CARBON NANOTUBES – A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

The carbon nanotubes (CNTs) are one of the unique and desirable discoveries within the field of nanotechnology. From their invention in the year 1991 by researcher Iijima, CNTs have been a great interest of area in many pharmaceutical and engineering fields because of their small size, lightweight, high tensile strength, and their good conductivity. CNTs are the hardest material invested by any human researcher till now; they are graphite in nature having sp^2 hybridization. They are having three classes: SWCNTs, DWCNTs, and MWCNTs based on their unique structure. CNTs are produced using different methods like the Arc discharge method, laser ablation method, and chemical vapor deposition. CNTs used in various applications because of their unique properties like mechanical, thermal, electrical and optical. They are used in applications like biomedicine, in the drug delivery system, like sensors, like implants, in tissue engineering, and in anticancer treatment.

Keywords: Carbon nanotube, Functionalization, Dispersion, Properties, Structure.

1. INTRODUCTION

In the current situation of novel drug delivery systems, carbon nanotube (CNTs) is one of the new and most promising approaches in pharmaceutical research and development. It was first explored in the year 1991 by a scientist named Iijima.[1] CNTs are one of the members of the fullerenes group. CNTs are large molecules of pure carbon that are long, thin, tubular and cylindrical shape and having a size range between 2-3 nm. CNTs are also defined as tubular fullerene or cylindrical graphene having sp^2 hybridization carbon atoms.[2] CNTs are having specific properties and structures and can be used in various pharmaceutical applications like cancer treatment, Drug Delivery, biosensors, biomedicine imaging as organized materials for a branch of tissue engineering. CNTs are also used in intracellular delivery of tiny drug entities, deoxyribonucleic acid, plasmids, short interfering ribonucleic acid, and proteins**.** [3] CNTs are allotropes, which is having a tubular figure and prepared from graphite. They are classified into three categories, 1. Single-walled (SWCNTs), 2. Double-walled (DWCNTs) 3. Multi-walled (MWCNTs). [1]

2. HISTORY

In the year 1952, Scientist Lukyanovich and Scientist Radushkevich bring out a research report in the “soviet scholarly diary of physical science”, where he introduces carbon strands that have empty graphitic nature and having a size of around 50 nm. In the year 1979, at Pennsylvania state college, Scientist john Abrahamson offered confirmation of carbon CNT at the fourteenth biennial course of carbon. In the year 1981, a group of Soviet researchers offers the result of the synthetic and auxiliary game plan of carbon Nano extend molecule framed by a thermal catalytical lopsided of carbon monoxide (CO). At long last during the year 1991 after all the exploration work Japanese researcher and specialist Iilima has found carbon nanotube by c*ircular segment release strategy at NEC (Nippon electric organization).[1,2,3,4]

3. ADVANTAGE OF CNTs [1,2,3]

1. High electrical along with warm conductivity
2. Very high elasticity
3. Highly adaptable and flexible (~18% lengthening before disappointment)
4. High perspective proportions
5. Good field emanation

4. DISADVANTAGE OF CNT [1,2,3,4]

1. More current innovation so not as much testing has been completed
2. Lower lifetime (1750 hours contrasted with 6000 hours for silicon tips)

Higher possibilities required for field outflow as the cylinders are not all that very much restricted so the extractor cathode must be further away.

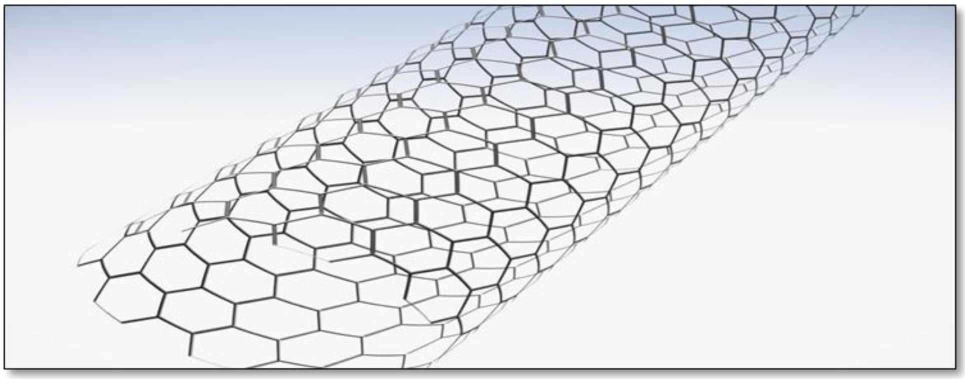
5. CNTs CLASSIFICATION

- Single-walled CNTs
- Double-walled CNTs
- Multi-walled CNTs

5.1 Single-walled CNTs

SWCNTs are arranged from a single realistic sheet which in completely moved upon CNTs, having a circuit of 1-2 nm. The range of SWCNTs is depended upon the detailing technique. SWCNTs blend required a particular impetus for the creation of nanotubes. Mass unify is troublesome into the combination of SWCNTs in light of the fact that they required the right reform overextension and uncommon air condition. For its synthesis, it requires a catalyst. SWCNTs are poorly purified and have no complex structure. It's easy to twist. [4, 5,6]

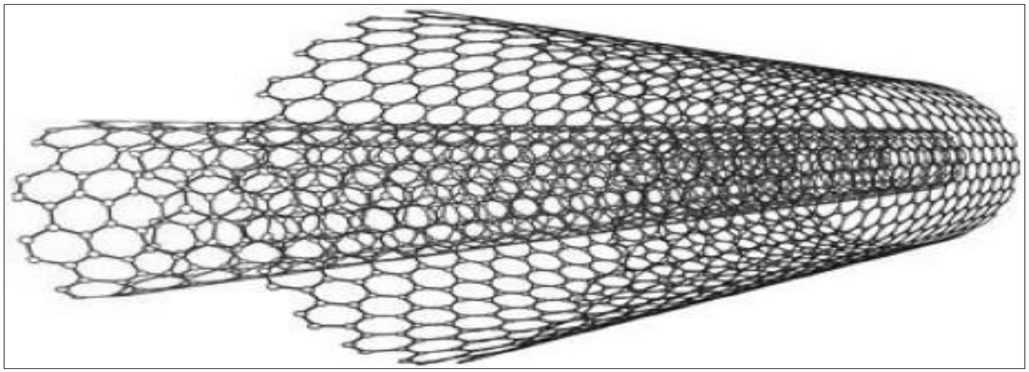
Figure:1 Single-walled carbon nanotube



5.2 Double-walled CNTs

Since the name is given, this CNT is comprised of two concentric CNTs where an external layer of the carbon chamber is completely encased inside the internal chamber (outside cylinder is encased in inside cylinder).[7]

Figure:2 Double-walled carbon nanotube [7]

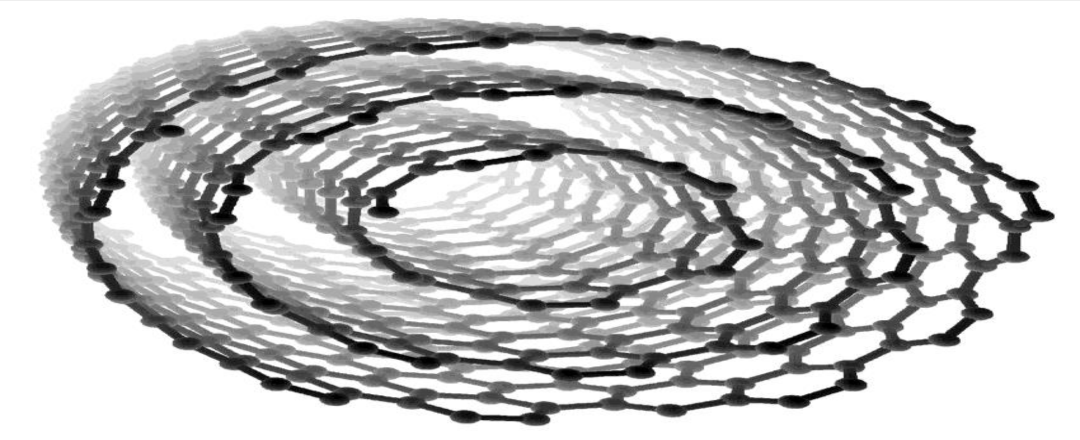


No catalyst is needed for its synthesis. MWCTs are highly pure and structurally complex. It's not easy to twist [4,5]

