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Nanotube: A New Approach to Novel Drug Delivery System

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Abstract

In present scenario the rise in nanotechnology has marked the greatest move forward in the development of more effective drug delivery systems. The novel nanotechnology has made the target drug delivery system quite easy and effective. Target drug delivery system is a method of delivering the active compound of the medicine to the affected site in the body. Through nanotechnology the transfer of drug is usually in more controlled and apt amount. Nanotubes help transfer the drug to the site of action without interfering with the functioning of non-target cells. This paper discusses the basic outline of what nanotubes are, particularly emphasizing on the carbon nanotubes. In this paper discussion on discovery of nanotubes and structure and functioning of the carbon nanotubes is also done. The recent usage of nanotubes in research of medicine is focused in making target drug delivery systems for therapies like cardiovascular therapy and in making of anti-infectious medicines. These usages of carbon nanotubes are also discussed in the paper.

Keywords: Nanotubes, carbon nanotubes (CNT), target drug delivery, cardiovascular therapy.

INTRODUCTION

A drug delivery system is defined as an engineered technology or a formulation that enables targeted delivery and controlled release of therapeutic agents. It allows therapeutic agents to reach its site of action selectively without affecting the non target cells, organs or tissues. This system is responsible for determining the rate of drug release in the body and also the site where the drug has to be released. The various ways of intake of medicines can be through inhalation, skin absorption, and intravenous injections or by swallowing them. For every medication different method of intake can be used as each intake method has its own merit and demerit. In order to improve the usage of prevailing medications there is a need for more efficient and effective drug delivery method either by improvising the existing ones or by discovering the new ones. For example, a new method of medicine intake has been designed which is called 'micro-needle array 'it allows medication to get absorbed through the skin. In the micro-needle array method, microscopic needles that are thinner than a hair strand are designed to contain medicine in them. These deliver the medication in a painless manner because the needles are so thin and small that they do not reach the nerves in the skin even though they penetrate the skin. Another such innovation in drug delivery system is the invention of the nano-tubes. With the advancement in the field of biotechnology there is easy availability of medications that can target diseases more precisely and accurately. Research has been carried out in order to design and formulated those drugs which can be used for specific diseases and health condition. The main purpose of designing targeted drug is to minimize chance of commencing dug resistance which is also the concern when the broad-spectrum antibiotics are used heavily. This technology has been extensively used in the field of medicine and is used in manufacture of nano-medicines as nano particles are of high utility in drug design.

The size of nanoparticles is between 1 and 100 nm. This technology is highly used in development of nanomedicine such as nanofluids for drug delivery, biosensors and microarray tests for tissue engineering. Nanotechnology has enabled the production of curative agents also. Nanotechnology has brought significant reforms in the field of biomedicine by enabling the formation and discovery of target drug delivery systems and biosensors etc. Nanoparticles are the spheres of very small size that are composed of materials designed at the atomic or molecular level. Due to the small size of nanoparticles these function at the molecular level. Nanomedicines have been popularized a lot in today's time because the nanoparticles can be utilized as delivery agents by encapsulating drugs or attaching therapeutic drugs and delivering them to target tissues in a precise and controlled manner with the help of these small molecules. A research study showed that by the use of nanotechnology, the treatment for certain fatal diseases like glioblastoma and cancer is also possible. Nanotechnology serves the purpose of site-specific and target oriented drug delivery of a particular medicine and hence it proves beneficial for the treatment of chronic diseases like cancer and rheumatism. Various nano medicines are available now which can be used as chemotherapeutic agents, biological agents and immunotherapeutic agents in the treatment of various diseases.

Nanotubes: Discovery, characteristics and structure

The discovery of carbon nanotubes was done by Sumio lijima in 1991. Nanotubes have tremendous physical and chemical properties in terms of being helpful in making nano medicine. In the initial phases of nanoparticle-based therapy, lipids like liposomes and micelles were used. The liposomes and micelles are good at containing inorganic nanoparticles like gold etc and are also good at holding magnetic particles as well. This property of nanoparticles has enhanced the use of inorganic nanoparticles by emphasing on drug delivery, imaging and therapeutics functions. Nanoparticles also helps in preventing destruction or wastage of medicines in the gastrointestinal region and also help in the delivery of sparingly water-soluble drugs to their specific targeted locations.

