A Study On Carbon Nano Tube Based On Drug Delivery

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East West University, Dhaka

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Submitted By

Sushmita Sharmin Priya **Rabina Islam** **Tamanna Zaman Tisa**

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Under the Supervision of

Dr. M. Mofazzal Hossain

Professor

Department of Electronics and Communications Engineering

East West University

Declaration

This is to certify that the work presented in this thesis paper is the outcome of the investigation carried out by the candidates under the supervision of Dr. M. Mofazzal Hossain, in the department of Electronics and Communications Engineering (ECE), East West University, Dhaka-1212. It is also declared that this thesis has not been submitted anywhere else for the award of any degree or diploma or for any publication.

Authors:

Sushmita Sharmin Priya

St. # 2012-3-55-018

Rabina Islam

St. # 2013-1-55-014

Tamanna Zaman Tisa

St. #2013-1-55-026

Date: 21/12/2016

Supervisor:

Dr. M. Mofazzal Hossain

Date:21/12/2016

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Sushmita Sharmin Priya (2012-3-55-018)

Rabina Islam (2013-1-55-014)

Tamanna Zaman Tisa (2013-1-55-026)

Abstract

According to WHO (Word Health Organization) in 2005, about 7.6 million people died of cancer out of 58 million deaths worldwide. The traditional drug delivery system (e.g., radiation therapy, chemotherapy, surgery etc) used in cancer treatment has many side effects. Sometimes it damages normal cells near the area where therapy is used to kill cancer cell and become toxic when it crosses the permissible limit. Recently the SWCNTs (Single Walled Carbon Nanotube) has gained much attention for targeting drug delivery system because of its unique properties. In this case the fictionalization of SWCNT is a key in developing SWCNT based drug delivery system. We studied and found that surface area of armchair SWCNT is greater than that of zigzag SWCNT, and armchair gives more sites for fictionalization than zigzag. For fictionalization more sites means more or equal drug carrying and less use of SWCNT. As a result fewer side effects and less toxicity will be occurred in the normal cell in SWCNT based drug delivery system.

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Chapter 1

Introduction

1.1 Introduction

Carbon Nano-tubes (CNT) are considered ideal materials for several applications. Recently, CNThavecreated great interest in biology, where suitably modified Carbon Nano-tubes can serve as vaccine delivery systems or protein transports**. CNT** based drug-delivery also holds a great ability for cancer therapy.

During past years, the great progress has been made in the field of nanomaterial given their great potential in biomedical applications **.Carbon Nano-Tube** ,due to their unique properties , have become a popular implement in cancer diagnosis and therapy. They are considered one of the most promising nanomaterial with the capability of both detecting the cancerous cells and delivery drugs or small therapeutic molecules to these cell. For example, CNT can display metallic conductivity at the same time as- a) chemical and thermal stability, b)extremely high tensile strength and elasticity, c)the ability to absorb gas molecules as nano-capillaries, d)solubility when treated with surfactants and e) the potential of further chemical functionalization.

In this context, chemical functionalization is an especially attractive target, as it can improve solubility and processibility and allows the unique properties of **Carbon Nano-tubes** to be coupled to those of other types of materials .And we will also show how they have been presented into the diagnosis and treatment of cancer.

1.2 Cancer

Cancer is a term used for diseases in which abnormal cells divide without control and are able to attack other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems.

Most cancers are named for the organ or type of cell in which they start - for example, cancer that begins in the colon is called colon cancer; cancer that begins in melanocytes of the skin is called melanoma [1].

We all know that we have a great fear of cancer. It is a disease that can be painful, costly and severe fatal. It is created by abnormal cell division randomly. Papilloma virus is responsible for cancer. Cancer is not just one disease but many diseases. There are over 200 different types of cancer.

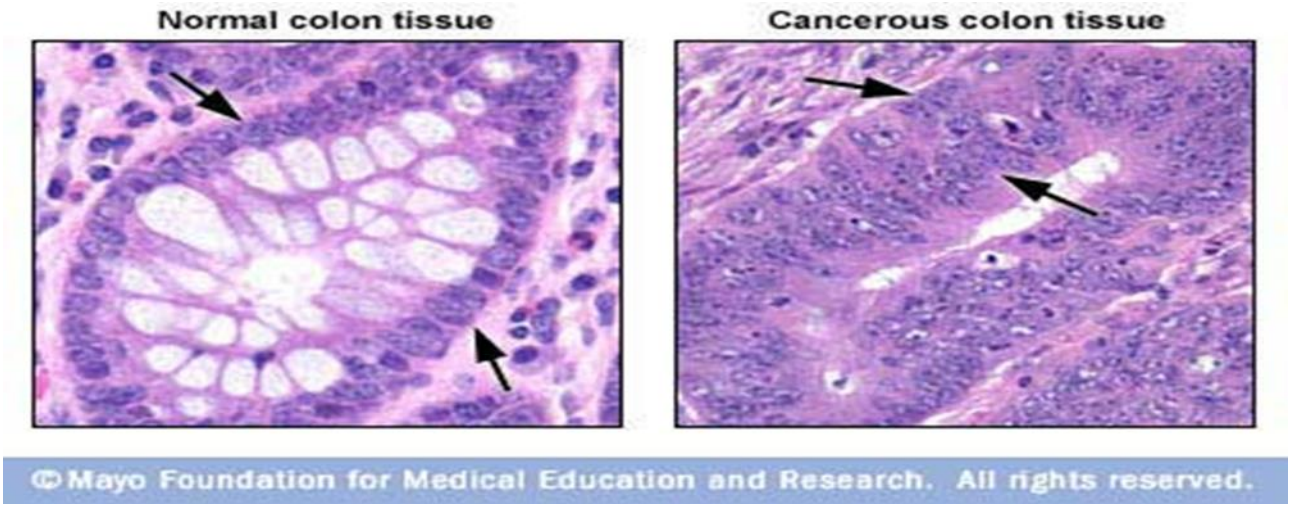

Fig 1.1 Cancerous colon tissue

1.2.1 What Causes Cancer

Cancer is ultimately the result of cells that uncontrollably grow and do not die. Normal cells in the body follow an orderly path of growth, division, and death. Programmed cell death is called apoptosis, and when this process breaks down, cancer begins to form. Unlike regular cells, cancer cells do not experience programmatic death and instead continue to grow and divide. This leads to a mass of abnormal cells that grows out of control [1].

1.3 Limitations of Traditional Cancer

From some resource,we get various types of ways that can help to reducecancer.

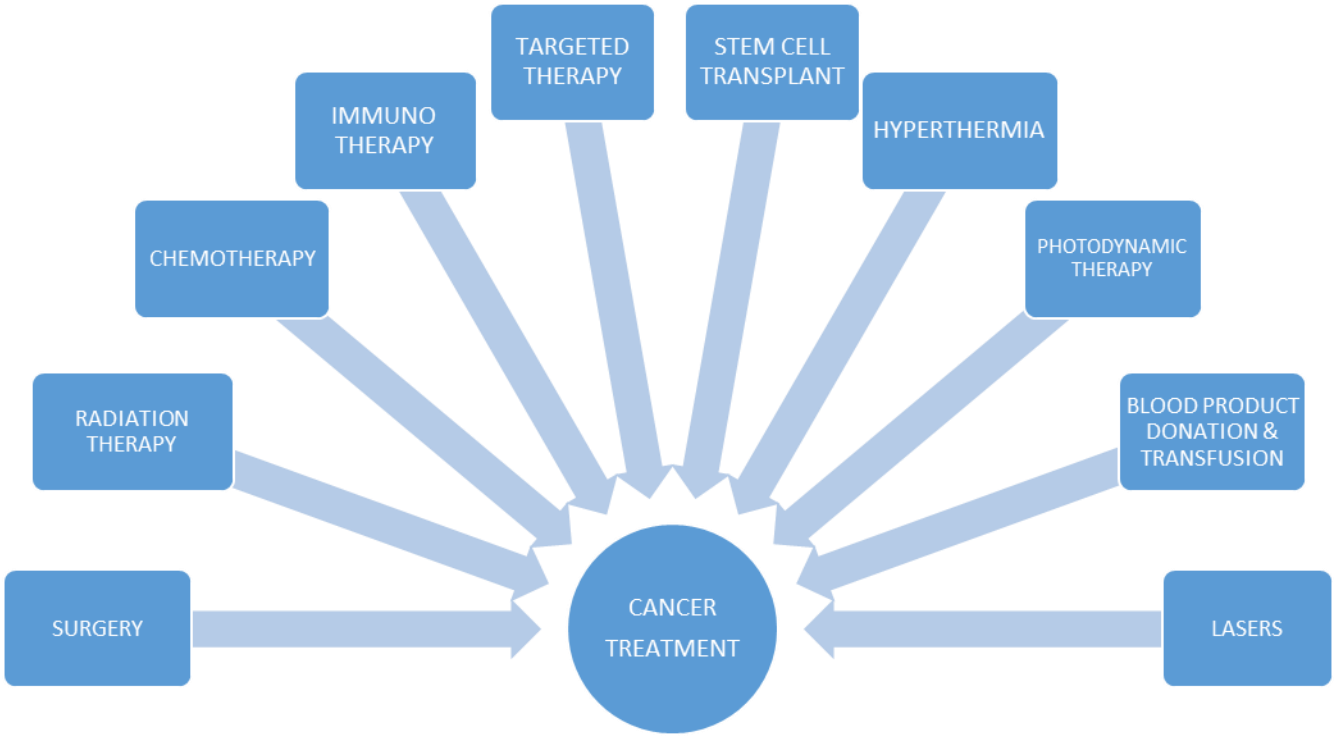

Fig 1.2 Procedures& techniques for cancer treatment.

But all of this process hasbad side effects that cause harmful effect in our body for future life. Now we have to find out how they might affect in our body if we are getting them.

1.3.1 Radiation Therapy

Radiation therapy is one of the most common treatments for cancer. It uses high-energy radiation to take-off tumors and kill cancer cells. Different types of rays such as X-rays, gamma-rays, and charged particles are used for removing cancer cells [2].