5.3 Multi-walled CNTs

MWCNTs have a multilayer of graphene move upon one another, having a width of 2-50 nm which depends upon the quantity of graphene cylinder present and the separation between this graphene cylinders is 0.34 nm. In the amalgamation of MWCNTs, they don't require any impetus and can be delivered by the mass union, having greater virtue then SWCNTs.[4, 5,6]

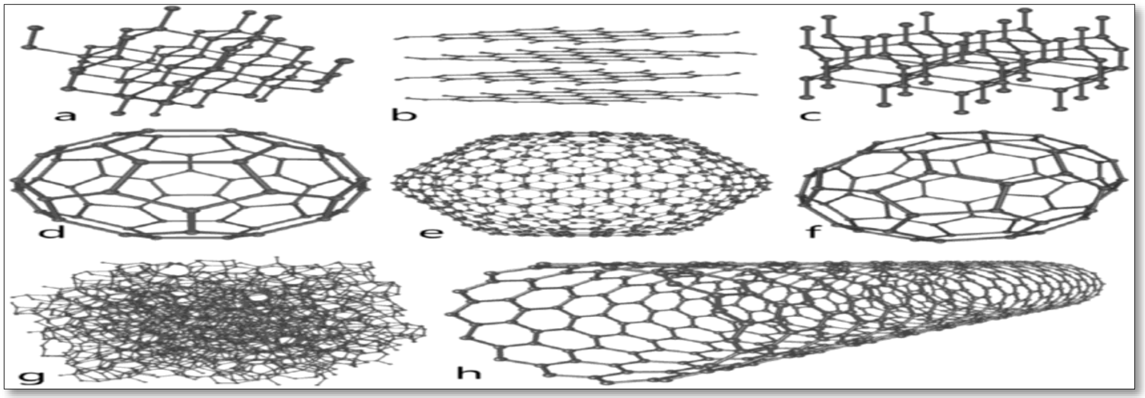
Figure: 3 Multi-walled carbon nanotube (ChemDraw)



6. STRUCTURE OF CNTs

CNTs are composed entirely of carbon, and SWCNT clean structure is described as roll-up, a tubular covering, a single layer of graphene piece and developed as of benzene category of hexagonal round carbon atoms. CNTs have distance end to end ratio between 1000, having a one-dimensional structure. The graphene sheet is a specific cylinder produced from the drill pattern, which represents a solo level of crystalline carbon. SWCNTs are consisting of two different ranges along with two different properties like physical properties and chemical properties. In which, the initial range is sidewall on the cylinder and another known as ending lid of the cylinder. The ending lid composition is the same as fullerene, they know as small molecule of fullerene (example- C_{60}). SWCNTs contain only 10 atoms, which surround the circumference, having only 1 atom thickness. MWCNTs are larger in structure along with multiple tubes arrange in one upon other, where the inside tube is completely covered with the outside tube making a multiple tube structure. MWCNTs are limited to the nanostructure with outer diameter should be less than 1nm if the diameter is more than 15 nm then it's known as carbon nanofibers. CNTs are different from carbon fibers, which are not single molecules but a strand of larger- layer graphite sheet.

Figure: 4 Eight allotropes of carbon a) diamond, b) graphite, c) lonsdaleite, d) C60 buckminsterfullerene, e) C540, Fullerite f) C70, g) amorphous carbon, and h) single-walled carbon nanotube [4]



Based on the different essential structures, CNTs are divided into three different classes. The first one is a zigzag carbon nanotube, the second one is chiral carbon nanotubes and the third one is an armchair carbon nanotube. They are made up of the way graphite is roll-on throughout its formation procedure. SWCNTs type is based on the rolling alignment of the relative member to a hexagonal complex of graphene's piece along with the radius of the closed cylinder.[1 ,4]

7. PRODUCTION METHODS OF CNTs

7.1 Arc Discharge production method

7.2 Laser Ablation production Method

7.3 Chemical steam deposition or vapor deposition

7.4 Vapor – phase growth

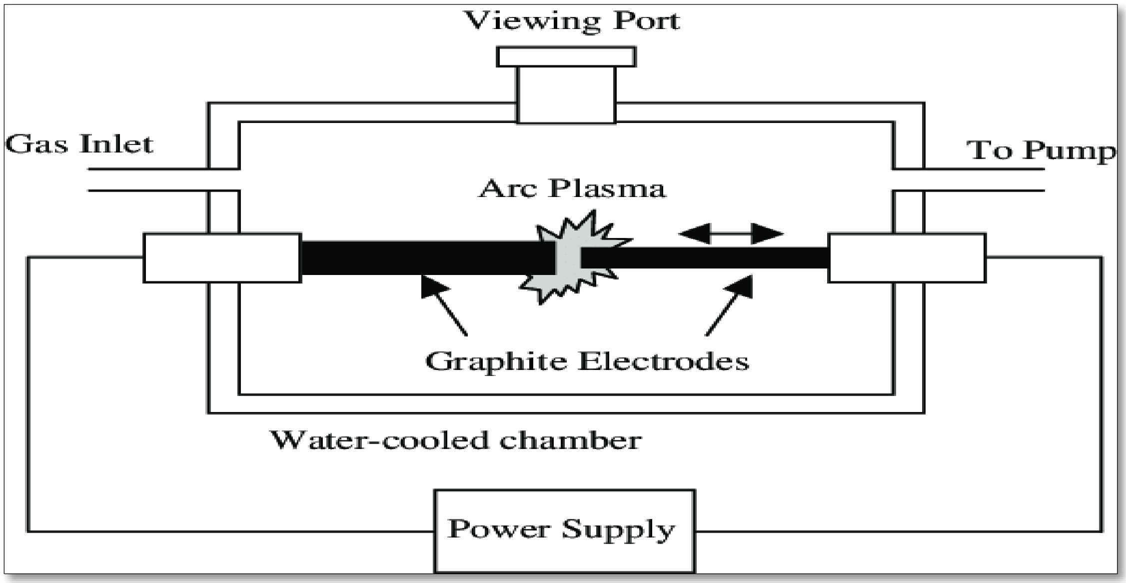
7.5 Flame synthesis method

7.6 The recent trend in the synthesis of CNTs

7.1 Arc discharge production method

Arc evaporation production technique is known as the best technique to produce the greatest quality of CNTs, It involves the passage of the current into two separate graphite electrodes having helium environment and the current passing between this electrode is 50 amps. Because of it, graphite will vaporization, which leads to condense of graphite on the wall of chemical reaction pan and other substances will condense on the cathode electrode.[8] This substance is accumulated on cathode known as CNTs. SWCNTs obtained after the addition of Copper (Co), Nickel (Ni) and additional metal on anode electrode.

Figure: 5 Graphic representation of arc- discharge equipment



Source: Research Gate

This method is known from the year 1950, with the aim of CNTs produces through the passage of carbon holding gas, like hydrocarbon, in excess of catalyst. The catalyst made up of nano-sized atoms of metal like Ferrous, Copper or Nickel. Nanosize atom catalyzes lead to degeneration of gaseous molecule in carbon, which leads to the generation of the tube with metal nanoparticles on the tip. [9]

In the year 1991, researcher Iijima informed the production of a new kind of limited carbon structure contains needle-type cylinders. This tubes synthesis with arc discharge disappearance production method, similar to the fullerene production. These carbon needles have a diameter range between 4- 30 nm and length equal to 1 mm, produce on the negative side of the electrode in this method, where negative carbon electrode use as a direct current supplier in a container containing argon gas which leads to vaporization(arc discharge) of carbon. Arc discharge production technique used to manufacture SWCNTs on a large scale. Big -level production of MWCNT using a variation of typical arc discharge production technique informed by researcher Ebbesen and researcher Ajayan in the year 1992.[10]

