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NANOTECHNOLOGY BASED TARGETED DRUG DELIVERY SYSTEM – REVIEW

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ABSTRACT

The sector of nanotechnology now has important roles in electronics, biology and medicinal drug. The most rising branch in pharmaceutical sciences known as "Pharmaceutical nanotechnology" introduces new instruments, openings and extension, which are required to have huge applications in sickness diagnostics and therapeutics. Nano technological application is significantly vital within the subject of drug because of its excessive specificity towards the target, so it is able to reduce toxic aspect results of medicine to normal cells. Decrease plasma variance of medications, high dissolvability, proficiency, lessens cost of items and upgrade of tolerance comfort are reasons that nanotechnology is utilized for sedate conveyance. The nanoparticle (NP) assumes an imperative part and it can conjugate with different medications by various strategies to convey medications to the objective site. The NP surface is designed with ligands to get affinity closer to precise cells and co-polymers to get safety from immune cells. The nanoparticles conjugated drug can eventually recognize the site and join to the target and enter to the cell by receptor mediated endocytosis. Then NPs are able to release drugs controllably to cure diseases. In this review specifically, we highlight the recent advances of this technology for medicine and drug delivery systems.

KEYWORDS

Drug delivery, Nanotechnology, Nanoparticle, Receptors and Conjugate.

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INTRODUCTION

Nanotechnology is a field of applied science and technology which aims to develop devices and dosage forms in the range of 1 to 100 nm. The packages of nanotechnology for remedy, analysis, tracking, and control of organic systems have currently been known as nanomedicine. The nanocarriers have been made of safe materials, including synthetic biodegradable polymers, lipids, and polysaccharides[1].

It involves the study of the control of matter on an atomic and molecular scale. This molecular level investigation is at a range usually below 100 nm. In easy phrases, a nanometer is one billionth of a meter and the homes of substances at this atomic or subatomic stage fluctuate drastically from houses of the equal substances at larger sizes. Even though, the initial homes of nanomaterials studied have been for its bodily, mechanical, electric, magnetic, chemical and organic programs, currently, interest has been geared toward its pharmaceutical application, especially inside the region of drug transport. That is because of the challenges with use of huge length substances in drug shipping, some of which consist of terrible bioavailability, *in vivo* balance, solubility, and intestinal absorption, sustained and centered transport to website of movement, therapeutic effectiveness, generalized facet effects, and plasma fluctuations of drugs. Of later, various explores in nanodrug transport had been intended to triumph over those requesting circumstances through the change and manufacture of nanostructures. It's been reported that, nanostructures have the ability to guard pills from the degradation in the gastrointestinal tract, the era can allow goal transport of medicine to diverse areas of the body. the technology permits the delivery of medicine which might be poorly water soluble and might provide approach of bypassing the liver, thereby stopping the primary bypass metabolism nanotechnology increases oral bioavailability of medication due to their specialised uptake mechanisms consisting of absorptive endocytosis and are able to continue to be in the blood circulate for a long time, liberating the included drug in a controlled style, main to less plasma fluctuations and minimized aspect-consequences. Nano scale size nanostructures are capable of penetrate tissues and are without problems taken up by way of cells, taking into consideration green shipping of medicine to target sites of movement. Take-up of nanostructures has been expressed to be 15-250 times more prominent than that of microparticles inside the 1-10 um run. Nanotechnology enhances general execution and adequacy of dose organization through growing 70 current advances in novel medication benefit structures their viability, wellbeing, quiet adherence, notwithstanding at last decreasing human services costs. It may also beautify the performance of medicine which can be not able to skip scientific trial stages. nanotechnology absolutely promises to serve as drug transport carrier of preference for the more tough conventional tablets used for the remedy and control of persistent sicknesses inclusive of cancer, bronchial asthma, high blood pressure, HIV and diabetes[2].

Nanoparticles primarily based specific drug targeting and delivery platforms reduce toxicity and other side consequences and also enhance the therapeutic index of the centered drug. In the primary objective of nanotechnology especially in cancer therapy is the development of suitable targeting delivery systems which has been taking the lead in what concerns overcoming the MDR problem. Such targeted delivery systems that are based 'Nanosizing' of drugs[3].