1.3.1.1 Radiation Therapy Kills Cancer Cell

Radiation therapy is used in a specific region of a human body where the cancer cells are created. Radiation therapy damages the DNA of cancer cells. It can damage DNA either directly or indirectly by producing charged particle or free radial which can damage the DNA. When DNA of cancer cells damage, the cells are stopping dividing and at the time these cancer cells are called die cells. Then they are removing from the body by natural process [2].

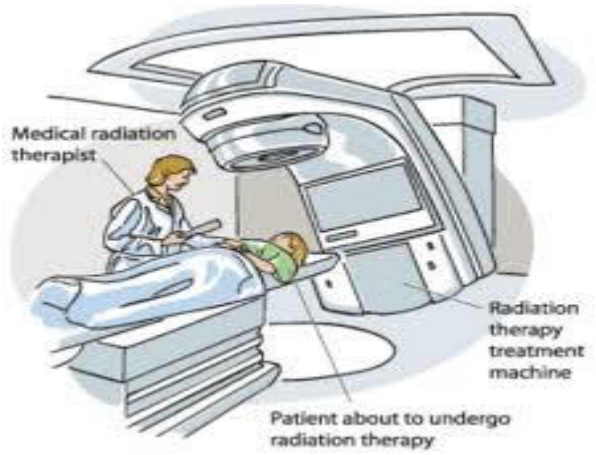

Fig1.4 Radiation therapy process

1.3.1.2 On which basis radiation therapy is given to a patient

The type of radiation therapy given by a radiation oncologist depends on many aspects, including: The types of cancer, the size of cancer, the location of cancers in the body, the distance of cancer tissues to the normal tissues, how far the radiation needs to travel into the body, the patient's general

health and medical history etc. It will also check the patient if he/she has other types of cancer treatment. The other factors are also important that the patient's age or other medical condition [2].

THE SIDE-EFFECTS OF RADIATION THERAPY-

Acute and chronic side effects are happened because of radiation therapy. Acute side effects occur at the time of treatment but Chronic side effects occurs after the treatment end. The symptoms of chronic side effects can be revealed in human body after a month or more than one year from the time when treatment is ended.

Acute radiation side-effects are caused by-

a) Radiation therapy damages the normal cells near the area of cancer cell. These effects cause skin irritation or damage at regions exposed to the radiation beams [2].

b) It is also responsible for damaging to the salivary glands or hair loss when the head or neck area is treated or urinary problems when the lower abdomen is treated [2].

Chronic radiation side-effects are caused by- Chronic side effects depends on the area of the body treated. These side effects may be occurred or may not be occurred, we are not sure about that this problem must be happened [2]. If it happens, then the causes are:

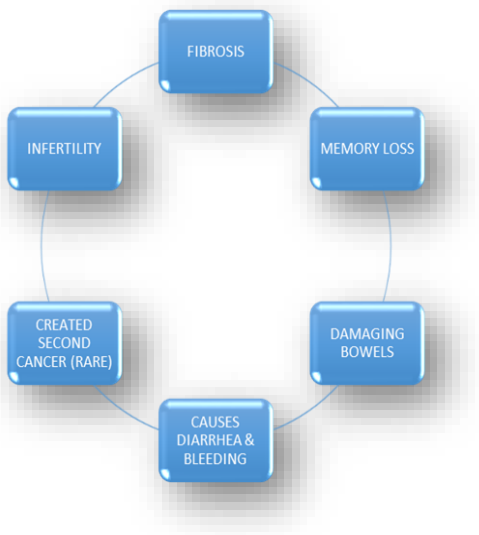

Fig 1.5 Causes of chronic radiation sideeffects.

1.3.2 Targeted Cancer Therapy

Researchers have learned about some of the differences in cancer cells (or other cells near them) that help them to grow. This has led to the development of drugs that "target" these differences. Treatment with these drugs is called Targeted therapy [3].

Targeted therapy drugs don't work the same way as standard chemotherapy (chemo) drugs. For example, many targeted drugs go after the cancer cells' inner workings – the programming that makes them different from normal, healthy cells, while leaving most healthy cells alone. These drugs tend to have side effects different from standard chemo drugs [3].

1.3.2.1 Side Effects Of Targeted Drugs

Some of the common and serious side effects caused by targeted therapy drugs are recorded here. They are-

a) High blood pressure
b) Bleeding or blood clotting problem
c) Slow wound healing
d) Heart damage
e) Autoimmune reaction
f) Swelling

a)High blood pressure

Some targeted drugs can cause high blood pressure. There isn't really anything that thepatient can do to prevent this, but the doctor will watch patient's blood pressure closely if he/she getting a drug that can cause this side effect. Some patients need medicine to bring their blood pressure down to safe levels during treatment. They should stay on this medicine until their doctor tells them it can be stopped [3].

b) Bleeding or blood clotting problem

Some targeted therapy drugs interfere with new blood vessel growth. Then it causes bleeding problem. The source of this kind of bleeding are from stomach and intestines Sometimes it can become a serious issue and even life threatening [3].

Some drugs can also cause blood clots in the lungs and legs, as well as heart attacks and strokes. If a patienthas problems with sudden swelling, pain, or tenderness in the arm or leg, chest pain, sudden shortness of breath, vision problems, weakness, seizures, or trouble speaking. These can be symptoms of serious problems caused by blood clots. Then the patient should get emergency help. These problems are rare and there's no way to prevent them [3].

c) Slow wound healing

Because of the targeted drug cancer treatment, patients face that any kind of wound cannot heal at a certain time. It needs more time to heal and sometimes wounds are not getting well. So patient should talk to the cancer doctor as soon as the patient know about a planned surgery or other procedure, including dental procedure so patient can find out what to do [3].

d) Heart damage

Some drugs can damage the heart, especially if used with certain chemotherapy drugs. Possible symptoms of heart damage might include chest pain, increased coughing, trouble breathing (especially at night), and rapid weight gain, dizziness, fainting, or swelling in the ankles or legs [3].

e) Auto-immune reaction

Certain targeted therapy drugs work by basically taking the brakes off the body's immune system. This can lead to serious side effects if the immune system starts to attack healthy parts of the body. In some people this can cause serious reactions in the lungs, intestines, liver, skin, eyes, nerves, hormone-making glands, or other organs. This isn't common but in some people it might be serious enough to be life threatening [3].

f) Swelling

Some targeted therapies cause facial swelling, especially around the eyes. They can also cause swelling in the feet and legs, as well as the hands. This usually doesn't need to be treated, but a diuretic (water pill) may be used in severe cases [3].

There are also some problems that are caused by targeted cancer therapy. They are listed below [4]

- Skin problem
- Nausea and vomiting
- Diarrhea or constipation
- Mouth sores
- Shortness of breath or trouble breathing
- Cough
- Feeling tired all the time
- Headache
- Hair loss
- Damage to organs such as the thyroid gland, liver, or kidneys
- Allergic reactions (while getting an IV drug)
- Increased risks of certain infections
- Second cancers

1.3.3 Cancer Surgery

Surgery is cutting away cancer tissue from the body. It is one of the main treatments for cancer [5].

Surgery can be used for lots of reasons [5]. It is used for -

a) diagnosing cancer

b) removing cancer

c) finding out how big the cancer is and if it has spread to other parts of the body

d) controlling symptoms of cancer

e) restoring parts of the body.

f) improving the appearance of part of the body.

1.3.3.1 Hazards of Cancer surgery

Any type of medical procedure has risks. Different procedures have different kinds of risks and side effects. So a patient should know about the detail if he/she wants surgery treatment.

There are possibilities of complications during surgery. It may be caused by the surgery itself, the drugs that are used, and patients overall health. Usually, the more complex the surgery is, the greater the risk of side effects [7].

Minor operations and taking tissue samples (biopsies) usually have less risk than a bigger surgery. Pain at the surgery site is the most common problem. Infections at the site and reactions to the drugs used to numb the area (local anesthesia) are also possible [7].

Some side effects are possible during and after surgery. Generally, these side effects are not expected to be life threatening [7]. They are shown below in a list-

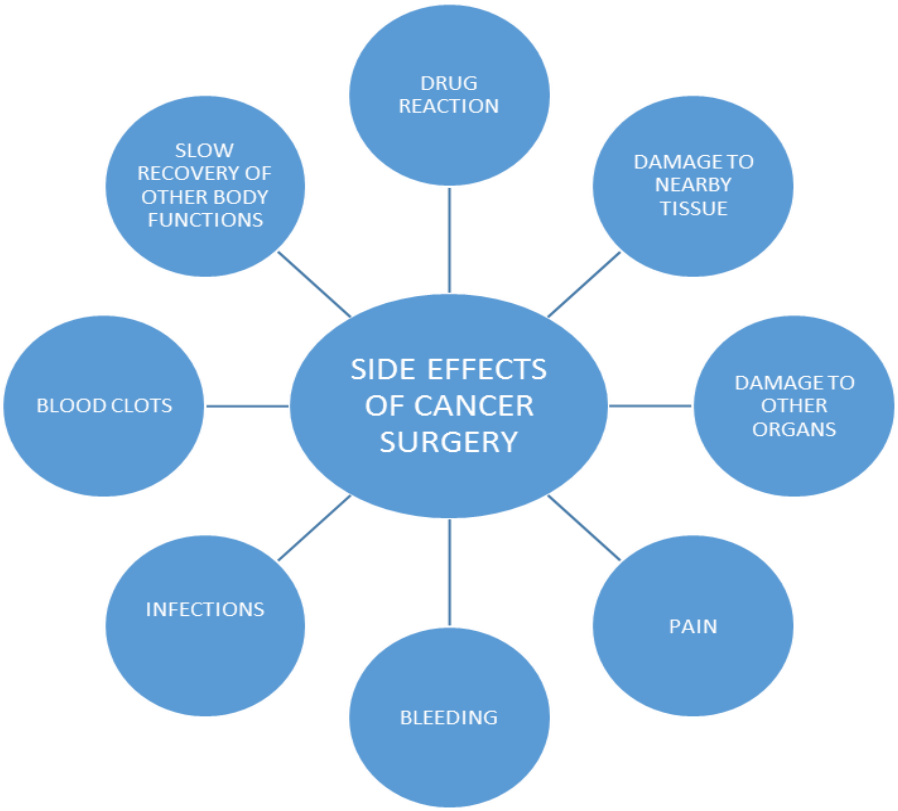

Fig 1.6 Possible side effects of Cancer Surgery.