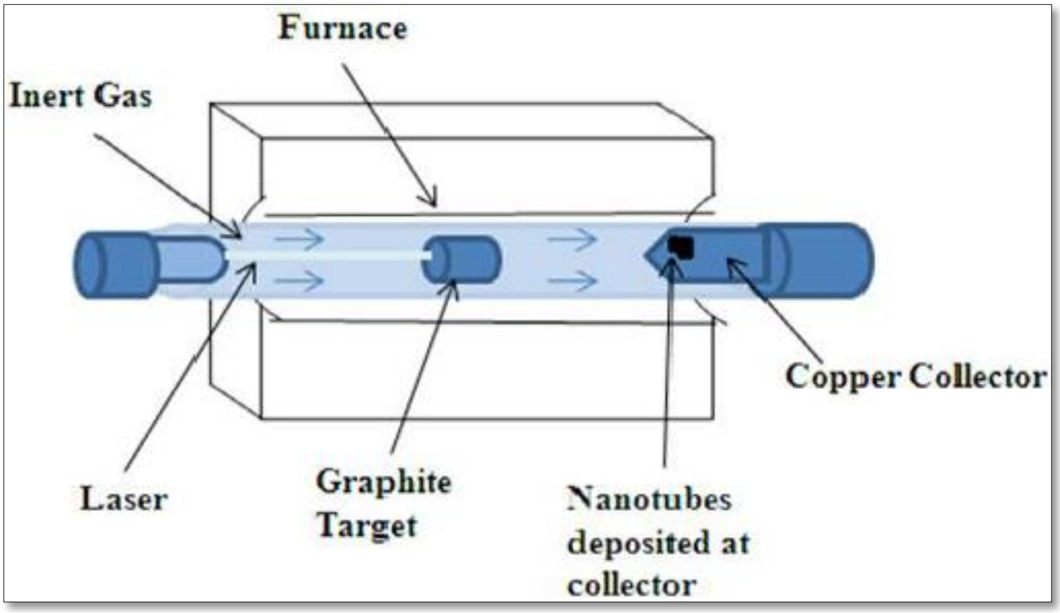
Researcher (C. Somu et.al.) has worked on the Synthesis of various forms of carbon nanotubes by arc discharge methods. Where he gave a review on a detailed analysis of Carbon Nanotubes synthesis developments over the past using the Arc Discharge process. It was seen that the main synthesis method for both SWCNTs and MWCNTs emerged after the discovery of CNTs by Ijima arc discharge.

It was seen that the carbonaceous matter was deposited mostly on the electrode with the lower current density i.e. with a larger diameter during a DC arc discharge process. If we use the AC arc discharge method with two equivalent electrodes, however, we are sure to find that the soot is deposited on the wall instead of the electrode, thereby increasing the yield of SWCNTs.In addition to the others, extremely careful conditions led to the formation of DWCNTs, so this method was a tool for the production of DWCNTs. It is also shown that the yield of the MWCNTs in the presence of liquid nitrogen increases. The yield of the SWCNTs and DWCNTs has been significantly improved by rotating the Anode i.e. Use the method of spinning plasma. It has also been found that there has been an improvement in the synthesis and purity of SWCNTs with the temperature increase up to 6000C.[11]

7.2 Laser Ablation Method

In the year 1996, researcher Smalley and coworkers produce a large number of SWCNTs using a laser ablation production technique in which graphite rod have a small quantity of Nickel and Copper at 12000C high temperature.[12] The cylinder continues to grow until a large number of catalyst atoms gather on the ending point of the nanotube. Bigger particle removes or turns into more- coated during tolerable carbon that becomes toxic to catalysis.[13] This process allows the elimination of the tube along with a fullerene-alike tip or else elimination along with a catalyst atom. Arc-discharge technique and laser-ablation technique both systems contain the benefit of large amounts of SWCNT production and having the drawback of its dependence upon vaporization of carbon particle from the solid objective at 3000.0C temperatures, and tubes are disorganized which makes defaulting in the purification process of the CNTs along with the application of CNT samples.[12]

Figure: 6 Schematic representation of laser ablation equipment [14]



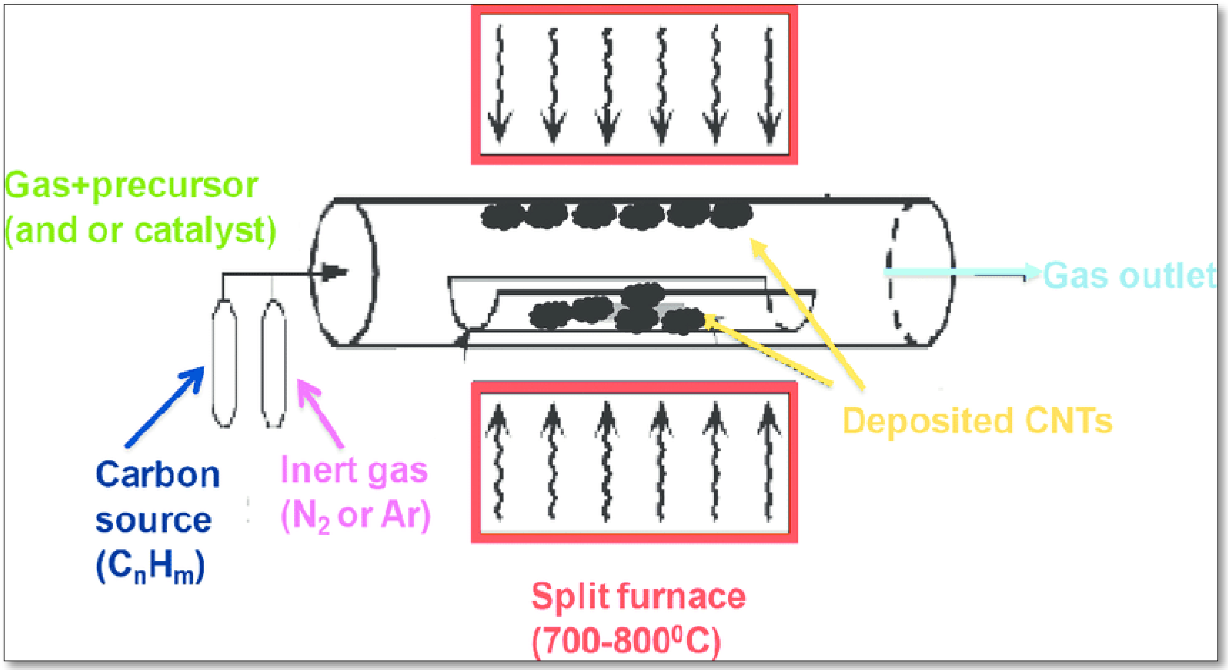
Researcher (Mitsuhiro K.*et.al.*) has worked on the production of single-wall carbon nanotubes by a XeCl excimer laser ablation. Possible mechanisms of growth were provided for pulsed and laser excitations. In order to prepare single-walled carbon nanotubes, different types of lasers are now widely used. For the synthesis of CNTs, a XeCl excimer laser with the oscillation wavelength was used in the UV field. The frequency of the oscillation and the duration of the pulse (FWHM) are 308 nm and 16 ns. The average energy is 58 mJ / pulse and the variability during the ablation is T0.5 percent. The chamber used for laser ablation is a 51 mm diameter ceramic pipe inserted in the center of an electric furnace with a maximum temperature of 1773 K available. A graphite target of 1.2%

Ni and 1.2% Co was put in the quartz tube with a diameter of 8 mm inserted in the ceramic tube mentioned above. It was found that SWNTs were formed at 1273 K, 1373 K, 1473 K and 1623 K in ablated carbonaceous soot. The 1623 K ablation recorded the highest SWNT yield. Raman spectroscopy and scanning and transmission electron microscopy estimated the diameter distribution and the length between 1.2 nm and 1.7 nm and 2 Am or above.[15]

7.3 Chemical Vapor deposition method

From the above production methods, two primary troubles are associated. The first one is the understanding of big- scale manufacturing and the second one is prearranged production. During the year 1996, CVD (chemical stem\vapor deposition) technique was invented for production nanotube. It's a technique developed to overcome the problem associated with the above two methods. It has the capability of both controlling the development path above the substrate and produced a large number of CNTs. through this method, a combination of hydrocarbon gas, $CH_{3,}$ acetylene, or else combination of ethylene and N_2 is inserting into reaction slab.[16] Throughout the reaction, CNTs obtaining on the substrate through the decay of hydrocarbon at high temperatures up to 700°C to 900°C at full of atmosphere force.[17]

Figure: 7 Schematic representation of Chemical Vapor Deposition [19]



This method has two main advantages. The first one it obtain CNTs at low temperature, even though in minor quality, and the second one is withdrawn of catalyst above the substrate, which permits CNTs to implement well-planned structures. [16]

