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AN OVERVIEW ON NANOTECHNOLOGY AND NANO-ENABLED DRUG DELIVERY SYSTEM

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ABSTRACT

Nanotechnology a next generation Techniques and rapidly developing subdivision have many advantages including highly specific medical interventions for prevention, diagnosis, and treatment of diseases, including cancer disease. Nanotechnology is an emerging branch of science for designing tools and devices of size 1–100 nm, with unique functions at the cellular, atomic and molecular levels. Over the past two decades, the rapid developments in nanotechnology have allowed the incorporation of multiple therapeutic, sensing, and targeting agents into nanoparticles, for detection, prevention, and treatment of cancer diseases. Nanoparticles offer many advantages as drug carrier systems since they can improve the solubility of poorly water-soluble drugs, modify pharmacokinetics, increase drug half-life by reducing immunogenicity, improve bioavailability, and diminish drug metabolism. They can also enable a tunable release of therapeutic compounds and the simultaneous delivery of two or more drugs for combination therapy. Carbon nanotube Techniques have been developed to produce nanotubes in sizeable quantities, including arc discharge, laser ablation, and chemical vapor deposition. The present article focuses on the current status and the future implications of nanotechnologies into diagnostic and therapeutic applications in various types of disease.

KEYWORDS

Nanotechnology, Nanomedicine, Devices Based on Nanotechnology, Nanotube, Nanodrugs and their biopharmaceutical characteristics.

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INTRODUCTION

A drug that is administered orally must survive in the harsh environment of the GI tract and should be absorbed. The bioavailability of drugs where dissolution is rate limiting becomes a challenge for effective delivery via the oral route. Hence, protective measures are required to avoid drug destruction on one hand and potentiation of absorption on the other hand in the GI tract. This

objective can be accomplished by incorporating the drug into various novel drug delivery systems[1]. Nanotechnology has the potential to offer solutions to these current obstacles in therapies, due to its unique size (1-100 nm) and large surface volume ratios.

Nanotechnologies may have properties of self-assembly, stability, specificity, drug encapsulation and biocompatibility as a result of their material composition. The use of nanometer size molecules, which range from 100 nm or even smaller attain their unique properties. Thus, nanotechnology can help in early detection of tumors and other diseases[2]. Nanparticles offer many advantages over their free drug counterparts. Notably, nanoparticles are capable of: (i) encapsulating and protecting drugs from degradation or deactivation prior to reaching target site *in vivo*, (ii) improving targeting over free drugs via presentation of tissue-specific targeting ligands, (iii) offering controlled drug release by modifying nanoparticle polymer composition, and (iv) production in large, reproducible, batches[3]. Nanotechnology is widely used in medicine in areas such as drug development, and imaging. Furthermore, the targeted delivery of drugs to diseased cells, such as cancer cells, this is an effective, and safer way of treating a disease. The potential applications of nanotechnology yare very vast; however, one of the greatest values of nanotechnology will be in the development of new and effective medical treatments[4-7].

The application of nanotechnology concepts to medicine joins two large-scale cross-disciplinary fields with an unprecedented societal and economical potential arising from the natural combination of specific achievements in the respective fields. Nanoparticles are currently being tested for molecular imaging to achieve a more precise diagnosis with high-quality images. In fact, contrast agents have been loaded onto nanoparticles for tumor and atherosclerosis diagnosis. Different nanoparticles have been used for molecular imaging with magnetic resonance images (MRI), ultrasound, fluorescence, nuclear, and computed tomography imaging. Application of nanoparticles and nanomaterials for the diagnostic and therapeutic purposes are now significantly extended in nanomedicine. Nanomedicine involves utilization of nanotechnology for the benefit of human health and wellbeing. The use of nanotechnology in various sectors of therapeutics has revolutionized the field of medicine where nanoparticles of dimensions ranging between 1 and 100 nm are designed and used for diagnostics, therapeutics and as biomedical tools for research[8-10].

Nanotechnology plays an important role in therapies of the future as bnanomedicinesQ by enabling this situation to happen, thus lowering doses required for efficacy as well as increasing the therapeutic indices and safety profiles of new therapeutics. Nanotechnology strategies are expected to involve the creation and/or manipulation of materials on the nanometer scale, either by scaling up from single groups of atoms or by refining or reducing bulk materials into nanoparticles. “Nanotechnology” was first defined by Tokyo Science University, Norio Taniguchi in 1974. Although the application of nanotechnology to medicine appears to be a relatively recent trend, the basic nanotechnology approaches for medical application dates back to several decades[11-14].