- Decrease drug resistance
- Decrease toxicity
- Enhance oral bioavailability
- Enhance rate of dissolution
- Enhance solubility
- Increase the stability of drug and formulation
- Increase drug targeting ability
- Increase patient compliance
- Increase surface area
- Reduce the dose needed

Nanotechnology in Drug Delivery[4,5]

Treatment that employs large size material for drug delivery presents problems such as poor bioviability, low solubility, a lack of targeted delivery and generalized side effects. The application of nanotechnology for drug transport affords the capability for superior remedies with focused delivery and fewer aspect effects.

Nanotechnology sedate conveyance applications happen through the utilization of outlined nanomaterials notwithstanding shaping conveyance

frameworks from nanoscale atoms alongside liposomes.

Benefits of nanotechnology to drug delivery

1. Improve the ability to deliver drugs that are poorly water soluble.
2. Reduce drug accumulation within healthy tissue because of target specific action.
3. Help hold the medication in the body sufficiently long for viable treatment.
4. The extension of drug bioactivity through protection from the biological environment.
5. Allow for the transportation of medications crosswise over epithelial and endothelial hindrances.
6. Combine therapeutic and diagnostic modalities into one agent.

The Enhanced Permeability and Retention Effect (EPR)

A vital discovery for drug shipping nanotechnology programs is the enhanced permeability and retention impact. Molecules on the nanoscale have a tendency to accumulate in tumor tissue greater than in everyday tissue. That is because fast developing tumors have a great oxygen demand and require the short era of blood vessels. The veins delivered are fundamentally unprecedented and include pores which allow nanoscale particles to saturate through to the tumor tissue. As fast growing tumors also lack functioning lymphatic systems, the enhanced permeability and retention effect should allow for targeted delivery of chemotherapeutic drugs.

Research have analyzed which varieties of tumors have responded pleasant to selective drug launch via the improved permeability and retention impact. Information from clinical trials found that lung, breast and ovarian cancers have the high-quality response with extra expression of the polymer drug conjugate tested. The effects indicated an excessive superior permeability and retention effect in those tumor types. It has been recommended that patient choice as pre-screening the individual upgraded porousness and maintenance impact will build up the clinical capability of this medication conveyance framework further[6,7].

Nanotechnology-based drug delivery systems

- Smart drug delivery systems
- Polymer–drug conjugates
- Multifunctional drug carriers
- Organic/inorganic composites

Smart drug delivery systems

It is widely recognized that medicines need to ideally be launched at the target sites in a managed manner to enhance their healing efficiency, meanwhile, to reduce the aspect outcomes. Inheriting from the managed release Nano platforms, the loaded drugs can act "smart". Since the stage progress of polyacrylamide gels was seen by Tanaka in 1978[8], the exploration on stage change of polymeric gels was significantly supported. Thermal-sensitive liposomes was first announced for medicate conveyance amid a similar period[9]. Gradually, the stimuli-responsive biomaterials have been developed and widely used for controlled drug delivery. With the development of nanotechnology and nanomaterial's, drugs can also be conjugated with different nanoparticles. By using the superb size and surface properties, the nanomaterials are going about as a standout amongst the most encouraging savvy DDSs.

One of the most extreme super accomplishments inside the medication conveyance territory turned into the change of Smart Drug Delivery frameworks (SDDS), otherwise called stimuli- sensitive delivery systems. The concept is based totally on rapid transitions of a physicochemical belongings of polymer systems upon a stimulus. This stimulus includes physical (temperature, mechanical stress, ultrasound, electricity, light), chemical (pH, ionic strength), or biological (enzymes, biomolecules) signals and such stimuli can either be internal, resulting from changes in the physiological condition of a living subject, or ''external'' signals, artificially induced to provoke desired events. SDDS gives a programmable and unsurprising medication discharge profile in response to differing incitement sources[10].

Relying at the favoured applications, one may also design specific drug delivery systems for stronger therapeutic performance with low systemic toxicity

and side effects. SDDS has several benefits compared to traditional drug transport structures. The traditional managed release structures are based totally at the predetermined drug release rate regardless of the environmental situation on the time of software. On the other hand, SDDS is based on the release-on-demand strategy, allowing a drug carrier to liberate a therapeutic drug only when it is required in response to a specific stimulation. The decent case of SDDS has been self-directed insulin conveyance structures that can react to changes inside the ecological glucose level[11,12]. One of the maximum extensively used SDDS has been polymeric micelles. Many polymeric micelles consisting of hydrophobic and hydrophilic polymer blocks have been evolved. They were determined to dissolve water-insoluble capsules, including doxorubicin or paclitaxel, at high concentrations. At the point when controlled to the edge, tranquilize discharge from polymeric micelles typically relies upon basic dissemination, debasement of the micelle squares, or interruption of the micelles by means of body parts.