Researcher (Sunny E.I *et.al*,) has worked on Catalytic Production of Carbon Nanotubes in a Swirled Fluid Chemical Vapor Deposition Reactor. The catalytic chemical vapor deposition process, catalytic carbon graphitization was used to illustrate the synthesis of acetylene carbon nanotubes. A basic kinetic mechanism and model described the catalytic graphitization of carbon to CNTs from C2H2 and graphite using the

CCVD process. Catalytic graphitization of C2H2 to CNTs using the CCVD technique was used to synthesize CNTs and nanoparticles at various temperatures of 850–1100 C and atmospheric pressure, and the kinetic model was obtained using the Langmuir-Hinshelwood method. At 11000 C, an optimal output level of 8.2 mg / s and 4725 ppm of acetylene feed was reached. The production rate of CNTs decreased as the hydrogen flow rate increased. The equations and experiments of the computed model are in good conformity.[18]

7.4 Vapor- phase growth production method

It,s a new method also known as the converted type of CVD technique. Central dissimilarity in this technique is CNTs produced straight from reaction gas plus catalytic metal within the slab, not including any substrate. Two heating system is located within the reaction slab. Catalyst use inside this process is ferrocene. Carbon catalytic vaporization is maintaining a small temperature in the initial furnace. Fine catalytic atoms are produced now and after they arrive at the subsequent furnace, at that time fresh carbons absorbed within this medium through diffusion, where they transformed into CNTs [10,20]

7.5 The flame synthesis production method

The flame synthesis technique is another method where CNTs able to produce. During this technique, hydrocarbon blazes re-used. These blazes give out beginning growths of nanotubes. A gas such as carbon monoxide, methane, $C_2H_{4,}$ ethane, and C_2H_6, they present inside the after-flame portion and have a great source for carbon. This reaction is exoergic and releases chemical power within the outline of heat which assists inside blaze which holds endothermic carbon displacement reactions. Catalysts are necessary for the supply reaction place for the deposition of rock-solid black carbon. CNTs grow in this method is a similar way as inside CVD methods. In a suitable catalyst, flame and reaction condition is supplier, a big quantity of CNTs can produce commercially.[21]

Researcher (Yuan-Yao Li*et.et.al*) has worked on the Synthesis of Carbon Nanocapsules and carbon nanotubes by an acetylene flame method where he investigated the production of Carbon Nanocapsules and carbon nanotubes (CNTs) using a system of acetylene flame. In a well-controlled combustion process, MWNTs with a diameter ranging from 20 to 30 nm were successfully synthesized with the presence of CoCl2 catalysts in the reaction. The temperature of the reaction played an important role in MWNT synthesis. Besides the MWNTs, the method is capable of producing Nanocapsules of carbon without the involvement of a catalyst. [22]

7.6 Current trend into the production of CNTs

Modern nebulizer spray pyrolysis technique has been utilizing for production for MWCNTs. Nebulizer spray is a primary factor in this technique, where it’s obtained through the particular ultrasonic atomization method. MWCNTs have been produced through this technique with objectively homogeneous diameters within range bunches. (Yamaguchi T *et.al*, 2004) Utilization of ultrasonic nebulizer, where ferrocene used as catalyst, ethanol used as a solvent and carbon supply sprayed inside the tubular heating system at 800^0C set temperature underneath argon movement within 1 L/min range. Ethanol used as a solvent and carbon supplement because of its muddy characterization, less cost, nontoxic by-product, and it easily can be handle. Elevated development of MWCNTs on the surface is formed. The benefit of using nebulizer spray is, it’s simple for production into industrial level manufacturing because reactants continuously fed into the furnace.[23]

8. FUNCTIONALIZATIONOF CNTs

CNTs are material virtually insoluble, or else barely dispersed, in solvents. To incorporate CNTs technology with biological background, the solubility of tubes mainly inside aqueous solutions should enhance. Numbers of dispersion and solubilization methods are examined and mainly two approaches are presented.[24] The first approach is a procedure made up of the non-covalent bond functionalization CNTs by surface-active agents, peptide, polymer, nucleic acids, and oligomers. The merit of this procedure is the protection of the electronic structure of the aromatic surface of the nanotube. Its Characterization has fundamental importance for the use of CNTs like biosensors. The second approaches are to stand on CNT's covalent bond functionalization. Initial, CNTs are cut and pass through the oxidization process to produce a number of CNTs moreover it's derivative with dissimilar kinds of molecules. Nanotubes wall-sides work straight through adding reactions. The introduction of moieties on the outer surface of CNTs leads to induce repulsion among single CNTs permit them normally disperse inside solvents.[25]

Four basic approaches have been used to obtain dispersion**;**

8.1 Non-covalent bond functionalization

Many small or large molecules of drugs are adsorbed non-covalently over the wall layer of the CNTs. Therefore, via host-guest interaction, CNTs act as nano-reservoirs to absorb the drug molecule. The adsorption is a hydrophobic type. There are π-π stacking interactions between the CNTs and the adsorbed molecules of the chain. The hydrophobic force exists for loading drug molecules onto the CNTs in the case of lipophilic drug molecules. The voltage on the surface of CNTs induces the adsorption of charged molecules by ionic interactions due to chemical treatment. [26]

8.2 Covalent bond functionalization

The mixture of drug molecules or functional groups is comparatively safer in the covalent functionalization of CNTs.Covalent functionalization of CNTs, produced by oxidation of CNTs by strong acids, induce reduction and produce groups of carboxylic acids, resulting in increased dispensability in the aqueous medium. Alternatively, they are water-soluble by adding hydrophilic groups to the external walls and tips of CNTs.Covalent functionalization of CNTs is commonly used for drugs such as methotrexate and reactions to 1,3-cycloaddition. Characterizing covalent functionalized CNTs for accurate determination of the location of functionalization and mode of addition is a difficult task. [27]

8.3 Dispersion of CNTs using surfactant

Surface active agents used for nanotubes dispersion inside polymeric resources. Main surface-active agents for example polyethylene glycol, sodium decyl-sulfate, and dodecyl-benzene sodium sulfonate mostly use to decrease lump disposition of nanotubes inside the water and similar solvents. The high dispersive efficiency of CNTs depends upon the presence of benzene rings. To increase in adsorption ratio of surfactants, P- stacking interaction of benzene ring on the surface of CNTs sidewall is required. The figure demonstrates the mechanism through which surface-active agents micelles defeat weak Van der Waal’s bonds.[28]

9. PROPERTIES OF CNTs

CNTs have an extremely elevated surface region, high phase ratios, and superior mechanical resistance. CNTs tensile power is 100 times greater than that of steel, and the coppers have an approach to electrical and thermal conductivity. These specific properties make CNTs excellent candidates for registered appropriate buyer products as a cartridge in various polymers and pots. It was also anticipated that CNT-based on the field-effect transistors (FETs) will quickly be giving their analog counterparts based on silicon. Because of their special electrical, mechanical as well as thermal behavior, CNTs are also superior encapsulating agents. [29, 30]

9.1 Electrical characteristics of CNTs [29, 30]

CNTs have chiral-shaped electrical characteristics. Researchers have demonstrated that CNTs have particular conductive characteristics. These were the foremost findings to propose that the electronic characteristics of CNTs are more influenced by geometric variations such as defects, chirality, distinct size ranges, and crystalline tubular structure. SWCNTs are resistivity-type metals ranging between 0.34 × 10–4 to 1.0 × 10–4 ohm-cm from carbon atom bonding within. CNTs, prearranged in a hexagonal pattern, every carbon atom is covalently linked by sp2 molecular hybridization to three distinct neighboring carbons. Thus, in all parts, the fourth valence e- leftovers free, and these free e- are arranged in an irregular pattern across all atoms, giving the electrical behavior of CNTs. CNTs can be applied in sophisticated electronics in transistors and further switching applications. The significant aspect of CNT emitters is that at a reduced voltage the discharge can be achieved.