Carbon Nanotubes are cylindrical structures made up of carbon atoms and these are helpful in the process of drug delivery system. Nanotubes are carbon allotropes which are generally similar in aspects like thermal and electrical conductivity, have high mechanical strength and have good chemical inertness. Hence, these nanostructures play a crucial role in nanoscience, such as nanomedicine. The carbon anotubes can be classified in two forms:

(i) Single-walled carbon nanotubes (SWCNs): Single layer of grapheme constitutes the fundamental structure of the single-walled carbon Nanotube and catalyst is also used in this synthesis. High quantity synthesis of single walled carbon nanotube is difficult because it also needs properly controlled environmental factors. These Nanotubes have poor purity and there are higher chances of defect during the functionalization. These accumulate less in the body. The single walled carbon CNTs are highly malleable and can be easily twisted and molded. Characterization and evaluation of these is very easy.

(ii) Multiple-walled carbon tubes (MWCNs): These are made up of multiple graphene layers. These can be produced without the catalyst and hence their bulk synthesis is easy. Purity of multi-walled carbon Nanotube is high and a chance of defect is less but once occurred it is difficult to improve. These have more accumulation in the body. It has a very complex structure and is not very malleable and cannot be easily modified.

SWCNs contain one single graphite sheet which is cylindrical in shape. It has a diameter ranging from 0.4 to 3.0 nm. In contrary to this, MWCNs are an array of tubes, hence named as multi walled. There is a distance between the layers, and there is significant space between the graphite layers. The number of layers present in the MWCNs determines the diameter of the Nanotube. The inner diameter lies between 0.4 nm to a few nanometers and the outer diameter lies between 2 to 100 nm. There is some structural divergence that exists between SWCN and MWCN which is very distinct. For example, the length of the tubes of MWCNs has length in micrometer, whereas in case of SWCN, length is from 1 μm to a few centimeters. The SWCN have well-defined diameters, whereas in case of MWCN there are some structural defects, which makes them relatively less defined in terms of diameters and inturn structure. Hence MWCN are relatively less stable materials.

Functionality of Carbon Nanotubes:

In terms of functionality nanotubes have evolved tremendously since their discovery and have been contributing greatly in the field of target drug delivery systems. With the use of carbon nanotubes in the present drug delivery system, it gives the hope that the new advancements can be done in this field. Use of CNTs can prove advantageous over other types of delivery systems in the following ways:

a) CNTs diminish side effects by targeting agents.
b) It can be used as a carrier of drugs to provide therapeutic effects.
c) It can work without any side effects and can help avoid any adverse impact on the immune system.
d) It can be used as a diagnostic agent to monitor certain parts of the body.
e) It has a capacity of retaining several copies of drugs.

Use of SWCNs was attempted by Heisner et. al. who formulated triply functionalized SWCNs joined to doxorubicin as a cure against colon cancer. That system consisted of carcinoembryonic antigen (a monoclonal antibody) to identify tumor makers and fluorescein dye to track nanotubes within cells. After this the application of this system was done on human colon cancer cells, where fluorescence visualization via confocal microscopy showed that SWCNs–doxorubicin conjugate was taken up by cancerous cells and the release of doxorubicin, SWCNs remained in the cytoplasmic region of the cancer cells, while active pharmaceutical ingredients (API) fully reached the nucleus section where doxorubicin exerted its effects. This study proves that multiple functionalizations are beneficial to keep a check on the bioactivity of pharmaceutical compounds.

Functionalization of the CNTs is very commonly done. It is done through various techniques such as, covalent functionalization and non-covalent functionalization. Functionalisation is the process through which modification is possible in the nanotubes. Modifications in nanotubes can help in minimizing cytotoxicity and increasing biocompability.

Modifications in CNT

1. Covalent Modification:

Through covalent modification it is ensured that more stable derivatizations can be introduced in various functional groups on CNTs like halogens, carbenes, and arynes, etc. This technique facilitates the dispersion of CNTs because it allows the hydrophilic moieties of carbon present in the CNTs to ensure joining of these functional groups. Recently an approach to this is addition of required molecule through 1,3-dipolar cycloaddition reactions. In this the condensation of α-amino acids with an aldehyde results in azomethineylides that are made up of carbanion neighboring immonium ion. Once the ylides undergo cycloaddition reactions with dipolarophiles such as CNTs, they produce pyrrolidine intermediates. This pyrrolidine intermediate anchores the functional groups on to CNTs. Another very relevant form of covalent modifications is the oxidation of CNTs, which generates oxygen-containing functional groups like carbonyl, hydroxyl, and carboxylic acids etc. on both tips and defect sites of the molecule. Carboxylic acids have hydrophilic character and it allows further attachment of some other highly hydrophilic residues. Oxygen derivatives being of poor reactivity they require preactivation either by acyl chlorides or by a coupling agents such as carbodiimides and hydroxybenzotriazole. Therefore use of covalent modification system is still under extensive study and there are a lot of things yet to be discovered about it.