The growing fields of nanoscience and nanotechnology have transformed many sectors of industry, with breakthrough applications in the areas of biotechnology, electronic, cosmetics, food sciences, and pharmaceutics. In particular, strategic application of nanotechnologies to pharmaceutical research and development has led to the successful development of nanodrugs, described as drug delivery systems developed to operate at the nanometer size range with novel engineered properties that provide medical benefits in the clinical treatment of several diseases[15-19].Nanomaterials are being used in the production of consumer products such as sunscreens, cosmetics and food products such as is bottles made with nanocomposites that minimize the leakage of carbon dioxide out of the bottle thus increasing the shelf life of carbonated everages without having to use heavier glass bottles or more expensive cans.

Another example is food storage bins with silver nanoparticles embedded in the plastic. The silver nanoparticles kill bacteria from any food previously stored in the bins, minimizing harmful bacteria[20-22]. Nanotechnology will offer the tools to explore the frontiers of medical science at a cellular level. It can provide novel techniques in the treatment of a multitude of diseases including cardiovascular disorders[23,24].

NANOTECHNOLOGY[1-7]

'Nano' is derived from the Greek word, which means 'dwarf'. Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization, and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale (one billionth of a meter). Therefore, nanomaterial or a nanodevice can be considered as a particle with a maximum size of 1 × 10−7 m. The term 'nanotechnology' was first used in 1974when Norio Taniguchi, a researcher at the University of Tokyo used it to refer to the ability to engineer materials precisely at the nanometer level. Nanotechnology is widely used in medicine in areas such as drug development, and imaging. Furthermore, the targeted delivery of drugs to diseased cells, such as cancer cells, this is an effective, and safer way of treating a disease. The potential applications of nanotechnology are very vast; however, one of the greatest values of nanotechnology will be in the development of new and effective medical treatments.

NANOMEDICINE[8-12].

The applications of nano- technology in medicine led to the emergence of a new discipline in science known as 'nanomedicine'. Nanomedicine is the study of nanomaterials to improve diagnosis, control, prevention and treatment of diseases. This goal is achieved by selective delivery of active ingredients, including pharmaceuticals, diagnostic agents, and therapeutic moieties, to a target site using nanomaterials. Nanotherapeutics, nanodiagnostics, engineered nanodevices, nanostructures and nanomedical devices are the tools of nanomedicine to monitor, control, repair and reconstruct a biological system at molecular or even atomic levels.

DEVICES BASED ON NANOTECHNOLOGY[1-20]

Nanoshells

Nanoshells (NS) are gold coated miniscule beads. The wavelength of light which the beads absorb is related to the thickness of the coatings. Thus, by manipulating the thickness of the layers making up the NS, the beads can be designed that absorb specific wavelength of light. The most useful NS are those that absorb near infrared light that can easily penetrate several centimeters in human tissues. Absorption of light by NS creates an intense heat that is lethal to cells. Metal NS which are intense near-infrared absorbers are effective both *in-vivo* and *in-vitro* on human breast carcinoma cells.

Quantum dotes

These are tiny crystals that glow when these are stimulated by ultraviolet light. The latex beads filled with these crystals when stimulated by light, emit the color that lights up the sequence of interest. By combining different sized quantum dotes within a single bead, probes can be created that release a distinct spectrum of various colors and intensities of lights, serving as sort of spectral bar code. Latex beads filled with crystals can be designed to bind to specific DNA sequences. When the crystals are stimulated by light, the colors they emit serve as dyes and light up the sequences of interest.

Liposomes

Liposomes are self-assembling, spherical, closed colloidal structures composed of lipid bilayers that surround a central aqueous space. Liposomal formulations have shown an ability to improve the pharmacokinetics and pharmacodynamics of associated drugs. Liposome based formulations of several anticancer agents have been approved for the treatment of metastatic breast cancer and Kaposi's sarcoma.

Cantilevers

Tiny bars anchored at one end can be engineered to bind to molecules associated with cancer. These molecules may bind to altered DNA proteins that are present in certain types of cancer monitoring the bending of cantilevers; it would be possible to tell whether the cancer molecules are present and hence detect early molecular events in the development of cancer cells.