9.2 Mechanical characteristics of CNTs

As of now, CNTs are the most grounded issue in disposition. The audit of the writing says CNTs are well-manufactured materials, especially inside the pivotal course. The Young's modulus esteems under 270 to 950 GPA and having high pliable power in the middle of 11–63 GPA. Such a significant number of data have appeared in the spiral course that, CNTs be moldable. The underlying outspread adaptability TEM study demonstrated that two nearby nanotubes be fit for distorted by the powers of Vander Waal.[31] Later than that, independent gatherings of researchers directed Nano-cooperation through a nuclear power magnifying instrument (AFM) to quantitatively assess the spiral adaptability of MWCNTs and tapping technique, where AFM was connected to watch SWCNTs. The discoveries saw that in the outspread course, CNTs are inconceivably smooth. CNTs outspread course adaptability is required, principally for the production of CNT Nano measured material even its mechanical qualities, where coordinated funnels are acquainted with significant crossways stress when an intertwined design is pressurized. Because of one of the unbelievably solid holdings in nature is the carbon-carbon bonding found inside graphite, CNTs have amazingly brilliant power as they are the hardest game plan still delivered by any analyst.[32]

Material	**Young's modulus** (GPa)	**Tensile Strength** (GPa)	**Density** (g/cm3)
Single wall nanotube	1054	150	N/A
Multiwall nanotube	1200	150	2.6
Steel	208	0.4	7.8
Epoxy	3.5	0.005	1.25

Wood	16	0.008	0.6

Table -1 Comparison of Mechanical Properties of CNTs with other string materials[33]

Looking at CNTs in TEM has uncovered that they are versatile and don't break when turning. Scientist Treacy, who originally estimated the amplitudes of warm vibrations in CNTs in the TEM technique, led the Underlying exertion to build up Young's modulus for each MWCNT.

They demonstrated that nanotubes having Y = 1 to 1.8 TPA modulus of mean Young modulus which is outstandingly enormous contrasted with generally open carbon filaments. The twisting capability of MWCNTs was legitimately dictated by various examination associations as a reason for substitution inside an AFM. It was found that the standards go for the Young module were between 0.32 to 1.47 TPA.[34] Scientist Falvo analyzed that these MWCNTs could be twisted at pointed edges without by an AFM tip to experience some configuration move. A single perfect nanotube is about 10 to 100 times stronger than steel per unit weight. The Young's modulus of the best nanotubes can be as high as 1000 GPA which is approximately 5x higher than steel. The tensile strength or breaking strain of nanotubes can be up to 63 GPa, around 50x higher than steel.[35]

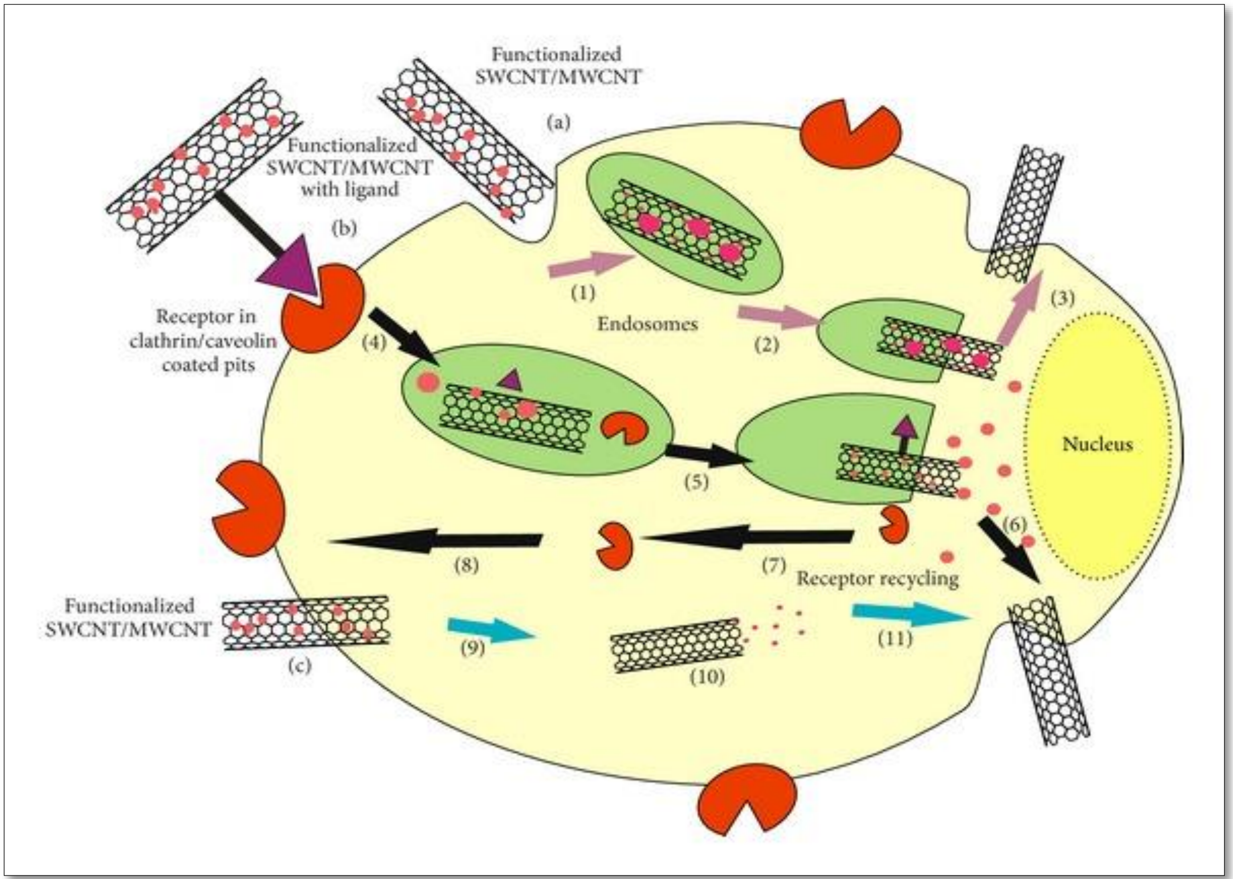
9.3 Thermal properties of CNTs

Not just due to their electronically just as mechanical attributes, however moreover because of warmth qualities, CNTs are of astounding criticalness and interest. Since their measurement is very minor, the quantum effects are basic and show straight proof of the 1-D gammadion of the phenomenon band arrangement in CNTs at abject temperature specific warmth and specific warm conductivity. The support of perfect and functionalized nanotubes in particular items that have the option to twofold the warm conductivity for a charge of only 1 percent, which demonstrates that blended nanotube segments can be useful for mechanical warm association importance.[32]

10. CELLULAR UPTAKE MECHANISM OF CNTs

It has been found that the internalized nanotubes at the cellular level are biocompatible and non-toxic. The advantages of SWCNTs and MWCNTs over other carriers are important due to their close-packed hexagonal cylindrical structure and sp2 hybridization, which makes them easy to work with the respective ligand or therapeutic mood. To conclude on the exact cellular uptake path of CNTs, it is thought that there are two different routes to cross the cell membrane. The first is the endocytosis-dependent pathway, which can be either mediated by a receptor or mediated by a non-receptor, and the second is based on an independent endocytosis pathway that includes diffusion, membrane fusion or direct transport of the extracellular material into the cell. The internalization cycle of CNTs depends on several parameters such as volume, distance, functional group nature, and hydrophobicity and CNT surface chemistry.[36] the endocytosis-dependent pathway is an energy- and temperature-dependent transport process involving the creation of a saccule or vesicle of extracellular materials within a segment of the cell membrane. In the case of receptor-mediated endocytosis legend, conjugated-drug-charged CNT binds to the complementary transmembrane receptor. Proteins and then enters the cell in clattering-coated vesicles as receptor-ligand complexes. [37] Following the development of internalization vesicles known as early endosomes and the ligand dissociates from the receptor due to a drop in pH. When the receptors are activated, the vesicles carrying the extracellular particle fuses with lysosomes and thus trigger the release of the drug particle by the action of lysozymes on the endosomes and the free receptors thus produced are recycled into the plasma membrane to combine with other ligand-conjugated CNTs.

Figure: 9 CNT Penetration pathways into the cell



(Source: Pubmed)[38]

(A) non-receptor-mediated endocytosis: (1) the membrane surrounding the drug-loaded with functional CNTs; (2) the internalization of the drug-loaded with CNTs; and (3) the release of the drug; (b) the receptor-mediated endocytosis: (4) the membrane surrounds the CNT-receptor conjugate by forming endosomes followed by internalization; (5) the release of the drug; and (6, 7, 8) the receptor regeneration;(C) independent endocytosis pathway: (9) direct drug-loaded penetration of functionalized CNT and (10) drug release.