2.Non- Covalent Modification:

The system of noncovalent modification is more favorable because such modifications are done through simple reactions and conditions like sonication and centrifuge, and removes the requirement of harsh reaction conditions and availability of strong reagents. This method of functionalization poses no threat to the aromaticity of CNTs and the structural integrity of graphene surface and tips. The only drawback of noncovalent conjugates is that they may dissociate from CNTs in biological fluids or may even undergo exchange with serum proteins. Such a situation may raise a concern of toxicity. In recent studies molecules commonly used in noncovalent functionalizations are surfactants, polymers, and biological materials such as proteins, nucleic acids, and peptides. Their attachment to CNTs is physical adsorption on the outer walls of CNTs; this attachment is due to the van der Walls forces, π–π, and CH–π interactions. Recent studies on non-covalent modification of CNTs have revealed that aromatic compounds are more adequate dispersive agents because of better π–π interactions. For example, sodium dodecyl sulfate can disperse CNTs at the concentration of just 0.1 mg/mL however, since sodium dodecyl benzene sulfonate (SDBS) bears aromatic residues, it can disperse CNTs with approximately 10-fold higher concentration. It can be concluded that the materials mentioned above bind to CNTs in divergent geometries; while polymeric materials wrap CNTs to maximize van der Waals interactions, surfactants form micelle-like assemblies around graphitic surface. But still extensive research is yet to happen to study the structures formed by these associations.

Uptake capacity

Drug loading is defined as a process in which active drugs are conjugated with the carriers to make them into a final form of the drug delivery system. CNTs possess a spherical shape and high surface area to volume ratio, these have tremendous potential to accommodate drugs. To increase the loading capacity of the nanotubes, the hydrophilic and amphiphilic molecules can be attached to them to do so. This enables the nanomaterials to pharmaceutical agents through multiple ways, like encapsulation inside the cavity, attaching on the surface upon functionalization, and adsorption on the wall or among the walls of CNTs.

Pros and Cons of using the Carbon Nanotube:

Pros	Cons
It has unique mechanical properties which offer it intense in-vivo stability.	These are non-biodegradable, hence harmful to the environment in general.
It has extremely large aspect ratio and can enable mass production of drug delivery system on a large scale.	Great variety of carbon Nanotube makes standardization and toxicology evaluation a cumbersome process.
It is best used for target drug delivery system and used in controlled release of drug at the site where it is needed.	Tissue tolerance and accumulation in body can be a cause of toxicity because there are unknown parameters in it that require toxicological profiling of material.

Recent Application of CNT in DDS

In the last twenty years advancement in the nanotechnology has increased the awareness about utility of nanotubes in the field of pharmacy and medicine. In the field of medicine, these materials have been used extensively as nanovehicles to deliver various active pharmaceutical ingredient, peptides, proteins, and siRNAs. Especially functionalized CNTs are highly versatile systems and are compatible with many routes off administration. According to studies done on CNTs it is found that carbon nanotubes are highly effective in functioning as nano-carriers for the following conditions:

1. Anti-neoplastic
2. Anti- inflammatory
3. Cardiovascular
4. Anti- infection

Anti-neoplastic:

Cancer is one of the most fatal diseases that cause worldwide death. It is evident through studies that to cure cancer the actual challenge is to deliver active pharmaceutical ingredient specifically to the cancerous region of the human body. Failure to distinguish healthy tissues results in various side effects such as cardiac or systemic toxicity and development of resistance to the active pharmaceutical ingredient. Another challenge is the multi drug resistance in chemotherapy that has to be removed during the treatment. In order to survive antineoplastic agents, tumor cells express P glycoprotein that pumps the therapeutic agents back outside tissue. Hence, antineoplastic activity is hindered even before the drug is given the chance of killing tumorous cells. To curb these novel technologies of drug delivery systems which will be potent enough to avaoid such rejection is of paramount importance. Till now nanoparticles-based drug delivery system is by far the best remedy to act as a vehicle for anti-neoplastic medicine to be transferred to the target tumor. CNTs are utilized to carry antineoplastic agents, including campthothecin and cisplatin etc. without causing any distortions in the medicine.