Dendrimers

Dendrimers are new class of macromolecules which have asymmetric core and form the 3-D spherical structure. These have branching shape which gives them vast amounts of surface area to which therapeutic agents or other biologically active molecules can be attached. A single dendrimer can carry a molecule that recognizes cancer cells, a therapeutic agent to kill those cells, and a molecule that recognizes the signals of cell death. It is said that dendrimers can be manipulated to release their contents only in the presence of certain trigger molecules associated with cancer.

Respirocytes

Respirocytes are hypothetical artificial red bloodcells are nanodevices which can function as red blood cells but with greater efficacy. These have higher capacity to deliver oxygen to tissues, supplying 236 times more oxygen per unit volume than natural red blood cells. These devices have sensors on the surface which can detect changes in the environment and the onboard nanocomputer will regulate the intake and output of the oxygen and carbon dioxide molecules. An infusion of one litre dose of 50 per cent respirocytes saline suspension in a human can theoretically keep the patient oxygenated up to four hours following cardiacarrest 19, 81. Respirocytes, considered as a device by FDAare regulated under the provisions of the Medical DeviceAmendments of 1976, the Safe Medical Devices Act of1990.

Microbivores

Microbivores are hypothetical structures which function as white blood cells in the blood stream designed to trap circulating microbes. They are expected to have greater efficacy than cellular blood cells in phagocytosis. The microbivores surface is arranged with processes which can extend in length and secure the microbe which gets in contact with it. The microbe will be gradually manoeuvred to the ingestion port and undergoes the process of morcellization and enzymatic degradation. The end products are released as amino acids, fatty acids, nucleotides and sugars. Application of the microbivores in human circulation could theoretically clears the blood stream in septicemia at a much greater rate than the natural defense mechanism with antibiotics.

Nanotubes

Nanotubes are smaller than nanopores. Nanotubes help to identify Dioxyribonucleic acid (DNA) changes associated with cancer cells. They are about half the diameter of a molecule of DNA. It helps to exactly pin point location of the changes. Mutated regions associated with cancer are first tagged with bulky molecules. The physical shape of the DNA can be traced with the help of the nano tube tip. A computer translates the information into topographical map. The bulky molecules identify the regions on the map where mutations are present. Since the location of mutations can influence the effects they have on a cell, these techniques are important in predicting disease.

CARBON NANOTUBES[42,43,44]

Carbon nanotubes (CNTs) are allotropes of carbon with a nanostructure that can have a length-to-diameter ratio greater than 1,000,000. Techniques have been developed to produce nanotubes in sizeable quantities, including arc discharge, laser ablation, and chemical vapor deposition. Developments in the past few years have illustrated the potentially revolutionizing impact of nanomaterials, especially in biomedical imaging, drug delivery, biosensing, and the design of functional nanocomposites. Methods to effectively interface proteins with nanomaterials for realizing these applications continue to evolve. The high surface-to-volume ratio offered by nanoparticles resulted in the concentration of the immobilized entity being considerably higher than that afforded

by other materials. CNTs are allotropes of carbon. They are tubular in shape, made of graphite. CNTs possess various novel properties that make them useful in the field of nanotechnology and pharmaceuticals. They are nanometers in diameter and several millimeters in length and have a very broad range of electronic, thermal, and structural properties. These properties vary with kind of nanotubes defined by its diameter, length, chirality or twist and wall nature. Their unique surface area, stiffness, strength and resilience have led to much excitement in the field of pharmacy.

HISTORY[45,46]

In 1981 a group of Soviet scientists published the results of chemical and structural characterization of carbon nanoparticles produced by a thermocatalytical disproportionation of carbon monoxide. Using TEM images and XRD patterns, the authors suggested that their "Carbon multi-layer tubular crystals" were formed by rolling graphene layers into cylinders In 1987, Howard G. Tennent of Hyperion Catalysis was issued a U.S. patent for the production of "cylindrical discrete carbon fibrils" with a "constant diameter between about 3.5 and about 70 nanometers, length 10^2 times the diameter, and an outer region of multiple essentially continuous layers of ordered carbon atoms and a distinct inner core". A large percentage of academic and popular literature attributes the discovery of hollow, nanometer sized tubes composed of graphitic carbon to SumioIijima of Nippon Electric Company in 1991. A 2006 editorial written by Marc Monthioux and Vladimir Kuznetsov in the journal Carbon has described origin of the carbon nanotube.