11. PURIFICATION OF CNTs

Aromatic SWCNTs contain many impurities of carbon species such as unstructured carbons, carbon nanoparticles, and conversion metals which have been implemented as catalysts. Graphite as wrapped sheets, amorphous carbon, metal catalyst, and the lesser fullerene is the primary residual content in the aromatic carbon structure. These residue influence the Secant's required characteristics But it is necessary to get hold of SWCNTs in investigating, as pure as possible without affecting their properties. The SWCNT samples must also be as homogeneous as probable in order to improve comprehend the characterization.[39]

11.1 Oxidation

SWCNT's oxidative treatment is one of the best approaches to remove carbonaceous impurities and clear the metal surface. But the chief demerit of the oxidation reaction is not only the residual content is oxidized, however along with that the SWCNTs are also pass through the oxidization process. Though spoil to SWCNTs is fewer than spoil to the residue which makes this method helpful in some purification of CNTs. These impurities have an extra open constitution. One more reason why impurities oxidization is favored is that all these residues are mainly fond of metal catalysts and it acts as an oxidizing reagent. Effectiveness, as well as the yield of this method, be most reliable on factors like content of metal, time of oxidation, atmosphere as well as an oxidizing agent.[39]

11.2 Acid treatment

Basically, treatment shall acid will eliminate the catalyst of metal. In this method initially, the plane area of metal should be exposed via oxidization or sonication process. After that catalyst of metal, it comes in contact with acid even solvated too and SWCNTs remain in hang structure. While utilizing reaction in nitric acid, the acid merely has outcome over the catalyst of metal and there is no effect of NO_3 is observed. It has no consequence on SWCNTs and further particles like carbon it is one of the biggest advantages of this method.[34]

11.3 Annealing

Because of the higher temperatures range of CNTs between 873 – 1873 Kelvin, the nanotubes shall be repositioned moreover impurities will be devoured. Due to a higher temperature range, it could convert the graphite containing carbon and the tiny fullerenes with pyrolysis and in elevated temperature (1873 K) performing vacuum action may cause the metal melting and because of that, it can easily remove.[35]

11.4 Ultra sonication purification method

Within this method, particles were divided because of an ultrasonic tremble. Because of variable Agglomerate, Nano-sized particles shall force to induce vibration and because of this vibration, it will become further dispersed. The division of these Particles through its impurity is most reliant on the surface-active agent, vehicle and reagent utilized in method. The vehicle affects the steadiness of dispersing tubes within this process. Within poor vehicles, SWCNTs have high stable if they are fond of metal. When utilization of method is done; the purification of SWCNTs relies on the given time. While tubes come in contact with acid on behalf of a little time phase, after then barely solvates of metals are utilized, however, for higher contact time, tubes shall too be chemically cut and then applied.[39]

12 APPLICATION OF CNTs

Nanotechnology is the largest, latest and well-developed technology, having a lot of benefits intended for new materials among enhanced properties and be able to utilize in a number of applications in various fields like Nano-medicine, energy, chemical sensors moreover in aerospace technology.CNT is the most hopeful approach, ever since its invention in the year 1991 via researcher Iijima.[4] Several scientists moreover researchers have devoted enough attempt to the development of the new properties and to increase the numerous novel applications use in different areas like materials science even in electronics and energy storage, where the main focused is on studies of nanotechnology and utilization of CNTs as fillers.[1,2]

12.1 CNTs as gene delivery platform

Nanotubes are used as a medium of genes (gene therapy) for the treatment of cancer and genetic disorders due to their special cylindrical shape and properties. These have been confirmed by their tubular existence as a vector for gene therapy.[40] Before being killed by the cell defense system, nanotubes complexed with DNA are found to release DNA, dramatically improving transfection. In respiratory syncytial virus

(RSV), a virus with severe bronchitis and asthma, nanostructures have an antiviral effect. In general, the treatment is done by combining nanoparticles with technologies for gene slicing. Here RNA fragments capable of inhibiting a protein (needed to multiply the virus) are encapsulated in nanotubes and administered as nasal sprays or drops. The promising results have been noted inhibiting further growth of the virus. For helical crystallization of proteins and growth of embryonic rat brain neurons, nanotubes are recorded. With 1-pyrene botanic acid and succinimidyl ester, streptavidin protein is successfully immobilized on CNT. Nanotubes and Nano horns can adhere to different antigens on their surface, thus acting in vaccines as a source of antigen.[41]

12.2 CNTs as Carrier for drug delivery

CNTs are examined among Amphotericin B targeting to various cells. A drug like cisplatin encapsulated oxidized SWCNHs have reported slowing discharge of Cisplatin in an aqueous environment. Discharge of Cisplatin has been efficient in discontinuing the enlargement of human lung cancer cells, where SWCNHs has been used as a carrier system that only did not demonstrate anticancer efficiency. The drug used in cancer like Polyphosphazene platinum known by CNTs had improved permeation, distribution and maintenance of the drug in the brain tumor because of controlled lipophobicity of CNTs. An antibiotic like Doxorubicin specified with CNTs is observed for the enhancement of permeation and the intracellular component. A mixture of gelatin CNTs used as hydro-gel and has been used as an important carrier system for biomedicine. The carrier system based on CNTs may be used as a victorious administration by the oral route of Erythropoietin (EPO), and it is not feasible due to the denaturation of erythropoietin by the GIT situations moreover enzymes.[10]

Researcher (Zhuang Liu et al.,) has work Drug Delivery with Carbon Nanotubes for In vivo Cancer Treatment. In tumor-targeted accumulation in mice, chemical-functional single-walled carbon nanotubes (SWNT) have shown promise and show biocompatibility, excretion, and low toxicity. Where they used paclitaxel (PTX), a widely used cancer chemotherapy drug, is conjugated to branch polyethylene glycol chains on SWNTs to obtain a water-soluble SWNT-PTX conjugate by means of a cleavable ester bond. WNT-PTX provides higher efficacy in suppressing tumor growth than clinical Taxol in a murine 4T1 model of breast cancer as a result of prolonged blood circulation and 10-fold higher PTX tumor uptake through SWNT delivery, likely through increased permeability and retention. Pharmaceutical molecules carried into the reticuloendothelial system are released from SWNTs and excreted through the biliary Pathway without having noticeable toxic effects on healthy organs.[42]

12.3 CNTs as filler

CNTs are utilized as fillers inside different assets to shape Nano-compound are principally formed and accomplishment into nanotechnology. Researchers are chipping away at Nano-composite so they can utilize carbon nanotubes the same as filler in numerous materials. The primary reason for carbon nanotubes' embodiment inside divergent polymeric and further assets is to redesign properties of these assets. Analyst Garcia-Gutierrez has arranged Melt-prepared infused shaped in which poly-butylene terephthalate utilized as polymer moreover SWCNTs nanocomposites are utilized as embodying specialist and this procedure will impact on polymer frame of mind during shearing with the format the crystallization conduct of PBT. Specialist Soichia establishes elasticity and yield quality expanded with an expansion of SWCNT stacking inside polyimide Nano-composite.[43] With great scattering, they additionally improve the mechanical assets of polyimide. The PA66 materials were implanted onto the outside of MWCNTs. In which the chain span of PA diminished with an expansion of MWCNTs, the warm rot temperature of PA-MWCNTs was advanced than unadulterated PA66 composite, and capacity quality was improved through expansion of MWCNTs.[39]

Researcher S. Peeterbroeck has prepared A new type of materials using direct melt mixing, based on EVA, clays and multi-walled carbon nanotubes. The presence of nanofillers has improved both the thermal and mechanical properties of the resulting modern binary and ternary nanocomposites. By incorporating organo-modified clays and carbon nanotubes together, a synergistic effect is observed: the thermal and flame retardant properties of the corresponding EVA matrices are improved.[44]

12.4 Artificial Implants

Normally the body cannot accept implants, it shows refusal response for implants during after administration ache. Because of its small diameter CNTs can attach among further proteins plus amino acids and avoid refusal of Implants. CNTs utilize like implants in the shape of synthetic joints devoid of human body refusal response. Because of high tensile power, CNTs filled easily with calcium along with easily arranged inside the organization of bone and it serves as a bone surrogate. [39]