Bleeding-

Bleeding is part of any surgery and is usually controlled. Bleeding can happen either inside the body (internally) or outside the body (externally). Bleeding can occur if a blood vessel was not sealed off during surgery or if a wound opens up[7].

Blood clots

Blood clots can form in the deep veins of the legs after surgery, especially if a person stays in bed for a long time. Such a clot can become a serious problem if it breaks loose and travels to another part of the body, such as a lung. This is a big reason why you'll be encouraged to get out of bed to sit, stand, and walk as soon as possible[7].

Damage to nearby tissues

Sometimes because of the surgery, it damages cancer tissue as well as the nearby tissues. It also damages internal organs and blood vessels during surgery[7].

Drug reactions

Some people have reactions to the drugs used (anesthesia) or other medicines needed during surgery. Although it is a rare case, these can be serious because they can cause dangerously low blood pressure, heart rate, breathing rate. That's why doctors will be watched closely these signs throughout the surgery to look for this [7].

Damage to other organs

Surgery can lead to problems with other organs, such as the lungs, heart, or kidneys. These problems are very rare but can be life-threatening. They are more likely to happen to people who already have problems with these organs. This is why doctors get a complete medical history and do tests to look for possible risks before surgery is done [7].

Pain

Almost everyone has some pain after surgery. Pain is normal, but it should not be allowed to slow down your recovery. There are many ways to deal with surgical pain. Medicines for pain range from aspirin and acetaminophen (Tylenol®) to stronger drugs, like codeine and morphine [7].

Infections

Infection at the site of the incision (cut) is a possible problem. Doctors take great care to reduce this risk by cleaning the area and keeping the area around it sterile, but infections do happen. Antibiotics, either as a pill or given through a vein in patient's arm (IV), are able to treat most infections. A lung infection (pneumonia) can occur, especially in patients with reduced lung function, such as smokers. Doing deep breathing exercises as soon as possible after surgery helps lessen this risk. Other

infections can develop within the body, especially if the stomach or intestines were opened during the operation. Doctors take great care to try to prevent this. But if it happens, antibiotics will be needed [7].

Slow recovery of other body functions

Some body functions, such as bowel activity, can be slow to recover and can sometimes become serious, too. Getting out of bed and walking around as soon as possible after surgery can help lower this risk[7].

Possible long-term side effects of cancer surgery

Long-term side effects depend on the type of surgery done. Such as, it may effect on fertility if surgery is being done on reproductive organs. Or people who have colorectal cancer surgery may need an opening in the belly to which the end of the colon is attached (a colostomy). Men having their prostate removed (radical prostatectomy) are at risk for losing control of their urine (incontinence) or becoming unable to get or keep an erection (impotence) [7] .

1.3.4 Chemotherapy

Chemotherapy is a type of cancer treatment that uses drugs to destroy cancer cells. It is also known as chemo. More specifically, Chemotherapy is the use of medication (chemicals) to treat cancer disease.

1.3.4.1 Goals of Chemotherapy

The purpose of chemotherapy treatment is to get relief from cancer .the goal are include [8]

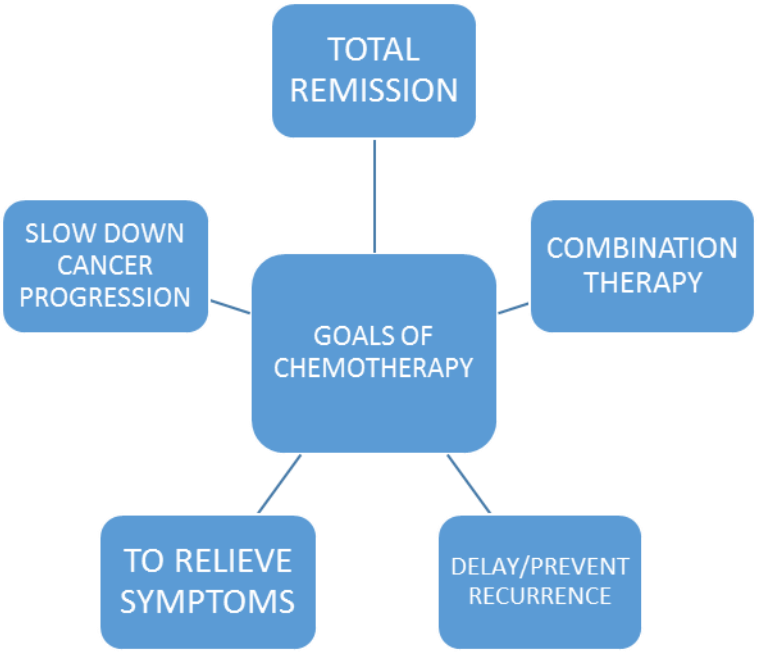

Fig 1.7the goals of chemotherapy

1.3.4.2 How Does Chemotherapy Work

Chemotherapy is used as the cancer treatment [8]. Chemotherapy can:

a) Make a tumor smaller before surgery or radiation therapy. This is called neo-adjuvant chemotherapy.
b) Destroy cancer cells that may remain after surgery or radiation therapy. This is called adjuvant chemotherapy.
c) Help radiation therapy and biological therapy work well.
d) Destroy cancer cells that have come back (recurrent cancer) or spread to other parts of your body (metastatic cancer).

1.3.4.3 Side Effects of Chemotherapy

Chemotherapy is considered a systemic therapy. This means it may affect the entire body. Chemo drugs target rapidly growing cancer cells, but they can also affect healthy cells that grow rapidly. The effect of these drugs on both cancer and normal cells often causes chemo side effects. For example:

a) A number of blood cells that divide rapidly can be damaged along with cancer cells during chemo[9]:

- White blood cells help protect the body from infection. A low white blood cell count is known as neutropenia. If your white blood cell count gets too low you could get a serious infection.
- Red blood cells carry oxygen throughout your body. A low red blood is known as anemia. Anemia can lead to fatigue, chest pain, and more serious complications.
- Platelets are structures in the blood that help stop bleeding. A low platelet cell count is known as thrombocytopenia. A low platelet count can cause bruising and bleeding.

b) Hair follicles have cells that can be affected by chemo, leading to hair loss, also called alopecia.

c) The normal cells most likely to be damaged by chemo are [10]

- Blood-forming cells in the bone marrow

- Cells in the mouth, digestive tract, and reproductive system.

d) Some chemo drugs can damage cells in the heart, kidneys, bladder, lungs, and nervous system.

Common side effects of chemotherapy

Most people worry about whether they'll have side effects from chemo, and, if so, what they'll be like. Here are some of the more common side effects caused by chemotherapy [11]:

- Fatigue
- Hair loss
- Easy bruising and bleeding
- Infection

- Anemia (low red blood cell counts)
- Nausea and vomiting
- Appetite changes
- Constipation
- Diarrhea
- Mouth, tongue, and throat problems such as sores and pain with swallowing
- Nerve and muscle problems such as numbness, tingling, and pain
- Skin and nail changes such as dry skin and color change
- Urine and bladder changes and kidney problems
- Weight changes
- Chemo brain that affects concentration and focus
- Mood changes
- Changes in libido and sexual function
- Fertility problems

1.3.5 Cancer Immunotherapy

Immunotherapy is treatment that uses certain portions of a person's immune system to fight diseases such as cancer. This can be done in a couple of ways:

1) Stimulating patient's own immune system to work harder or smarter to attack cancer cells.

2) Givingpatient's immune system components, such as man-made immune system proteins.

Some types of immunotherapy are also sometimes called biologic therapy or biotherapy [12] .

1.3.5.1 Side Effects

The most common side effects of immunotherapy are[11]:

- Flu-like symptoms.
- Fatigue.
- Rashes.
- Fever.

- Drops in blood pressure.
- Less common side effects are:
- Colitis or other gastrointestinal problems.
- Thyroid problems.

1.3.6 Lasers in Cancer Treatment

The word LASER means Light**A**mplification by **S**timulated **E**mission of **R**adiation. Laser light is different from regular light. The light from the sun or from a light bulb has many wavelengths and spreads out in all directions. Laser light, on the other hand, has a single wavelength and can be focused in a very thin beam. This makes it both powerful and precise. Lasers can be used instead of blades (scalpels) for very careful surgical work, such as repairing a damaged retina in the eye or cutting through body tissue [14] . Laser ablation can[13]

- Destroy small areas of precancerous cells
- Shrink or destroy tumors
- Relieve some cancer symptoms such as bleeding or blockage

1.3.6.1 The Risks of Laser Treatment

Laser therapy has some risks. The risks for skin therapy include[13]:

- bleeding
- infection
- pain
- scarring
- changes in skin color
- pneumonia
- confusion after waking from the operation
- heart attack
- stroke
- Treatments can also be expensive and are therefore not accessible to everyone.

1.3.7 Photodynamic Therapy

Photodynamic therapy (PDT) is a treatment that uses special drugs, called photosensitizing agents, along with light to kill cancer cells. The drugs only work after they have been activated or "turned on" by certain kinds of light. PDT may also be called photo-radiation therapy, phototherapy, or photo chemotherapy[15].