COMPONENTS OF CARBON NANOTUBES[47,48]

Carbon

Carbon, element six on the periodic table, is one of the most abundant substances on earth. Existing alone or in combination with other elements, compounds of carbon are prevalent in both solid and gaseous phases at room temperature and ambient pressures. It is the central element in essential organic compounds such as proteins, lipids, hydrocarbons, and polymers.

Graphite

Graphite is the most common, natural equilibrium form of pure carbon in solid structure. It is stable at both ambient pressures and temperatures and is universally found in pencil lead and lubricants. Thought to be the stiffest material in existence, graphite is anisotropic and possesses characteristics of high thermal conductivity. Graphite's crystal structure is illustrated in Figure No.1. Solid graphite is formed by stacking sheets of carbon atoms, called graphenes, in a honeycomb lattice. Each carbon atom is covalently bonded to three neighboring carbon atoms[1].

Fullerenes

In the mid-1980s, Smalley and co-workers at Rice University developed the chemistry of fullerenes. Fullerenes are geometric cage-like structures of carbon atoms that are composed of hexagonal and pentagonal faces. The first closed, convex structure formed was the C_{60} molecule. Named after the architect known for designing geodesic domes, R. Buckminster Fuller, buckminsterfullerene is a closed cage of 60 carbon atoms where each side of a pentagon is the adjacent side of a hexagon similar to a soccer ball (the C_{60} molecule is often referred to as a bucky ball). A few years later, their discovery led to the synthesis of carbon nanotubes[2].

Abbreviations

Chol, cholesterol; DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; DSPE, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine; DSPG, 1,2-distearoyl-sn-glycero-3-phosphoglycerol; IP, intraperitoneal; IV, intravenous; PC, phosphatidylcholine; PG, phosphatidylglycerol; PEG, polyethylene glycol; PLA, polylactic acid; PLGA, poly(lactic-co-glycolic acid); RES, reticuloendothelial system; siRNA, small interfering ribonucleic acid; VIP, vasoactive intestinal peptide.

Table No.1: Nanodrugs and Their Biopharmaceutical Characteristics[15-24]

Formulation	System	Route	Observed pharmacokinetics/pharmacodynamics in vivo
Dendrimers			
Doxorubicin	Polylysinedendrimer	IV	Prolonged systemic exposure Enhanced accumulation in tumor tissues
Flurbiprofen	Poly(amidoamin) dendrimer	IV	High distribution and retention in site of inflammation
Flurbiprofen	Poly(amidoamin) dendrimer	IV	Prolonged systemic exposure
Engineered nanoparticles			
Carbendazim	Nanocrystals	Oral	Improved oral bioavailability
Cilostazol	Nanocrystals	Oral	Improved oral bioavailability
Curcumin	Nanocrystals	Oral	Improved oral bioavailability
Danazol	Nanocrystals	Oral	Improved oral bioavailability
Diclofenac	SoluMatrix™ fine particle technology	Oral	Faster absorption and prompt pain relief
Fenofibrate	Nanocrystals	Oral	Improved oral bioavailability
Indomethacin	SoluMatrix fine particle technology	Oral	Faster absorption
Megestrol acetate	Nanocrystals	Oral	Improved oral bioavailability
Nitrendipine	Nanocrystals	Oral	Improved oral bioavailability
Nobiletin	Nanosized amorphous particles	Oral	Improved oral bioavailability and hepatoprotection
Tranilast	Nanocrystals	Oral	Improved oral bioavailability and rapid absorption
Lipid nanosystems			
Cinnarizine	Self-emulsifying drug delivery system	Oral	Improved oral bioavailability
Coenzyme Q10	Solid self-emulsifying drug delivery system	Oral	Improved oral bioavailability
Cyclosporin A	Self-emulsifying drug delivery system	Oral	Improved oral bioavailability with low variability
Halofantrine	Self-emulsifying drug delivery system	Oral	Improved oral bioavailability
Simvastatin	Self-emulsifying drug delivery system	Oral	Improved oral bioavailability
Liposomes			
Amikacin	Liposome(Phospholipid/Chol)	IV	Extended half-life of the drug in vitreous
Amphotericin B	Liposome (PC/Chol/DSPG)	IV	Increased systemic exposure, decreased RES uptake
Cytarabine/ daunorubicin	Liposome (DSPC/DSPG/Chol)	IV	Decreased clearance
Doxorubicin	Liposome, PEGylated liposome	IV	High distribution in neoplastic tissue
O-palmitoyltilisolol	Liposome (PC/Chol)	IV	High distribution and retention in the vitreous
Paclitaxel	Liposome (PC/PG)	IV	Prolonged systemic exposure