Researcher Vohrer U. has work on a huge variety of industrial applications, low voltage artificial muscles which has great importance. Carbon nanotube sheets also are known as bucky paper with suitable electromechanical properties were described. An experimental set-up has been developed that allows the analysis of actuation forces vertically to the sheet plane for the first time. The filtration technique used single-walled carbon nanotubes (SWNT) from the arc discharge or HiPco process as well as multi-walled carbon nanotubes (MWNT) as received or after further purification steps. Many parameters affect the electromechanical properties such as the sheet size, the electrolyte used, the voltage applied, etc. However, the nanotube material itself and the procedure for the production of bucky paper must also be considered intensively to avoid large differences between different batches and to produce indiscriminate and reproducible nanotube carbon sheets. [45]

12.5 CNTs as a Catalyst

CNTs can act as a catalyst, by encapsulation of catalyst at the molecular level in a large quantity and after the administration of CNTs, it will release in the required rate and at the required time. Which leads to a reduction of frequency and quantity of catalyst.[2]

Researcher Avelino C. has worked on Catalytic activity of palladium supported on single-wall carbon nanotubes compared to palladium supported on activated carbon Study of the Heck and Suzuki couplings, aerobic alcohol oxidation and selective hydrogenation. Palladium nanoparticles (2–10 nm) were deposited on single-wall carbon nanotubes (SWNT) by spontaneous reduction of Pd(OAc)2 or oxime carbapalladacycle. For the Heck reaction of styrene and iodobenzene and for the Suzuki coupling of phenylboronic and iodobenzene, these catalysts have higher catalytic activity than palladium over activated carbon (Pd / C). This fact was attributed as reflecting the size particle's dramatic influence on the palladium catalyst activity for C-C bond forming reactions compared to other less demanding reaction types from the particle size point of view. In comparison to the reactions of Heck and Suzuki, Pd / C is more active than palladium nanoparticles deposited on SWNT for catalytic oxidation of cinnamaldehyde by molecular oxygen and 3-phenylpropionate aldehyde hydrogenation.[46]

12.6 Preservative

CNTs go about as a cancer prevention agent in nature. Therefore, they are utilized to shield drug definitions from antimicrobial development and oxidation. In view of their cell reinforcement property, they are utilized in anti-aging beauty care products and with ZnO, they are utilized like sunscreen dermatological for counteracting the oxidation of makeup definition. [1, 2, 4]

CNTs as a Diagnostic Tool

Protein-consolidated otherwise protein-compound packed CNTs, in light of the fact that their fluorescence limit in presence of bio-particles has been utilized like implantable biosensor. Indeed, even in Nano-capsules pack with attractive materials and radioisotope chemicals can be utilized as biosensors. Nano-size machines and engines with CNTs can be utilized in the investigation of cells and organic frameworks. [47]

Researcher Shun-Rong Ji has given a review on Carbon nanotubes in cancer diagnosis and therapy. Carbon nanotubes (CNTs) have become a popular tool in cancer diagnosis and therapy because of their unique physicochemical properties. These are known to be one of the most promising nanomaterials with the potential to both identify cancer cells and supply these cells with drugs or small therapeutic molecules. They are considered to be one of the most promising nanomaterials with the ability to both detect cancer cells and supply these cells with drugs or small therapeutic molecules. CNTs have been explored in almost every form of cancer treatment over the past several years, including drug delivery, lymphatic targeted chemotherapy, therapy, photodynamic therapy, and gene therapy. Surgery continues to play a major role in early cancer survival through the removal of observable tumors among all cancer treatment options such as surgery, chemotherapy, radiotherapy, thermotherapy, and immunotherapy, etc. Patients with advanced cancer, palliative surgery, chemotherapy, and radiotherapy are required. Even in patients with radical tumor resection, radiochemotherapy and other therapies are sometimes prescribed to avoid residual micrometastases relapse.[48]

12.7 CNTs in engineering

In hereditary designing, CNTs are utilized to misuse genomes and particles in the advancement of bioimaging genomes, proteomics and tissue building. As a result of their cylindrical nature, it has demonstrated that they are utilized as a vector in quality treatment. The DNA breeze around SWCNT by interfacing its particular nucleosides and change in its electrostatic properties. This nature of CNTs makes its potential application in diagnostics and therapeutics. [49]

Researcher Sheetal Gavankar has worked on The Role of Scale and Technology Maturity in Life Cycle Assessment of Emerging Technologies. Where she study the Life cycle assessment (LCA) was applied to evaluate emerging technologies, where there is usually a lack of large-scale production data. This research presents a structured scheme for preparation levels of technology and production to contextualize the development stage of technology. The carbon nanotube (CNT) LCA found that irrespective of the synthesis technique, the production of CNT would become less energy-intensive with higher readiness levels. They examine the effect of production volume on LCA results was analyzed using primary data from a commercial CNT manufacturer with a production volume of approximately 100 grams per day and the engineering design of a scaled-up process with a production capacity of 1 ton per day. This study shows that LCAs on emerging technologies based on outdated data should be viewed in accordance with their readiness levels of technology and manufacturing and highlights the need to standardize and communicate information in life cycle procurement processes on these readiness levels and scale of output. [50]

12.8 CNS as a sensor

Sensors are a distinguishing gadget that is utilized generally in various fields. CNTs are utilized to improve the effectiveness of biosensors and sub-atomic sensors by joining them. Researcher Wood and Wagner presumed that CNTs are exceptionally delicate to polymer-inserting forms, on the grounds that the CNTs somewhat disfigure within the sight of various fluid media.[1,2,4]

Researcher Giovanni N has worked on The controlled deposition of metal oxides onto carbon nanotubes by atomic layer deposition: examples and a case study on the application of V2O4 coated nanotubes in gas sensing. Where they research on the manufacture of composites of metal oxide–CNTs, a newly introduced atomic layer deposition method was used. The reaction of a metal alkoxide with acetic acid in ALD has been shown to result in a homogeneous coating of the outer and inner surface of the carbon nanotubes at a well-controlled thickness. The electrical and gas sensing properties of the nano heterostructures of V2O4–CNTs synthesized under this protocol have been investigated. Composite sensors showed better performance than uncoated CNTs-based sensors, indicating that the strict contacts between V2O4 coating and CNTs lead to improving sensing performance. The sensors ' thermal treatment plays a key role. Indeed, both the as-deposited film's basic resistance and the sensitivity to NO2 increase by adequate pretreatment of the sensors in the air at temperatures between 150 and 200 1C. This suggests that the sensor response can be further improved by optimizing the expansion of the depletion layer with respect to the thickness of the multi-walled CNTs. By a suitable in-situ thermal treatment, the electrical properties of the vanadium oxide-carbon nanotube composite can be finely tuned. [51]

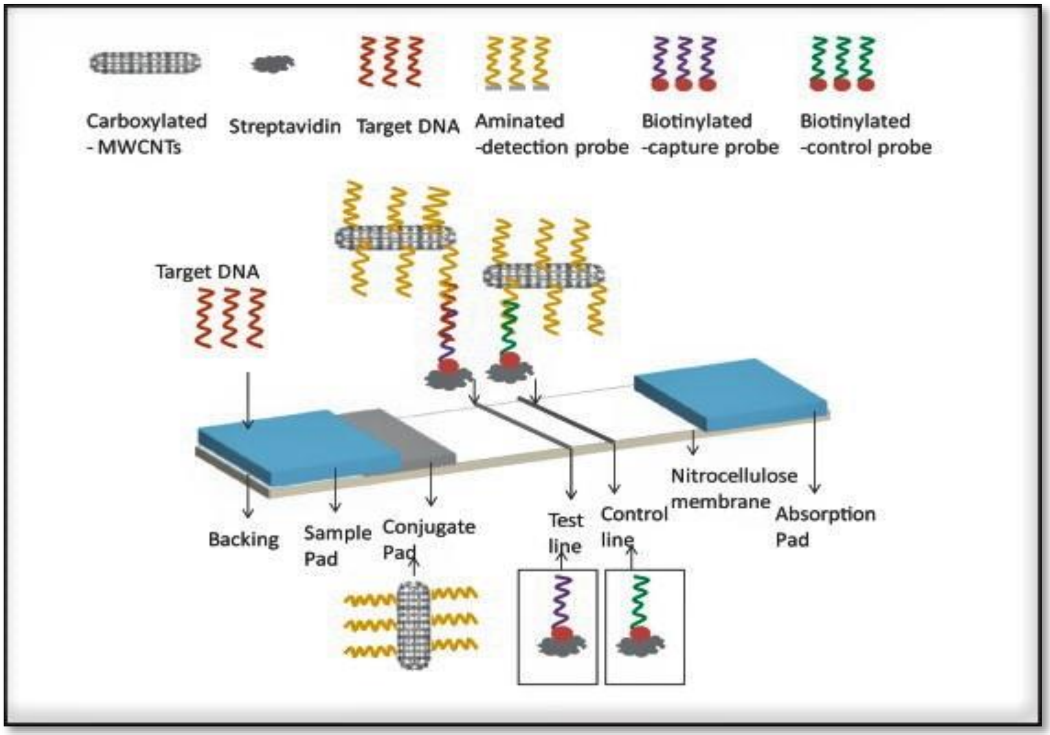
12.8.1 Adsorption mechanism of CNTs as sensors