1.3.7.1 The Risks of Photodynamic Therapy

The major possible side effects PDT are photosensitivity reactions (reactions triggered by light) and swelling in the treated area. Swelling may cause pain or trouble swallowing or breathing. Other minor side effects are possible, too. Possible side effects include nausea, vomiting, fever, dehydration, Skin changes, headache, scarring and narrowing of the esophagus, hiccups, trouble swallowing, and fluid collecting around the lungs. In people treated for lung cancer, possible side effects include shortness of breath, coughing up blood, fever, pneumonia, and bronchitis [16].

1.4 Review of CNT-based Drug Delivery

In the past decade, the rapid development of nanotechnology has brought many fascinating ideas and opportunities to disease diagnosis and treatment. Sp2 carbon nanomaterial's, notably zero-dimensional (0D) fullerenes, 1D carbon nanotubes (CNTs), and 2D graphene, have gained significant interest from various fields and generated huge impacts in the materials research community since their discovery in 1985, 1991, and 2004. Graphene is a mono-layered sp2-bonded carbon sheet. Single-walled carbon nanotubes (SWNTs) and multi-walled carbon nanotubes (MWNTs) are cylindrical tubes of sp2 carbon, conceptualized by rolling up single- or multi-layered graphene, respectively.

Carbon nanotubes and graphene are both low-dimensional sp2 carbon nanomaterial exhibiting many unique physical and chemical properties that are interesting in a wide range of areas including nanomedicine. Since 2004, carbon nanotubes have been extensively explored as drug delivery carriers for the intracellular transport of chemotherapy drugs, proteins, and genes. In vivo cancer treatment with carbon nanotubes has been demonstrated in animal experiments by several different

groups. Recently, graphene, another allotrope of carbon, has also shown promise in various biomedical applications.

1.5 Thesis Outline

In chapter 1 we discuss briefly about Cancer and the related treatment of this disease. As like radiation therapy, chemotherapy, cancer immunotherapy etc. Here also mentioned the reason of why traditional treatment doesn't work on the cancer. At the end of this chapter we have a review of NT-based drug delivery.

In chapter 2 we have focused on the history of Carbon Nanotubes. Also discussed the properties and applications of CNT. Here also we have a view on the types of CNT and the methods of CNT's synthesis.

In chapter 3 here we review on the soluble mechanism for functionalized SWCNT. We have a briefly discussion on SWCNT functionalization and also about the surface area and the number sites for functionalization.

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Chapter 2

Single Walled Carbon Nano-Tube

2.1 Carbon Nanotube

Carbon nanotubes (CNTs) are allotropes of carbon[2].It is made by graphite and constructed in cylindrical tubes with nanometer in diameter and several millimeters in length. **carbon nanotubes** are 2D. Carbon nanotubes (CNTs), discovered by Japanese scientist Iijima in 1991 [3].

2.2 The History of Carbon Nanotubes

The history of carbon nanotubes is not completely clear. That's why proper credit goes to the person that invented the carbon nanotube has been the subject of several high tech debates among the scientific groups. The initial history of nanotubes started in the 1970s. A preparation of the planned carbon filaments was completed byMorinobu Endo who was earning his Ph.D. at the University of Orleans, France. The growth of these carbon filaments were initially thought to be the first carbon nanotubes. However, they failed to meet the quantity requirements for width and thus were deemed. This was still a highly important development in the history of carbon nanotubes, but it just wasn't the right time to be considered the first known invention. Giving the proper credit to who invented carbon nanotubes would not come along for another 20 years. In 1991 the true first invention of nanotube was finally made. It appears as though there was a race between Russian nanotechnologists and sumiolijimaof IBM.[18-20]

The molecules were first discovered by Iijima in 1991[9] when he was studying the synthesis of fullerenes by using electric arc discharge technique. The high resolution transmission electron microscopy (HRTEM) was employed for observation of that phenomenon. Carbon nanotubes that Iijima observed were so called multi-walled carbon nanotubes (MWNTs) ,Russian dolls containing at least two graphitic layers, and generally have inner diameters of around 4 nm. Two years later in 1993, Iijima and Ichihashi of NEC and Bethune and colleagues of the IBMAlmaden Research Center in California synthesized single-walled carbon nanotubes (SWNTs) as sho The SWNTs were synthesized by the same route of producing MWNTs but adding some metal particles to the carbon

electrodes. The appearance of SWNT is quite different to that of MWNT. The individual tubes have very small diameters (typically ~ 1nm), and are curled and looped rather than straight. In the early 1990s, two research groups predicted electronic properties of individual SWNTs . From their calculations, they found that SWNTs can be either metallic or semiconducting depending on their chirality and diameter. By the end of that decade, these particular predictions were confirmed by experiments . In the meantime, a lot of reviews which provide a comprehensive overview with respect to the synthesis, characterization, applications, and the basic mechanical and electronic properties of carbon nanotube have appeared. In the following sections, the structure, synthesis, properties and applications of CNTs are discussed in details. Because of many interesting properties that carbon nanotubes exhibit, CNTs have emerged to be one of the most intensively studied nanostructure materials[21-25].

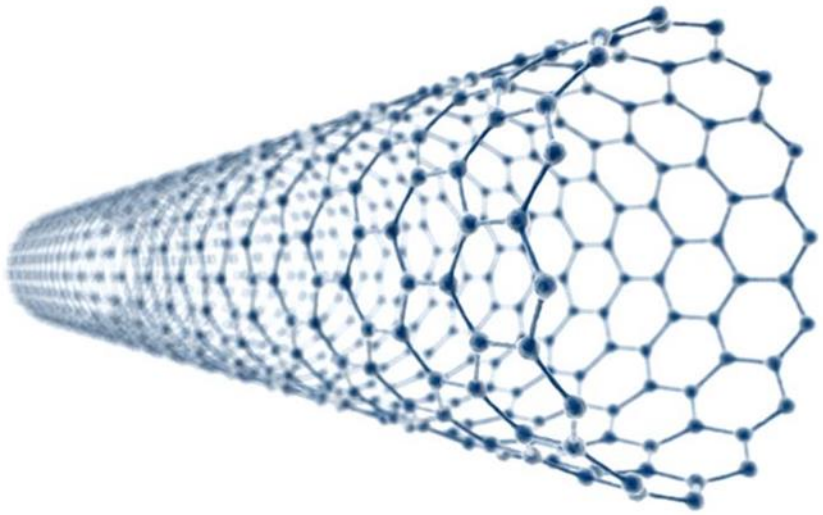

Fig 2.1 Structure of CNT

2.3 Properties& Application of CNT

Properties

Carbon Nanotube has some great properties that can make them useful in many applications in nanotechnology. Their unique surface area, stiffness, strength and resilience have led to much excitement in the field of pharmacy.[4]

The properties and characteristics of**CNTs** are still being research heavily. Scientist found that **CNT**canpass through membranes, carrying therapeutic drugs, vaccines and nucleic acids deep into the cell to targets previously unreachable. Overall, recent studies regarding **CNT**s have shown a very promising glimpse of what lies ahead in the future of medicines.[4] So, we can summarize the characteristics of **CNT** are:

- CNTs have High Electrical Conductivity
- CNTs have Very High Tensile Strength
- CNTs are Highly Flexible- can be bent considerably without damage
- CNTs are Very Elastic ~18% elongation to failure
- CNTs have High Thermal Conductivity
- CNTs have a Low Thermal Expansion Coefficient
- CNTs are Good Electron Field Emitters
- CNTs Aspect Ratio[19]

.

Comparison of mechanical properties[1][2][3][4]

Material	Young's modulus (TPa)	Tensile strength (GPa)	Elongation at break (%)
SWNT[E]	~1 (from 1 to 5)	13–53	16
Armchair SWNT[T]	0.94	126.2	23.1
Zigzag SWNT[T]	0.94	94.5	15.6–17.5
Chiral SWNT	0.92		
MWNT[E]	0.2[5]–0.8[6]–0.95[5]	11[5]–63[5]–150[6]	
Stainless steel[E]	0.186[8]–0.214[9]	0.38[8]–1.55[9]	15–50
Kevlar–29&149[E]	0.06–0.18[7]	3.6–3.8[7]	~2

Applications of CNT

- CNTs Thermal Conductivity
- CNTs Field Emission
- CNTs Conductive Properties
- CNTs Energy Storage
- CNTs Conductive Adhesive
- Molecular Electronics based on CNTs
- CNTs Thermal Materials
- CNTs Structural Applications
- CNTs Fibers & Fabrics
- CNTs Catalyst Supports
- CNTs Biomedical Applications
- CNTs Air & Water Filtration[19]

2.4 Carbon Nanotube in Drug delivery

1. Carbon Nanotubes Used for Cancer Therapy
2. Carbon Nanotubes for Infection Therapy
3. Carbon Nanotubes for Gene Therapy by DNA Delivery
4. Carbon Nanotubes for Tissue Regeneration
5. an Carbon Nanotubes for Neurodegenerative Diseases and Alzheimer Syndrome Artificial Implants
6. Carbon Nanotubes as Antioxidants
7. Carbon Nanotubes as Biosensor Vehicles for Diagnostic and Detection
8. Toxicity of Carbon Nanotubes

2.5 Types of CNT

- **SWCNT(Single Walled Carbon Nanotube)**
- **MWCNT(Multi Walled Carbon Nanotube)**

2.6 MWCNT (Multi Wall Carbon Nanotube)

Multiwalled carbon nanotubes can be formed in two structural models: Russian Doll model and Parchment model. When a carbon nanotube contains another nanotube inside it and the outer nanotube has a greater diameter than thinner nanotube, it is called the Russian Doll model. On other hand, when a single graphene sheet is wrapped around itself manifold times, the same as a rolled up scroll of paper, it is called the Parchment model[20]. The Russian Doll structure is observed more commonly. Its individual shells can be described as SWNTs, which can be metallic or semiconducting. Because of statistical probability and restrictions on the relative diameters of the individual tubes, one of the shells, and thus the whole MWNT, is usually a zero-gap metal.