Prednisolone	Liposome (PC/Chol/10% DSPE-PEG2000)	IV	Increased and prolonged systemic exposure
Solid lipid nanoparticles			
Azido-Thymidine	Solid lipid nanoparticles	IV	Enhanced permeability and retention to brain
Clozapine	Solid lipid nanoparticles	IV	Increased systemic exposure, decreased clearance
Diclofenac Na	Solid-in-oil nanosuspensions	Dermal	Increased percutaneous absorption
Insulin	Lectin-modified solid lipid nanoparticles	Oral	Improved oral bioavailability
Lidocaine	Solid lipid nanoparticles	Dermal	Controlled dermal permeation and duration of action
Micelles			
Camptothecin	Block copolymeric micelles	IV	Prolonged systemic exposure
Doxorubicin	Block copolymeric micelles	IV	Increased systemic exposure, decreased clearance
Paclitaxel	Block copolymeric micelles	IV	Increased systemic exposure, decreased clearance
Pilocarpine	Block copolymeric micelles	Ocular	Increased miotic activity
Tranilast	Self-micellizing solid dispersion	Oral	Improved oral bioavailability
Polymeric nanoparticles			
Celecoxib	Ethyl cellulose/casein nanoparticles	Oral	Improved oral bioavailability
Clotrimazole/econazole	PLGA and alginate nanoparticles	Oral	Improved oral bioavailability
Docetaxel	PLA-PEG nanoparticles	IV	Extended half-life, enhanced antitumor effect
Doxorubicin	PLGA nanoparticles	IV, IP	Extended half-life, reduced distribution to heart
Glucagon	PLGA nanoparticles	Pulmonary	Extended half-life and enhanced bioavailability
Insulin	Hydrogel nanoparticles	Oral	Improved oral bioavailability
Paclitaxel	Albumin nanoparticles	IV	Low inter-/intrapatient variability, tumor targeting
Rifampicin	PLGA nanoparticles	Oral	Improved oral bioavailability
siRNA	Chitosan analog nanoparticles	Oral	Improved systemic distribution and gene silencing
VIP derivative	PLGA nanoparticles	Pulmonary	Enhanced anti-inflammatory effects