CNTs are a new type of adsorbent and for many reasons have a significant position in carbon-based sensor materials. Secondly, they have chemically inert surfaces and highly specific surfaces for physical adsorption, offering directly a variety of well-defined adsorption sites for adsorbed molecules.[52] Different load distribution resulting from the transfer of load and different adsorption energy attributed to gas morphology coexisted in the adsorption process provide a qualitative and quantitative explanation for the increased or decreased conductivity of the CNT sensor gas adsorption experiment, and it separates the particular gas from the others [53]

12.8.2 CNTs as DNA detection sensors

Researcher W. Qiu has worked on Carbon nanotube-based lateral flow biosensor for sensitive and rapid detection of DNA sequence, where he gives the principle of proof-of-concept by a target DNA and a pair of DNA samples that are identical to the target DNA in two different locations. The sample solution with target DNA has usually been added to the sample surface. The solution subsequently migrated by capillary action, then the hybridization reactions between the target DNA and the MWCNTs–DNA conjugate detection DNA sample occurred, and the shaped complexes (MWCNTs–DNA–target DNA) proceeded to migrate along the line. Upon entering the test zone, the complexes were captured in the second h by the biotinylated capture DNA sample immobilized in the test zone. Due to the accumulation of MWCNTs on the test zone, a typical black band could be observed. Once the solution passed through the control zone, the biotinylated control DNA probe collected the excess MWCNTs – DNA conjugates, thereby creating a second black band. Only the black band in the control zone is observed in the absence of target DNA. In this case, the control zone's black band (control line) shows the LFB is working properly. Simply observe the color shift of the test zone and quantitative analysis is done by analyzing the LFB picture images with Image J software. [54]

Figure: 10 Schematic representation of the principle of DNA measurement on MWCNT-based lateral flow biosensor [54]



13. LIMITATION OF CNTs [55, 56]

- CNTs have an absence of dissolvability in many solvents good with the organic condition most likely watery based.
- CNTs can be created just in the event that they are basically and synthetically reproducible bunches with indistinguishable attributes.
- CNTs are trouble in keeping up high caliber and least polluting influences

14. METHODS FOR OPENING, FILLING AND CAPPING OF CNTs [57, 58]

Carbon nanotubes are capped and thus there are essentially two approaches for drug loading that include carbon nanotubes being filled during synthesis or after synthesis. Adding the contents of the in-situ nanotubes appears to be a less efficient approach, yielding about 10% while the post-synthesis process can be better controlled and yields of 50-100% can be achieved. The effective method depends on the material to be introduced into the CNT. Melting temperature, reactivity, surface tension, and product resistance are included in the parameters. Post-synthesis processing of CNTs means that the ends must be opened. This can be done by passing electrical currents through the CNT, by hitting the CNT with acid that most corrodes the twisted sections of the tube (i.e. the ends), or by oxidizing with carbon dioxide. Including foreign particles in CNTs are two forms. One classification is decoration, which is the bonding mechanism between a functional unit and CNTs.[57] This is difficult as carbon is rather inert, so a more reactive attachment surface is formed by oxidization. The functional unit is bonded either inside or outside the walls. Capillarity is the most common mechanism to fill CNTs. The capillarity limiting factor is the diameter of the CNT and the material's surface tension. In aqueous solutions, hydrophobic forces and van-der Waals also play a role. It is possible to lower this stress for chemicals with higher surface pressures by producing an effective matrix that can be chemically reduced to the original product once the CNT has been filled. The CNTs are capped after filling by transferring a current that fuses the closed ends.[58]

14.1 Drug loading [58]

It may be internal or external to locate the drug to be delivered by the CNT. Internalization or encapsulation is focused on the incorporation of Van der Waals into the CNT and is ideally used for drugs that are responsive to external conditions and easily break down.

15. TOXICITY OF CNTs [59, 60]

Concerns have been raised over possible toxicity problems with carbon nanotubes. Data and understanding of their impact on biological systems are currently lacking. Given the likely widespread use of CNTs in the future, understanding their impact on biological systems is imperative before they can be used in the delivery of mainstream drugs. Also, the main factors of possible cytotoxicity are the most desirable properties of Nano-materials for biomedical applications, i.e. their small size, large surface area, high reactivity, and high aspect ratio.[59] The study suggests that SWCNTs can induce adverse cellular responses through molecular signaling activation associated with oxidative stress (cancer induction). Several groups have already observed that CNTs may exhibit asbestos fiber-like behavior in mice experiments. When comparing the structure of both compounds, this concern becomes understandable. Chrysotile asbestos (left) and MWCNT (right) structures are shown above. The main problem with asbestos (and the question with CNTs) is that they quickly become airborne and are carried into the lungs due to their Nano-scale and lightweight. CNTs resembling asbestos fibers contribute to this concern in terms of aspect ratio, bio-persistence, and reactivity. Whilst there is good reason to be concerned about the potential similarities to asbestos fibers, there is evidence to suggest that industrially produced MWCNTs in high doses do not result in cell death in lung epithelial in the way that asbestos fibers do. No big adverse effects are caused by long-term exposure to pure MWCNTs at low concentrations.[60]

16. FACTORS AFFECTING CNTs [60]

The following is a list of factors found to influence the degree of toxicity of CNTs;

- Concentration / dose of CNTs.
- SWCNTs or MWCNTs
- Length of the tubes
- Catalyst residues leftover during synthesis or functionalization
- Degree of aggregation
- Oxidization
- Functionalization

Two appear to yield the most concomitant results; concentration and performance. [61]

16.1.1 Concentration / dose of CNTs

Using rat erythrocytes (red blood cells) it has been shown that no adverse effects on cells were observed at MWCNT concentrations of 25 μg / mL. However, erythrocyte hemolysis (cell membrane breaking) was increased at concentrations of 50 µg / mL. One likely explanation is that the MWCNTs agglomerate at these higher concentrations, which seems to accelerate the process of hemolysis. High dose levels and prolonged incubation times both increase toxicity and reduce the viability of cells.**[62]**

16.1.2 Functionalization

The focus of a large body of research has been the degree to which functionalization affects CNT toxicity. It is also likely to be one of the research areas that attract the greatest focus as active and passive targeting is directly linked to the CNT's form and degree of functionality. It has been shown that an SWCNT's degree of freedom will dramatically reduce its cytotoxicity.[63]

CONCLUSION

This review on CNTSs uncovers the diagram on grouping, structure, scattering strategies, blend, decontamination techniques, and use of CNTs alongside their properties, advantages, and restriction. CNTs have the additional favorable position of being forthcoming Nano-gadgets for controlled medication conveyance. The exceptional physical properties of CNTs make a large group of use potential outcomes, some determined as an expansion of customary carbon fiber applications, yet many are new conceivable outcomes, in view of the novel electronic and mechanical properties of CNTs. The fervor in this field emerges because of the adaptability of this material and the likelihood to foresee properties dependent on its well-characterized impeccable precious stone cross-section. The properties and attributes of CNTs are as yet being looked into and researchers have started to tap the capability of these structures. Single and various walled carbon nanotubes have officially demonstrated to fill in as more secure and progressively viable plausibility to past medication conveyance strategies. CNTs can go through films, they can convey helpful medications, immunizations, and nucleic acids profound into the cell to targets site which is already inaccessible. CNTs likewise fill in as perfect non-dangerous vehicles which, now and again, increment the solvency of the medication connected, which brings about more noteworthy viability and wellbeing of medication. By and large, late investigations with respect to CNTs have demonstrated an exceptionally encouraging event eventual fate of what lies ahead later on for drugs.

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