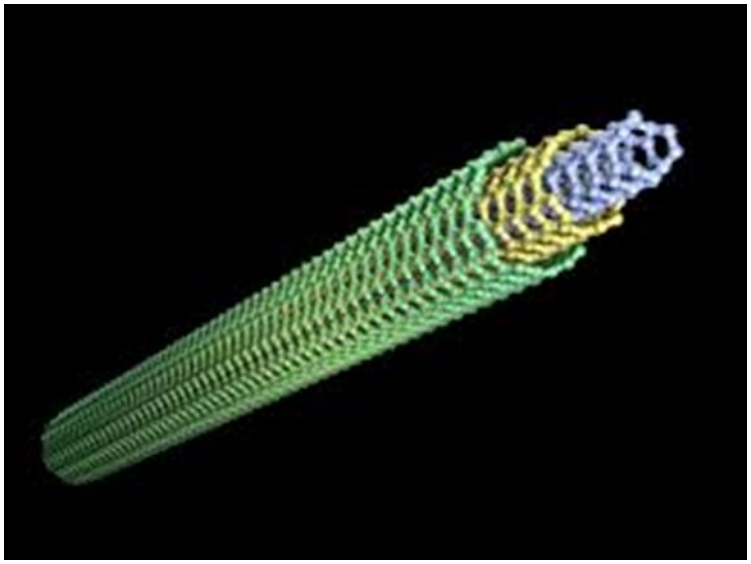

Fig 2.2 Structure of MWCNT

2.7 SWCNT (Single Wall Carbon Nanotube)

Nanotubes with single well are described as single-wall carbon nanotubes (SWCNTs) and were first informed in 1993 [20].Most of the single-walled carbon nanotube have a diameter of close to 1 nanometer, and can be many millions of times longer. Dependent on wrapping to a cylinder way, there are three different forms of SWCNTs such as armchair, chiral, and zigzag . A SWCNT's structure is characterized by a pair of indices (*n*, *m*) that describe the chiral vector and directly have an effect on electrical properties of nanotubes. The number of unit vectors in the honeycomb crystal lattice of graphene along two directions is determined by the integers and *m*. As a common opinion, when $m = 0$, the nanotubes are named zigzag nanotubes; when $n = \mathrm{m}$, the nanotubes are named armchair nanotubes, and other state are called chiral.

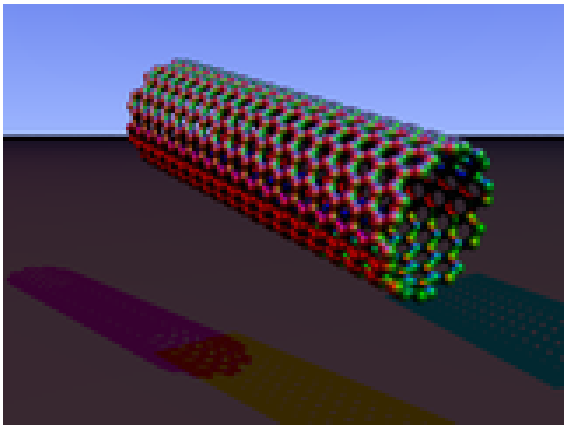

Fig 2.3 Armchair (*n*,*n*) i.e.: m=n

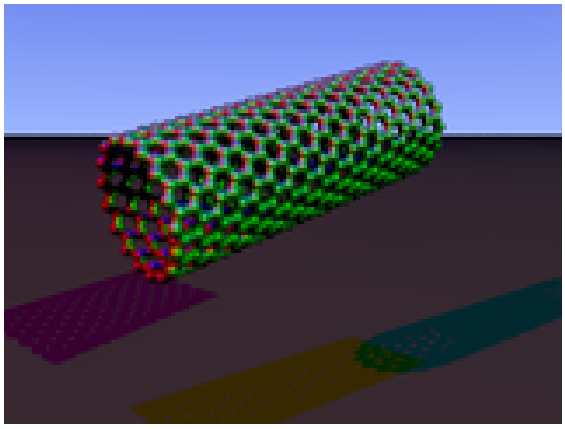

Fig 2.4 Zigzag (*n*,0)

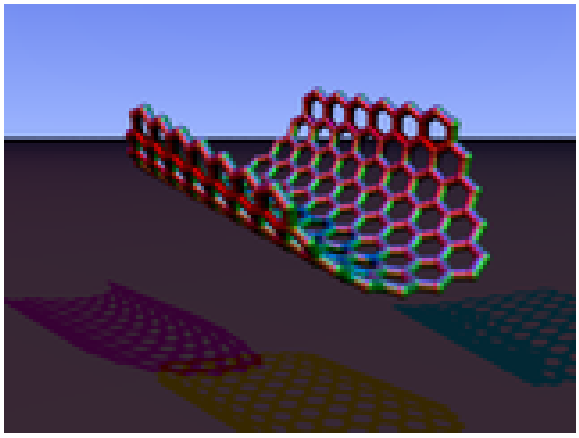

Fig 2.5 Chiral (*n*,*m*)

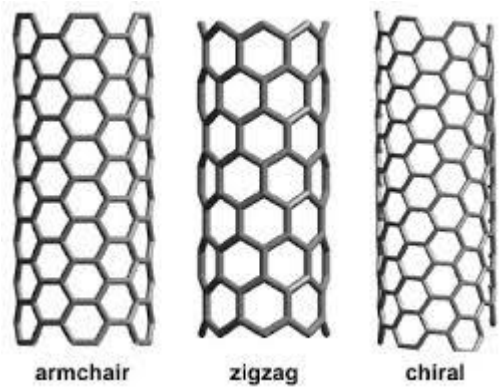

Fig 2.6 Structure of armchair, zigzag &chairal

The dashes arrows in Fig(4) show the circumferential vector C_h whose direction is also the direction of the roll-up for a CNT.

The chiral vector $C = na_1 + ma_2$

Where a_1 and a_2 are the lattice vectors of graphite. , and n and m are the chiral indices.

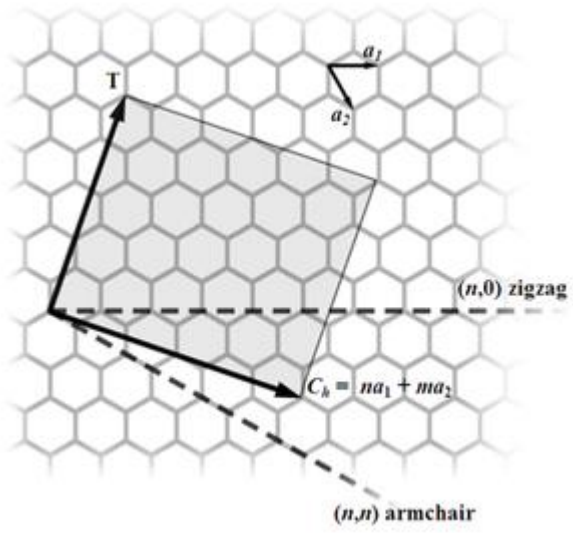

Fig 2.7 SWCNT

The diameter of a carbon tube can be calculated by

$$D=\frac{a\sqrt{3(n2+m2+nm)}}{\pi}\text{----------(1)}$$

Where$a=1.42\times3\sqrt{}$Å corresponds to the lattice constant in the graphite sheet.

When $n-m$ is a multiple of 3, then the nanotube is described as 'metallic' or highly conducting nanotubes, and if not, then the nanotube is a semi metallic or semiconductor.[20]

2.7.1 Methods of CNTs Synthesis

Carbon nanotubes can generally be produced using three main techniques. They are:

(1) Arc Discharge

(2) Laser Ablation

(3)Chemical Vapor Deposition (CVD) [21]

Arc Discharge

Arc discharge was the first recognized technique for producing MWNTs and SWNTs . The arc discharge technique generally involves the use of two high-purity graphite electrodes as the anode and the cathode. The electrodes were vaporized by the passage of a DC current (~100 A) through the two high-purity graphite separated (~ 1–2 mm) in 400 mbar of Helium atmosphere. After arc discharging for a period of time, a carbon rod is built up at the cathode. This method can mostly produce MWNTs but can also produce SWNT with the addition of metal catalyst such as Fe, Co, Ni, Y or Mo, on either the anode or the cathode. The quantity and quality such as lengths, diameters, purity and etc. The nanotubes obtained depend on various parameters such as the metal concentration, inert gas pressure, type of gas, plasma arc, temperature, the current and system geometry[13,14]

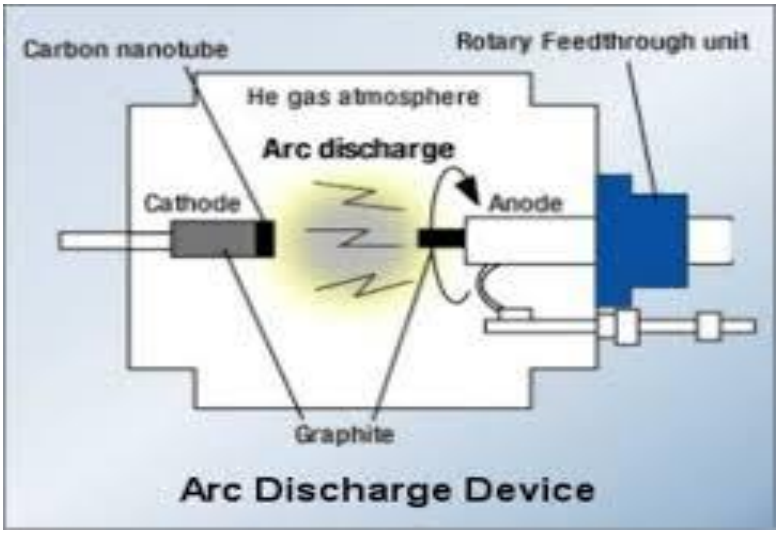

Fig 2.8 Arc Discharge Device

Laser Ablation

Smalley and co-workers were produced carbon nanotubes using laser ablation technique In 1995 [15]. , A high power laser was used to vaporize carbon from a graphite target at high temperature. Laser ablation can be used to produced both MWNTs and SWNTs. In order to generate SWNTs, metal particles as catalysts must be added to the graphite targets similar to the arc discharge technique. The quantity and quality of produced carbon nanotubes depend on several factors such as the amount and type of catalysts, laser power and wavelength, temperature, pressure, type of inert gas, and the fluid dynamics near the carbon target. The laser is focused onto a carbon targets containing 1.2 % of cobalt/nickel with 98.8 % of graphite composite that is placed in a 1200°C quartz tube furnace under the argon atmosphere (~500 Torr)[16].