Anti- inflammatory:

The nanotechnology has paved way for advance delivery of drugs at the areas affected by inflammation and infection. In order to improve the release profile of molecules and to improve the cellular intake properties more research is going on in this field. The area of stimulated drug release is also under study for curing inflammation. In this a stimulant triggers the release of the drug from its carrier. In this process, the nature of stimulant could range from a molecule like the release of insulin as a response to glucose or release could be triggered by physiological conditions like pH or temperature. These advancements can transform the way medical science attempts at curing various diseases and infections including inflammation as well.

Cardiovascular:

Cardiovascular diseases comprise of the diseases that are related to the heart and the blood vessels. According to World Health Organization, cardiovascular diseases are the primary cause of death in the world on a global scale. Until recently these cardiovascular diseases were cured with the help of conventional drug delivery system. The treatment of atherosclerosis and some other cardiovascular diseases such as cardiomyopathy, rheumatic heart disease, are restricted by the failure to transport anticardiovascular medicaments successfully across the endothelium. For example, rosiglitazone, activates receptor agonist that helps in curing atheroma by reducing macrophage infiltration into atherosclerotic lesions. However, some of its side effects like cytotoxicity and heart failure due to fluid retention over shadows the pharmaceutical benefits of this drug. By considering the mentioned side effects of this drug, there exist the needs for more effective drug transport systems that are useful in restoring the therapeutic efficiency of anticardiovascular agents. Other major reasons due to which there is high dependency on this novel transport system are:

(1) It improves the solubility of active pharmaceutical ingredients and increases the bioavailability of the active molecules in a drug.

(2) It avoids the chances of extreme active pharmaceutical ingredients loss by the way of urine discharge.

(3) It also improves the physical stability of the active pharmaceutical ingredients.

In order to deliver anti-cardiovascular agents without much complication, the following techniques that can be useful are macromolecular-aided, thiomermediated approaches, and silica particles. Among these techniques, the major focus is on the silica particles technique beacuse any success in drug delivery with this material brings forth other such techniques like carbon nanotubes (CNTs). With respect to the findings that silica-based nanomaterials are feaseable in the delivery of annexin V accelerates the use of nanomaterials in cardiovascular diseases. Similarly, CNTs also prove very advantageous in this context due to their distinct characteristics.

Anti-infective:

Various studies done in the field of medicine show that infectious diseases are yet one of the major concerns that needs to be worked upon for the well being of the human population. The major drawback of any delivery system is the resistance to the antibiotic against bacteria and the incapability to formulate newer versions of the antibiotics. In order to develop insight into it the scientists are doing elaborate research to study the complications and applications in drug delivery. The nanotubes are one such alternative that modern medicine is adopting because since CNTs are not any antibiotics as such so any medicine loaded onto them will safely reach the site of action and the existing bacteria will not be able to make any resistence towards the inorganic carbon nanotube. This technology will curb the limitation like most of the anti-infective APIs are not adequately absorbed by cells because of their poor solubility and weak cellular penetration ability, so CNTs will eliminate such problems. Nanotechnology-based drug delivery approaches, such as CNTs, are useful in concentrating drugs in pathogenic cell regions, and hence it will help to cope with bacterial resistance. CNTs can be indirectly augmented that enhances the solubility of therapeutic agents, which drug delivery systems are attached to hence enabling no wastage of the drug.

CONCLUSION

With the advancement in technology the medicine sector is highly benefitted as the nanotechnology has enabled the development of the target drug delivery systems. Through this paper it can be concluded that the carbon nanotubes are certainly a very potent method through which medicine can be subjected to the target area without affecting the non-target tissues. Carbon nanotubes can be used in cancer treatment to transfer the chemotherapeutic drugs only to the affected area. They can be also used in gene therapy. It can be concluded that nanotechnology has proven to be a boon to the mankind in terms of advanced medicine. Though this area of drug delivery system is highly effective still there is a lot of research yet to be done in the area of toxicology pertaining to carbon nanotubes and effective mass production of them.

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