large scale process
Rate of production	Low	Low	High
Nature of process	Batch type	Batch type	Continuous

By this we can say that CNT has an valunerable effect in killing destroying the cells selective cell killing can be achieved by using this novel.

Artificial implants

When an implant is inserted in to the body it considers it as an foreign body an shows rejection reaction, but when the nano tubes are used they get attached with amino acids and proteins, which help in avoiding the rejection. These can also be used as implants as artificial joints as they donot show post rejections, these tubes are filled with calcium inside due to their high flexibility and the strength they are seggretated and arranged in the shape of bones and can be used as the substitute of bones[31].

Diagnostic tools

Enzyme filled, protein filled or either tubes encapsulated with protein can get ability to fluroscence in the presence of specialized or specific bio molecules, this ability of the nano tubes of giving flurosence made them even to use as a biosensors. This can be useful in studying the characterization of cells and various biological systems[32,33].

Preservatives[34]

The nanotubes are anti oxidant in nature. This antioxidant nature of the nano tubes can be used in various type of cosmetics with anti ageing properties and various others creams, not only in the cosmetics and use of this property can also be used to store the drug formulations due to their anti oxidant property.

Gene therapy and drug delivery by carbon nano tubes

While administring the drugs by chemotherapy in the traditional and conventional methods they are inducing a vast range of effects and due to their poor selectivity, lack of specificity, poor distribution with in the cells, systemic toxicity, poor solubility, lack of proper permeability through various barriers in the biological system, and developed multi drug resistance[33] these became a major issue for treating the cancer, to come out with a solution for the problems researchers had found many new approaches like silica nano particles, silver nano particles, nano emulsions, quantum dots, liposomes, ethosomes, micilles, etc to get forward from those barriers. After than the carbon nano tubes were been identified as a source for the delivery of drugs, we have studied various properties of the nano tubes above, due to their novel and unique properties, these are considered as the best delivery system, these are not only meant for the but can also deliver vaccines, nucleic acids, proteins, genes. The functionalization of nano tubes can be helpful in performing this drug delivery process, for crossing of the membrane barriers CNT'S are linked with specific cell receptors so that they can easily cross the membrane easily. In recent times there has been a lot of advancements in the CNT's drug delivery system, the researches has found a more advanced novel approach which consists of tumor targeting ligands, this is known as SWNT-based tumor-targeted drug delivery system (DDS), functionalized single walled carbon nano tubes are used for delivering of anti cancer drugs, when the tubes reach the cancer cells site they identify the receptor on the cell surface and cause endocytosis and it releases the drug in to the cells effectively.

Carbon nanotubes are being used for delivering drugs for various types of cancers they are cross linked with the drug on to their surface or to their tip and delivering the medicine to the cellular level very effectively, CNT DDS is being used for, brain cancer[35], cervical cancer[36], liver cancer[37], breast cancer[38], blood cancer[39], colon cancer[40], stem cell therapies.

limitations of carbon nano tubes[34]

Due to their different structure nano tubes have an issue in the aqueous solubility, when considered in the biological system even they are high lightened with the same solubility issue, as they are only soluble in few solvents this is being reported.

Then comes the purity issue as we use metal particles they may contain a lot of impurities so the quality of the tubes need to be high with low impurities. The reproducibility of the carbon nano tubes with identical characteristics is also an another limitation.

CONCLUSION

Carbon nano tubes have an diversified applications in the field of nano technology and in many other fields due to their novel characetrizational properties. The unique properties of these nano tubes has took a great path in cancer therapy, they have proven that these are potent and more effective carriers than the previous therapies. As this article reviewed various synthesis methods properties and other related characteristics CNT's can be stated as the best other way to carry and deliver various kinds of therapeutic

agents. They have shown a promising result in their action, but a lot more details have to be explored on their mechanism and mode of action. These carbon nano tubes need in depth study about their cellular level behavior. Moreover, the encapsulation of other materials in the carbon nanotubes would open up a prospect for their bio-applications in medicine.

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