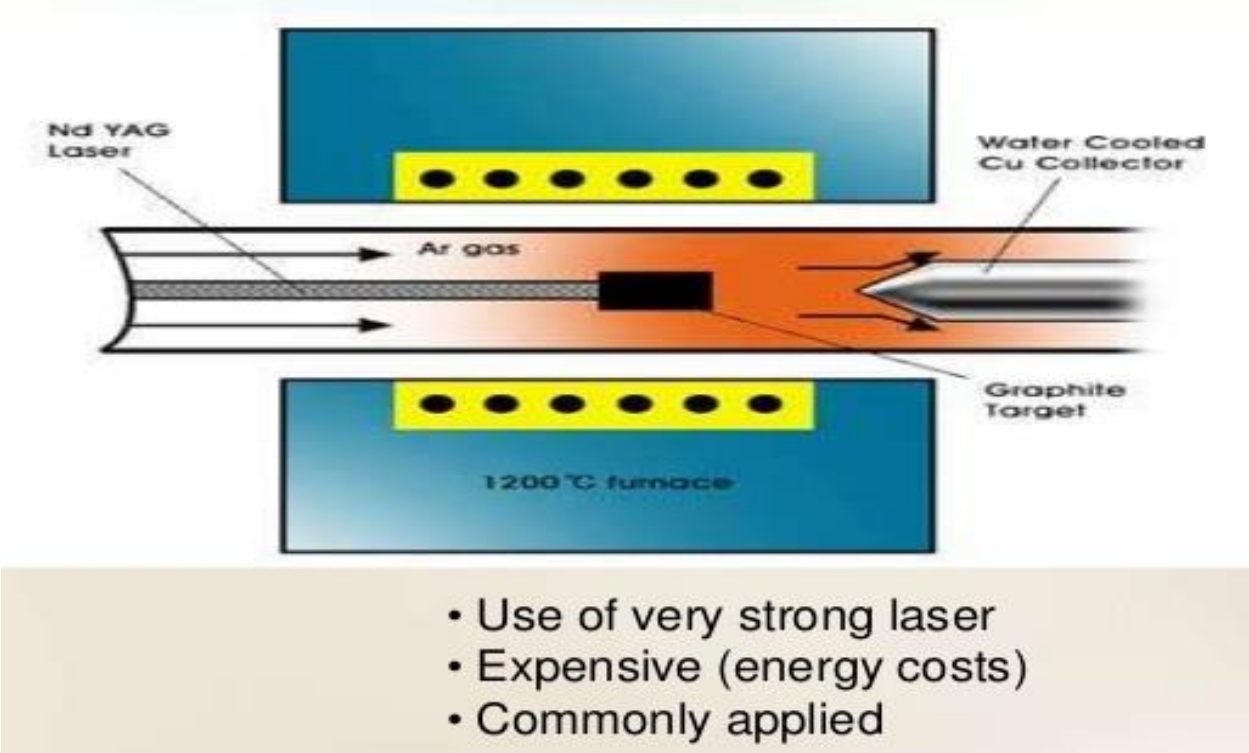

Fig 2.9 Laser ablation

Chemical Vapor Deposition (CVD)

Chemical vapor deposition (CVD) technique was first reported to produce MWNTs by Endo and his research groupIn 1993[17]. CVD technique can be achieved by taking a carbon source in the gas phase and using an energy source, such as plasma or a resistively heated coil, to transfer energy to a gaseous carbon molecule. The CVD process uses hydrocarbons as the carbon sources including methane, carbon monoxide and acetylene. The hydrocarbons flow through the quartz tube being in an oven at a high temperature (~ 720 C). . At high temperature, the hydrocarbons are broken to be the hydrogen carbon bond, producing pure carbon molecules. Then, the carbon will diffuse toward the substrate, which is heated and coated with a catalyst . Carbon nanotubes will be formed if the proper parameters are maintained. The advantages of the CVD process were low power input, lower temperature range, relatively high purity and, most importantly, possibility to scale up the process. Depending on the temperature CVD can produce both MWNTs and SWNTs . SWNTs will occur at a higher temperature than MWNTs[18].

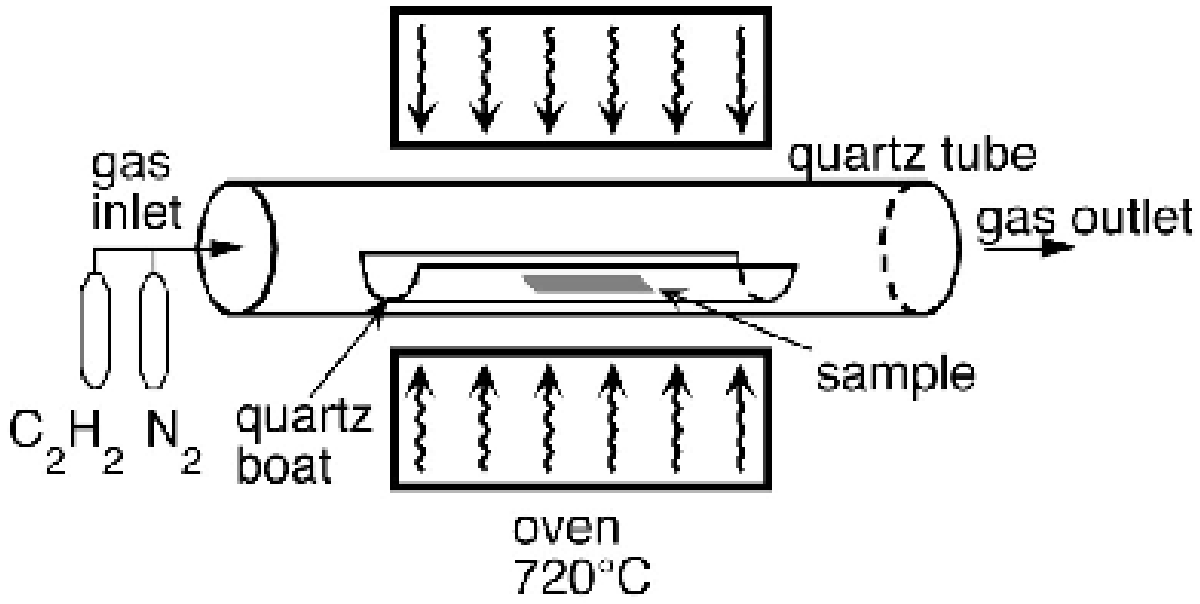

Fig 2.10 CVD

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CHAPTER 3

Carbon Nanotube Based Drug Delivery

The pure form of the carbon nanotube is hardly soluble in water and other possible fluids. Although solubility under the physiological condition is a key prerequisite to making CNT biocompatible with cell fluid in drug delivery systems. In addition, functionalized carbon nanotubes (f-CNT) can be linked to a wide variety of active molecules, including peptides, proteins, nucleic acids and other therapeutic agents [34].Functionalization is one of the several methods used to enhance the solubility of CNTs.

CNT can be oxidized using strong acids, resulting in the reduction of their length while generating carboxylic groups, which increases their dispersibility in aqueous solutions[35]. Alternatively, addition reaction to the CNT external walls and tips make them soluble in water [36].

Several approaches to the functionalization of SWCNTs have been developed, in both molecular and supramolecularchemistry in recent years. These approaches include defect functionalization, covalent functionalization of the sidewalls, noncovalentexohedral functionalization, and endohedral functionalization[13].

This kind of functionalization in SWCNT mainly starts at the defective sites which were produced during its manufacturing process. Some defects of the six-membered-ring carbon structure of the nanotubes, such as the inclusion of five- or seven-memberedrings in the carbon network, stem from the initial formation of the tubes[13].

It has ben investigated that pristine CNTs are chemically inert and insoluble in aqueous media and therefore of little use in biological or medical applications. Due to the hydrophobicity and tendency to aggregate, they are harmful to living cells in culturele[37, 38]. Therefore, CNTs are oxidized in strong acid to create hydroxyl and carboxyl groups [39], particularly at their ends, where the biomolecules or other nanomaterial's can be connected[40]. These oxidized CNTs are much more readily dispersed in aqueous solutions . It can be coupled to oligonucleotides, proteins, or peptides as well as CNTs have been used as vehicles to deliver macromolecules that are not able to pass through the cellular membrane by themselves into cells [35, 41].

CNT's toxicity will depend on many other factors than concentration, including their physical form, their diameter, their length, and the nature of attached molecules or nanomaterial. Since little is yet known about the toxicity of CNTs, particularly of oxidized CNTs, Bottini et al. compared in two types of CNTs (oxidized CNT and Pristine CNT) in a number of functional assays with human T lymphocytes. It is found that oxidized CNTs are more toxic than pristine CNT.Oxidized CNTs are more toxic and induce massive loss of cell viability through programmed cell death at a dose of 400 μg/ml, that corresponds to approximately 10 million carbon nanotubes per cell [42].In another study, Yang et al[43]revealed that SWCNTs suspended in Tween-80 following intra venous administration for three month showed low toxicities to the tested mice at a high dose of ~40 mg kg^{-1} .Toxicity resulted may be due to the oxidative stress created by SWCNTs accumulated in the liver and lungs of mice. Lam et al[44]established that SWCNT could be toxic if they reached the lungs. Warheitet al. conducted a similar study in rats, relating the granuloma formation probably due to aggregation of CNT.A study directed by McDevittet al[45], using antibody conjugated radiolabeled CNTs functionalized by 1,3- dipolar cycloaddition also showed slow urinal excretion and high CNT uptake in the liver and spleen.Yang et al[46], carried out the perusal to see the bio distribution of 13C enriched non-functionalized SWNTs over a month. The result showed high uptake of nanotube in liver, lung, and spleen without noticeable excretion within 28 days.