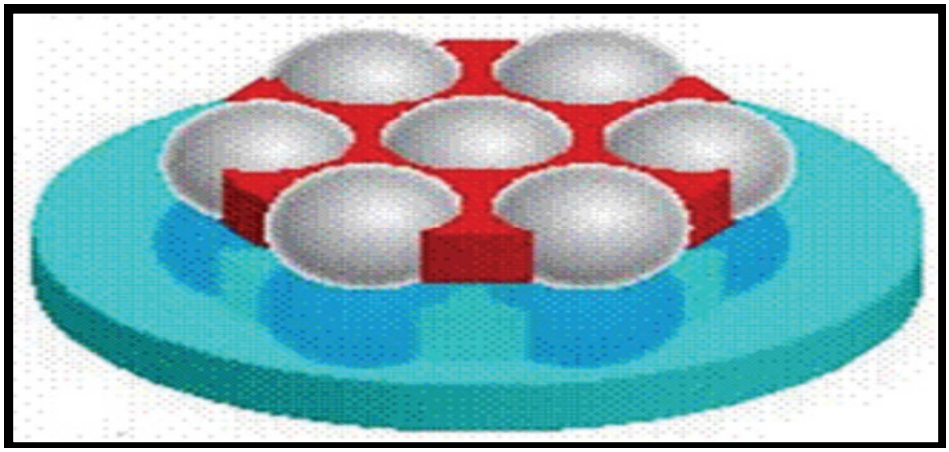

Figure No.1: Nanoshell

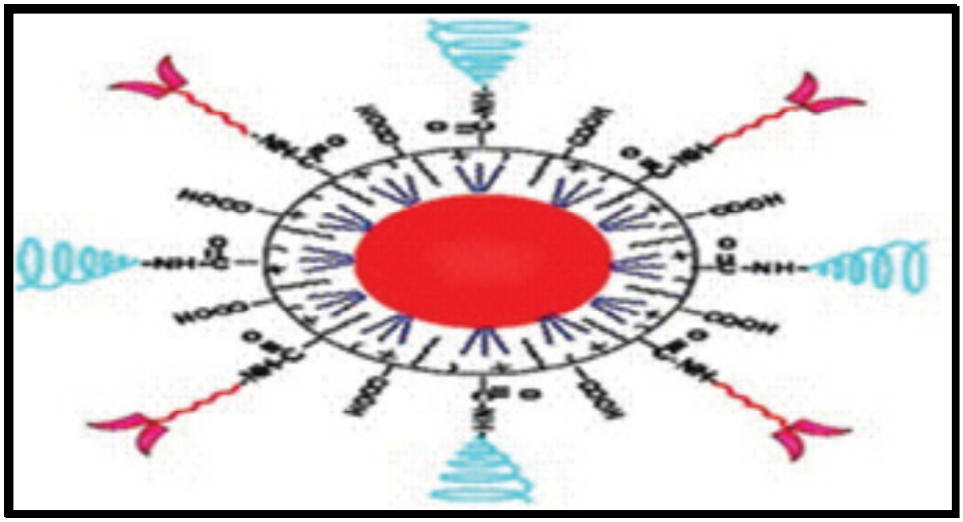

Figure No.2: Antibody conjugated quantum dotes

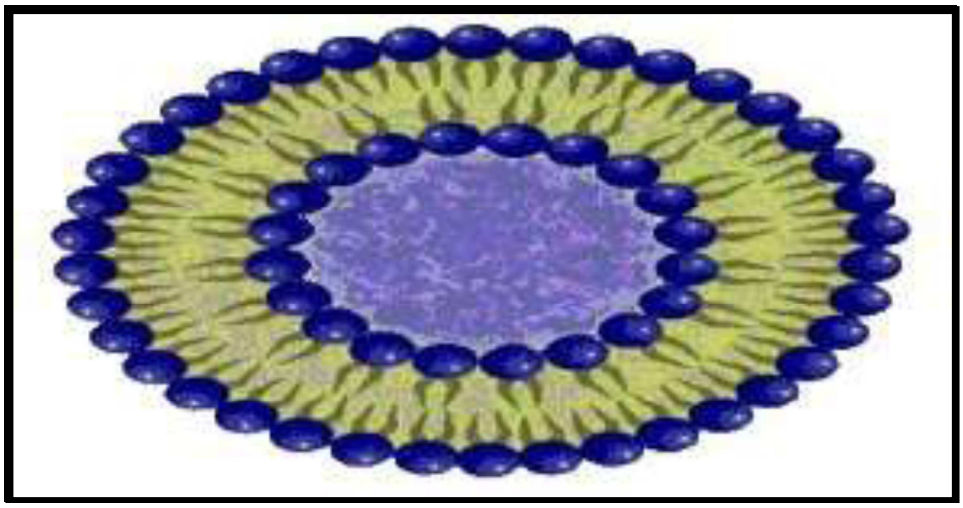

Figure No.3: Bilayer structure of liposomes

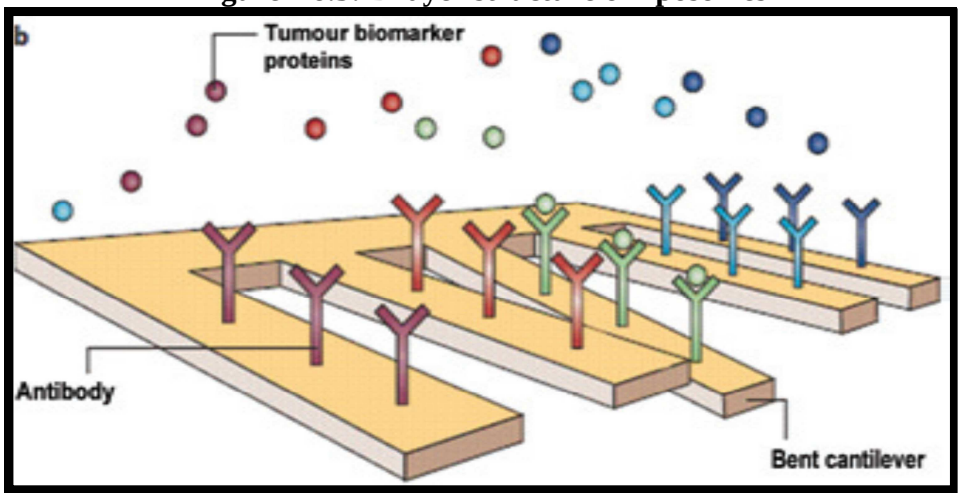

Figure No.4: Cantilever

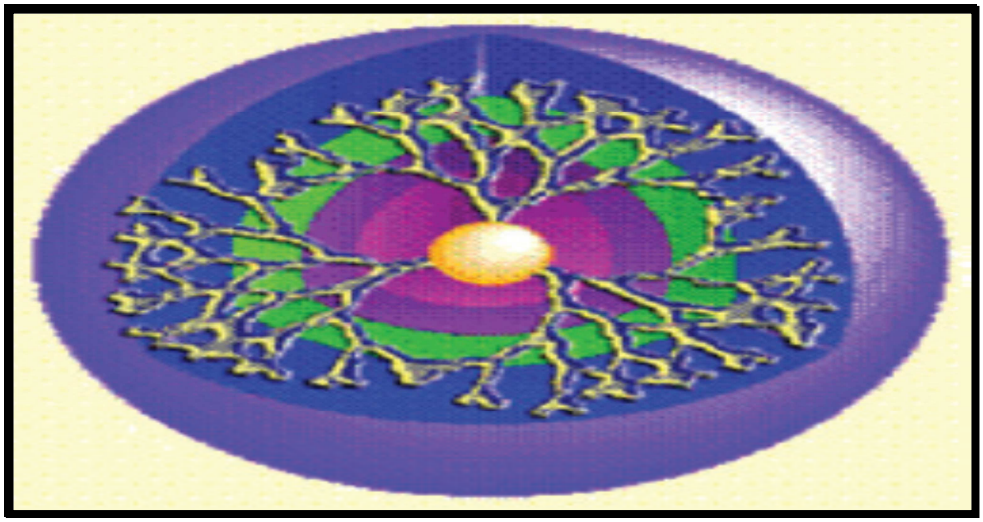

Figure No.5: Dendrimer

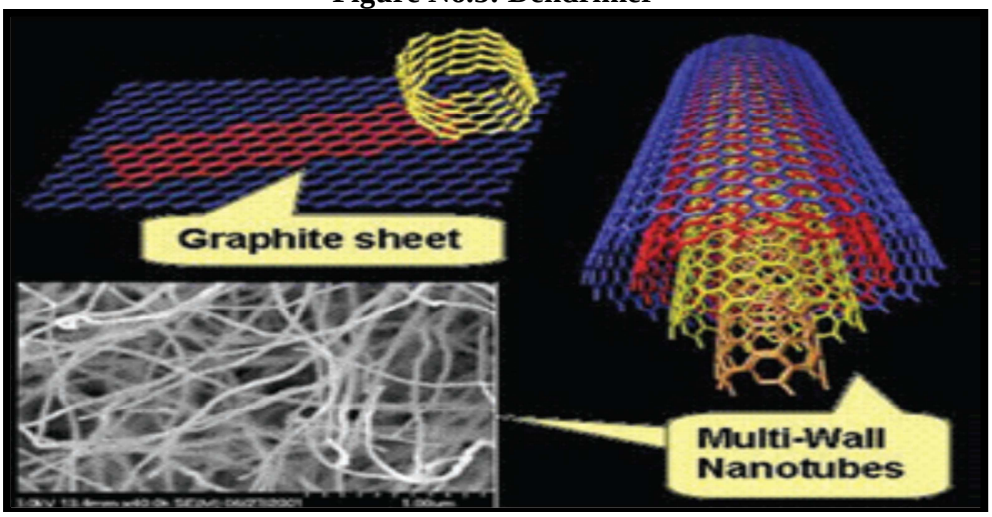

Figure No.6: Nanotube

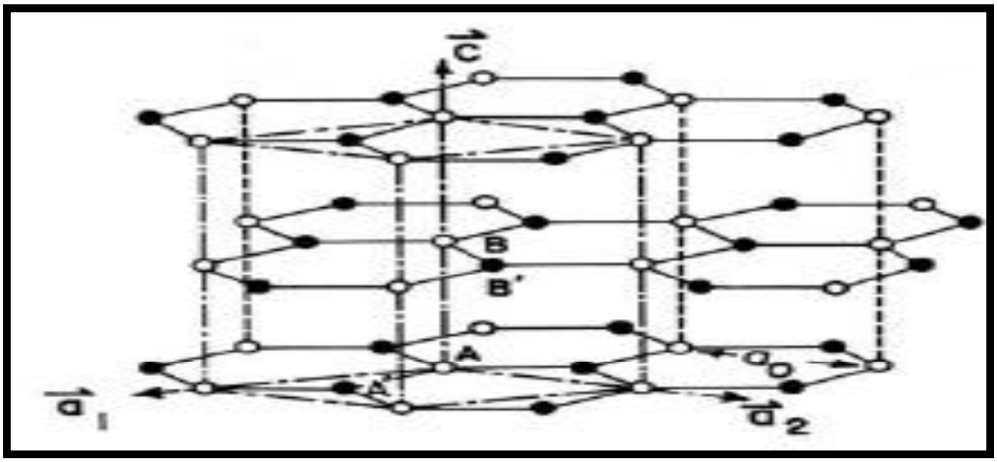

Figure No.7: Honeycomb Crystalline Lattice for Graphite

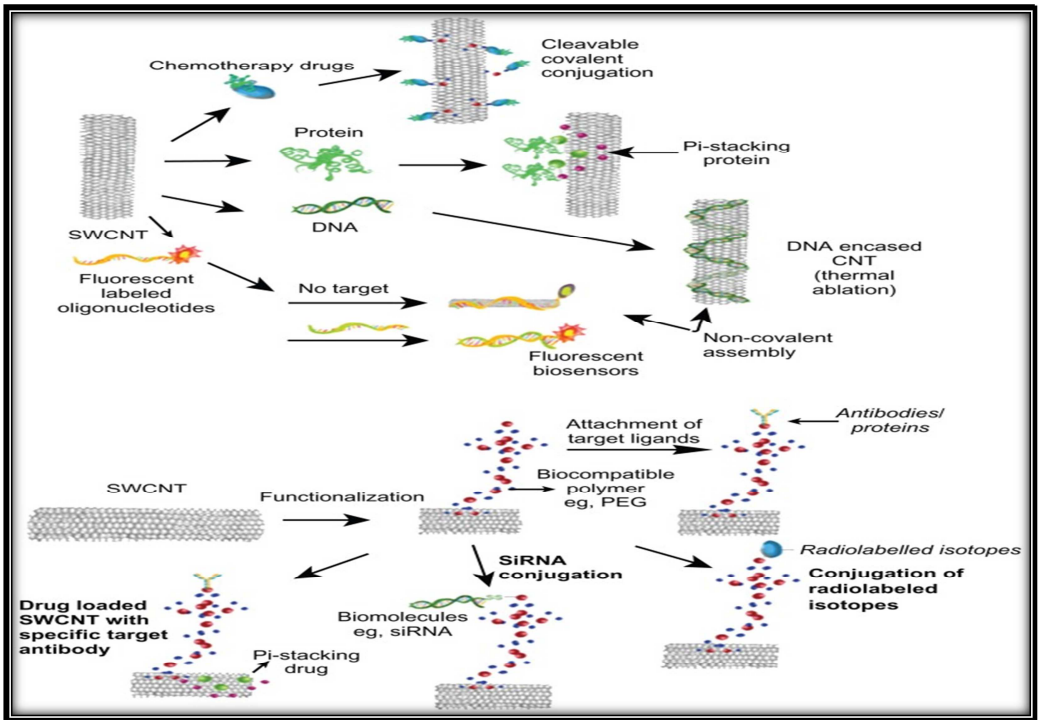

Figure No.8: Overview of functionalization of carbon nanotubes (CNTs) using different molecules and their biomedical application

CONCLUSION

Nano‑enabled technologies thus provides an alternative and superior approach to assess the onset or progression of diseases, to identify targets for treatment interventions as well as the ability to design more biocompatible, microbe resistant dental materials, and implants. Multifunctionality is the key advantage of nanoparticles over traditional approaches. Targeting ligands, imaging labels, Therapeutic drugs and many other functional moieties can all be integrated into the nanoparticle conjugate to allow for targeted molecular imaging and molecular therapy of cancer. Gold nanoparticle is unique in a sense because of its intriguing optical properties which can be exploited for both imaging and therapeutic applications. Nanotechnology also carries a significant potential for misuse and abuse on a scale and scope never seen before. Nanotechnology might cause adverse effects to human health and environment that are poorly understood. How the world reacts to the application of nanotechnology is yet to be seen. A successful future of nanotechnology will only be achieved through open sharing of ideas, research findings, testing, and forthright discussions. The future of nanomedicine will depend on rational design of nanotechnology materials and tools based on a detailed and thorough understanding of biological processes rather than forcing applications for some materials currently in vogue.

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CONFLICT OF INTEREST

We declare we have no conflict of interest.

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