In this study, it is aimed to analytically assess the effects of surface area of SWCNT in its different conformations during the defect-groupfunctionalization and also to establish a relationship with its toxicity.

3.1 Soluble Mechanisms for Functionalized SWCNT

SWCNT forms of carbon which is very pure and have insoluble characteristics in biological fluid. To carry a drug or therapeutic agents it needs to be soluble in cell fluid so that it can attack and interact with the cell completely.

The carbon in the SWCNT present as sp^2 hybridization form. The structure is as follows-

C(6) - $1s^2 2s^2 2p^2$

$C^*(6) = 1s^2 2s^2 2p_x^1 2p_y^1 2p_z^0$

$C^*(6) = 1s^2 2s^2 2p_x^1 2p_y^1 2p_z^1$

The structure of SWCNT is

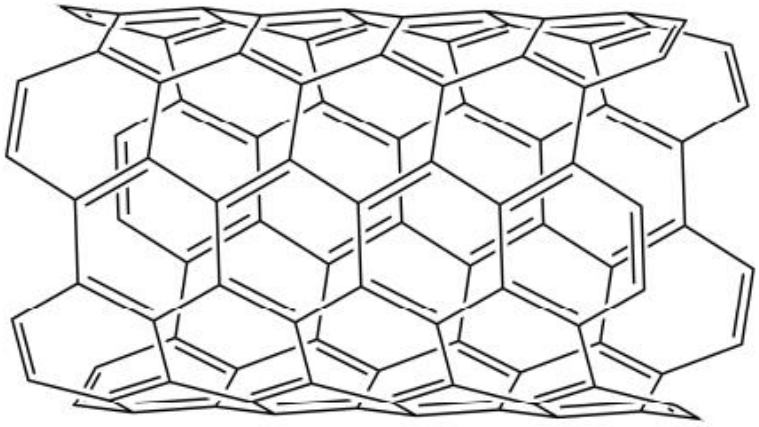


Fig 3.1 Structure of SWCNT

So there are multiple pi bonds present (double bond) in the structure.

Since, this form is insoluble in body fluid it has to be converted into some soluble form through some chemical fictionalization. That means it needs to react with other substance. So for reaction it needs some active site from where the reaction can occur.

In CNT (SW), those active sites are called defect site that were formed during the production of CNT. Though it is cylindrical in shape, still to give this a desired structure of cylinder all units of CNT are not hexagonal at all. It has some heptagonal and five carbon structure within the hexagonal structure present in 1-3% in the whole.

Carbon nanotubes (CNTs) are widely used for biomedical applications as intracellular transporters of biomolecules owing to their ability to cross cell membranes. Essentially three uptake mechanisms have been reported and they are phagocytosis, diffusion, and endocytosis . Phagocytosis seems to be the internalization pathway for CNT aggregates, bundles, cluster or single dispersed nanotubes whose length is 1 μm or more. Endocytosis is the internalization mechanism for nanotubes forming supramolecular structures, and diffusion is the internalization mechanism for submicron CNTs that do not form supramolecular complexes[47]. The conformation ofCNT perpendicular to the plasma membrane during uptakeresulted a mechanism identical to nanoneedle that perforate and diffuse through the lipid bilayer ofplasma membrane without inducing cell death. Dynamic simulation

studies have shown that amphiphilic nanotubes can theoretically migrate through artificial lipid bilayers via a similar mechanism[48, 49]. A second proficient way to observe CNT intracellular was improved by Weismann et al., who used near-infrared fluorescence[50].They showed that macrophage cells could ingest cabalistic amounts of nanotubes without perceptible toxic effects. The internalized tubes remained fluorescent and could be identified at wavelengths beyond 1100 nm. Therefore, there is fulcrum evidence that f-CNTs are capable of efficient cellular uptake by a mechanism that has not yet been clearly identified

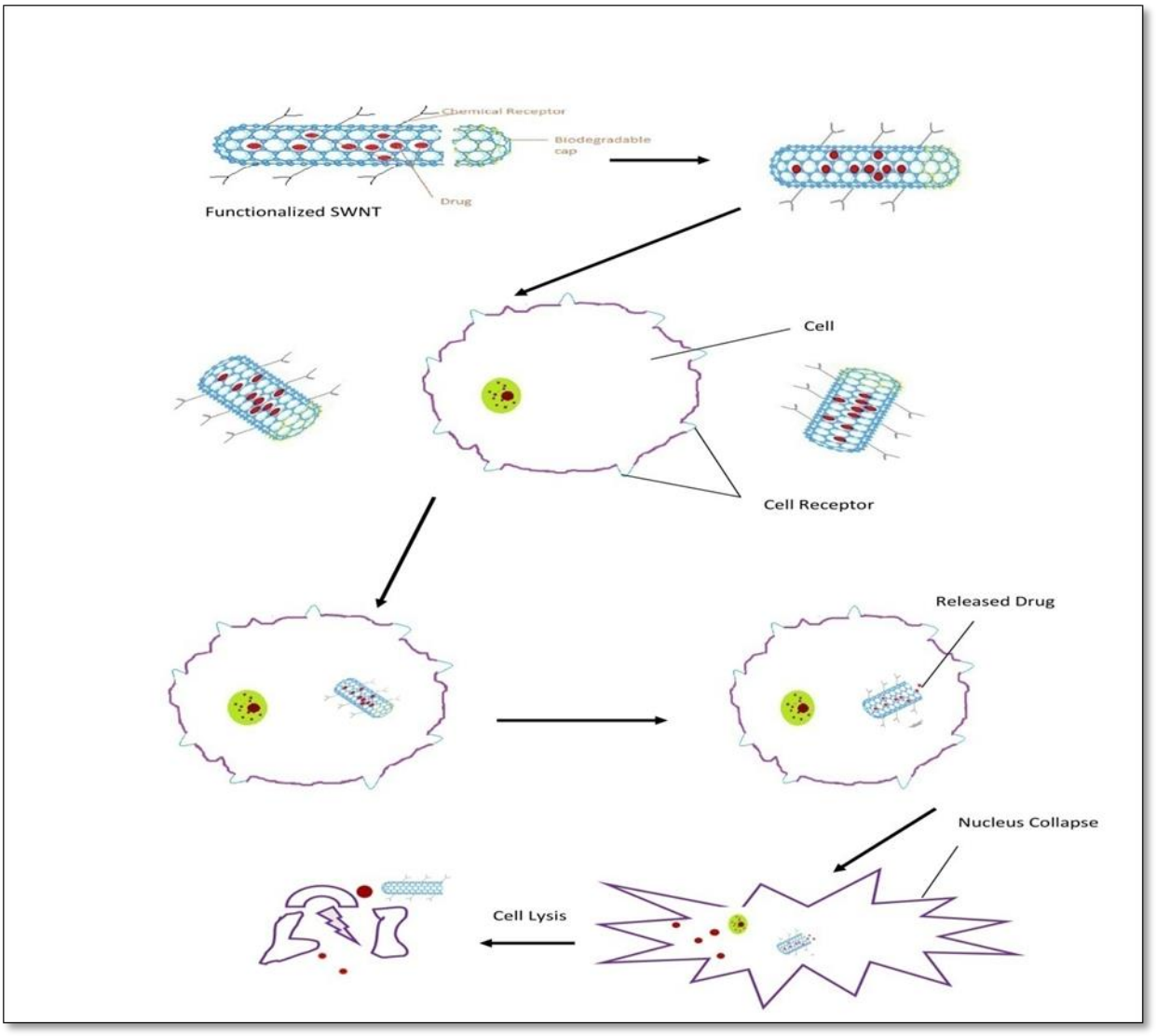
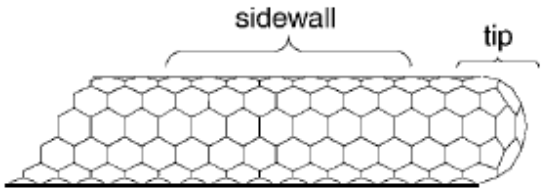


Fig 3.2 Solubilisation and Drug carrier mechanism of functionalized SWCNT

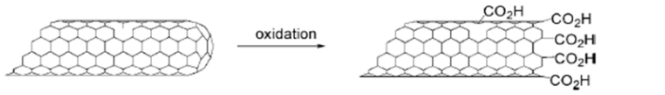
3.2 Carbon Nanotube Functionalization Chemistry

CNT are tubular objects with a high aspect ratio and a diameter in the Nano scale range [54] They can be classified by their structure into two main types: (i) single-walled carbon nanotubes(SWNT), which consist of a single layer of graphene sheet seamlessly rolled into a cylindrical tube[55] and (ii) multiwalled carbon nanotubes (MWNT), which comprise multiple layers of concentric cylinders with the space of about 0.34 nm between the adjacent layers.[56]

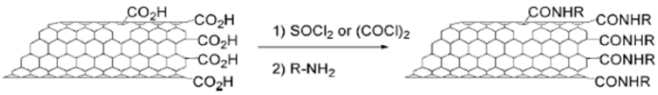
SCHEME 1. Molecular Structure of a Carbon Nanotube with Highlighted Tips and Sidewalls



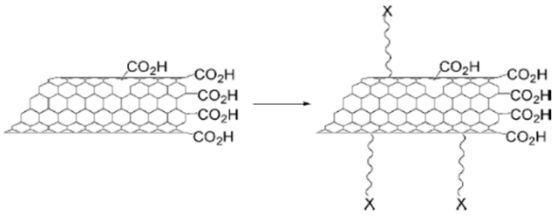
SCHEME 2. Oxidation of Carbon Nanotubes



SCHEME 3. Amidation Reaction of Oxidized Carbon Nanotubes



SCHEME 4. Functionalization of Carbon Nanotubes Using Addition Reactions (X = Functional Groups)



Scheme 1**:** From a chemical reactivity point of view, CNT can be differentiated in two zones: the tips and the sidewalls, which are shown in (scheme 1)

Scheme 2**:**The tips are reminiscent of the structure of a fullerene hemisphere and are relatively reactive.[57]The sidewalls can be approximately considered as curved graphite, the degree of curvature, of course, depending on the diameter of the tube.[58]However, whatever the diameter, the reactivity of the sidewalls is considerably lower than that of the tips. Therefore, most reactions are expected to occur at the tips first and then, in some cases, at the sidewalls, especially in the areas

wheredefects are present .This difference in reactivity has led to a selective oxidation of the tips,while the sidewalls remain inert.Since the as-produced CNT contain variable amounts of impurities, such as amorphous carbon and metallic nanoparticles,the initial efforts in their purification focused on the selective oxidation of the impurities with respect to the less reactive CNT. Use of strong oxidizing agents, such as concentrated nitric acid, led actually to purer materials.However,since the CNT tips do generally react under these conditions, the result is that the tubes open and the tips consist now of oxygenated functions, mainly carboxylic acids [59] Also, danglingbonds can react similarly, generating other functions at the sidewalls. All these things are shown in (scheme 2)

Scheme 3:The carboxylic functions can, in turn, lead to further derivatization. After conversion to acid chlorides, reaction with amines can afford the corresponding amides[60] This is shown in (Scheme 3).

Scheme 4: Another opportunity is given by the reactivity of the sidewalls. Cycle additions or radical reactions can be employed tocovalently attach molecular appendages to the CNT sidewalls4, which is shown in (Scheme 4).

3.3 Carbon Nanotubes as Nano containers

CNT can also be considered as Nano containers. Many molecules, ions, or metals can be possibly inserted [61] a number of different molecules, such as fullerenes, porphyries, and metals, have certainly been included in the internal space of CNT, mostly due to hydrophobic interactions[62]. Such constructs containing a metal or a metal complexcan clearly constitute potential candidates for the designof pharmaceuticals for diagnostic purposes and will be developed as novel contrast agents for different imaging modalities (Scheme 5).

3.4 Surface Area and Number of sites for Functionalization

Functionalized SWCNTs have some fundamental properties that lend themselves to targeted drug delivery and imaging, including: (i) Good biocompatibility, water solubility and low-toxicity following appropriate fictionalization; (ii) Excellent ability to cross cell membranes by clattering-mediated endocytosis; (iii) Bio distribution and pharmacokinetic properties that can be tuned by controlling the size, the surface chemistry, and the targeting groups; (iv) A high drug loading capacity and controlled drug release via pH, NIR light (Near Infrared light), temperature, etc.

For Armchair SWCNT the chiral indices are (n,n) .Therefore using equation (1) from chapter 2,

The diameter of armchair SWCNT is to be found –

Let, Armchair(5,5) ,D = $\frac{a}{\pi}\sqrt{25+25+25}$

$=\frac{0.249}{3.1416}\sqrt{75}$

$= 0.079\times 8.66$

$=0.686$ nm

So, radius, r = 0.343 nm

Similarly, for zigzag SWCNT the chiral indices are (n,0), so, using equation (1), the diameter of zigzag SWCNT is-

Let ,Zigzag(5,0), D = $\frac{a}{\pi}\sqrt{25+0+0}$

$=0.079\times 5$

$=0.395$ nm

So, radius, r = 0.1975 nm

Similarly, for chiral SWCNT the chiral indices are (n, m), so, using equation (1), the diameter of chiral SWCNT is-

Let ,chiral(5,10), D = $\frac{a}{\pi}\sqrt{25+100+250}$

$=01.045$ nm

So, radius, r = 0.5225 nm

Now we can write, Diameter : Chiral >Armchair >Zigzag

Surface area of chiral = 2πrh

$=2\times 3.1416\times 300\times 0.5225$ [for 300 nm longSWCNT]

$=984.89n$ nm^2

Surface area of ZigZag = 2πrh

$=2\times 3.1416\times 300\times 0.1975$ [for 300 nm longSWCNT]

$=372.2796n$ nm^2

Surface area of Armchair = 2πrh

$=2\times 3.1416\times 300\times 0.343$ [for 300 nm longSWCNT]

$=646.54128n$ nm^2

Now we can write, Surface Area : Chiral >Armchair >Zigzag

For 1319.472 nm^2 area, the number of C atoms is50,000[51-53].Therefore, for armchair SWCNT the number of C atoms in 646.54128n nm^2isapproximately 24,500n. Similarly, for zigzag SWCNT the number of C atoms in 372.2796n $nm^2$is approximately 14,107n.

It was shown that defects are present in the sidewalls of these pipes, as well as at the open ends[51, 52]**.** Theanalysis in which the evolution of CO or CO_2 upon heating the tubes was measured, demonstrated that about 5% of the C atoms in a pipe are localized at defects. Reactive groups, suitable for further functionalization of the tubes, lie at these defect positions[52].So, the number of sites for functionalization in case of armchair SWCNT isapproximately 1225n (24500n × 5%). And for zigzag SWCNT the number is approximately 705n (14,107n ×5%). Therefore, the number of functionalizable sites in armchair SWCNT is 1.73 times that of zigzag SWCNT.

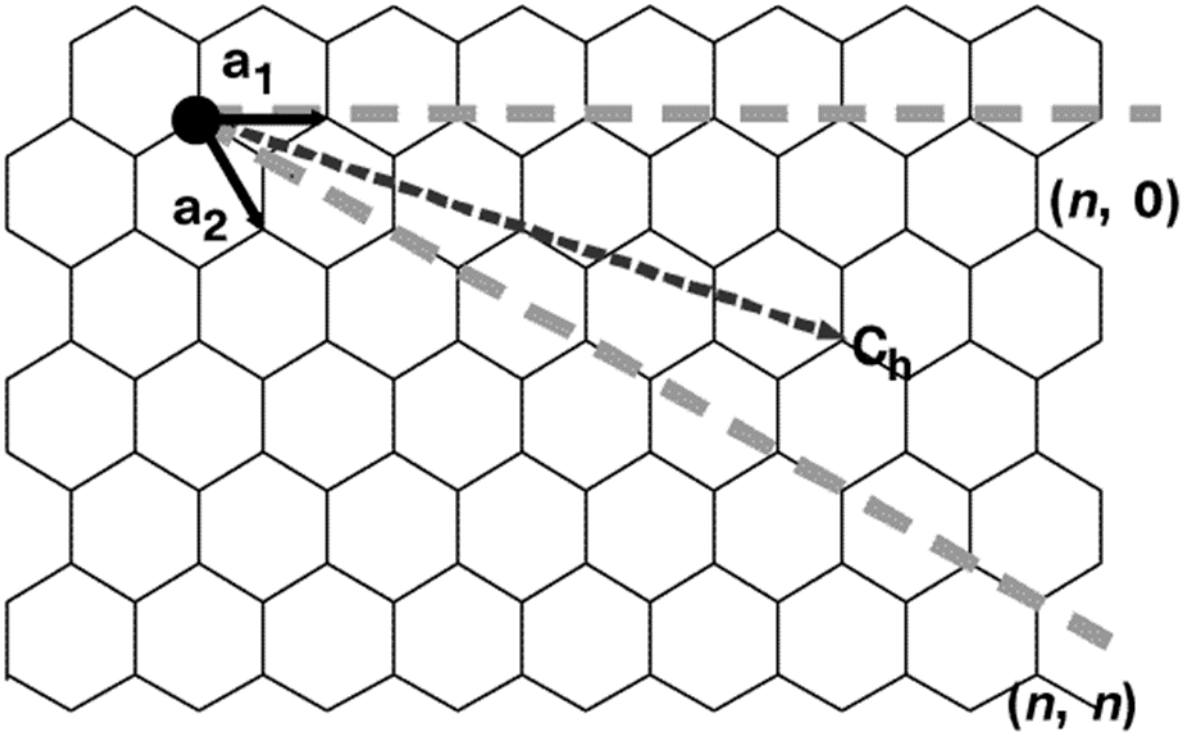


Fig 3.2 Surface area of SWCNT

Source: Odom, Teri Wang, Jin-Lin Huang, Philip Kim, and Charles M. Lieber. "Atomic structure and electronic properties of single-walled carbon nanotubes. “Nature 391, no. 6662 (1998): 62-64.

$\mathbf{c_h} = n\mathbf{a_1} + m\mathbf{a_2}$. The limiting cases of (n,0) zigzag and (n,n) armchair tubes are indicated with dashed lines. As represented here, the angle between the zigzag configuration and $\mathbf{c_h}$ is negative. Here, n= number of indices. Since the number of 'n' is higher in armchair, so the number of carbon atoms will be higher in armchair configuration compared to zigzag. As a result, it is more easier to functionalize armchair SWCNT than zigzag SWCNT. Due to more available active sites in armchair SWCNT, it is possible to get desired result by using less amount of SWCNT. It can be presumed that lesser amount of SWCNT can result less toxic effect to the cell as well as to the SWCNT carrier body.

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Chapter 4

Conclusion

In biological properties of SWCNT, organic functionalization has created a new horizon. The biocompatibility of SWCNT has been identified. The former SWCNT were highly toxic due to their insolubility. But when properly functionalized, SWCNT have a high tendency to cross cell membranes. In addition SWCNT can be charged with biologically active molecules, which can be delivered to the cell cytoplasm or nucleus. But most of the recent researches showed that SWCNT based drug delivery system can still become toxic to body cells due to lack of proper functionalization. Above all of this in this paper we have showed the comparatively better option for using SWCNT by calculating the surface area of two different types of SWCNTs. Here we noticed that the armchair SWCNT has higher surface than that of zigzag SWCNT. The larger surface of armchair is very effective as it has more available sites. If we can properly functionalize SWCNT we may have a novel carrier in drug delivery system.