Polymer-drug conjugates

Polymer-drug conjugates are drug molecules held in polymer molecules, which act as the delivery system for the drug. Polymer drugs have passed multidrug resistance (MDR) testing and hence may become a viable treatment for endocrine-related cancers. A cocktail of pendant drugs could be delivered by water-soluble polymer platforms. The physical and concoction characters of the polymers utilized as a part of polymer-tranquilize conjugates are primarily blended to drift through the kidneys and liver without being sifted through, allowing the medications to be utilized all the more proficiently. Conventional polymers utilized in polymer-drug conjugates can be degraded thru enzymatic pastime and acidity. Polymers at the moment are being synthesized to be touchy to precise enzymes which can be apparent in diseased tissue. The medicine continue to be connected to the polymer and are not activated until the enzymes associated with the diseased tissue are present. This procedure appreciably minimizes harm to healthful tissue[13,14].

One of the primary blessings of polymer-drug conjugates is prolonged circulation within the blood move through retarding degradation/ metabolism/ excretion prices of the conjugated drugs. Many peptide and protein drugs cannot be delivered by oral administration because of their huge molecular weights. Even when administered directly into the blood stream, they do not continue to be within the blood for a long time due to speedy degradation and metabolism, limiting the scientific programs. The circulate instances of those medicines have multiplied notably by using conjugation with polymers, which includes PEG.

These features are particularly attractive for the development of cancer chemotherapeutics, since the clinical use of anticancer drugs is often limited by their poor water solubility, short circulation life, metabolic instability, non-site-specific targeting, and dose-dependent toxicity. Many different polymeric carriers have been utilized for drug conjugation, including the well-studied PEG and N-(2-hydroxypropyl) methacrylamide (HPMA)[15]. Thus far, several PEG-drug conjugates have been approved by the FDA for clinical use, and many PEG-drug and HPMA-drug conjugates are now in clinical trials. For the development of theranostic polymer conjugates, several polymers are under investigation, such as HPMA, poly (L-glutamic acid), and polylysine.

Multifunctional drug carriers

A multifunctional drug delivery system (MDDS) refers to drug carrier that has multiple properties of prolonged blood circulation, passive or active localization at specific disease site, stimuli-sensitivity, ability to supply drug into intracellular target organelles, and/or imaging ability[16]. Technically consequently, it has or extra capabilities, infact, SDDS and polymer–drug conjugates mentioned above can be considered MDDS. Similarly to handing over tablets, MDDS can carry out the second one characteristic, including stimuli-responsiveness or hydrolysis internal cells. A couple of recommended MDDS incorporate the biotin-labeledph-delicate polymeric micelles in light of a total of pla-b-peg-b-phis-biotin

(pla=poly (l-lactic corrosive)) and peg-b-phis square copolymers by methods for lee *et al*[17] in which the focusing on moiety, biotin, wind up veiled till the supplier was revealed to a foreseen domain of pH 7.0. Once the nanocarrier turned into internalized to most cancers cells by way of ligand– receptor interactions, lowered pH (< 6.5) destabilized the carrier ensuing in a burst launch of the loaded drug and that of Lukyanov *et al*[18], where a pH-degradable PEG-b-phosphatidylethanolamine (PE) liposome had anti-myosin monoclonal antibody as well as TAT or biotin attached on its surface.

Organic/inorganic composites

Natural/inorganic composite substances were broadly examined for a long period. When inorganic levels in organic/inorganic composites come to be Nano sized, they're referred to as Nano composites. Natural/inorganic Nano composites are typically natural polymer composites with inorganic nanoscale constructing blocks. They combine the advantages of the inorganic material (e.g., rigidity, thermal stability) and the organic polymer (e.g., flexibility, dielectric, ductility, and process ability). Moreover, they normally additionally incorporate special homes of nanofillers leading to substances with advanced residences. A characterizing capacity of polymer nanocomposites is that the little size of the fillers prompts a sensational increment in interfacial place as contrasted and customary composites. This interfacial location creates a huge volume fraction of interfacial polymer with houses exceptional from the bulk polymer even at low loadings[19].

Different critical organic/inorganic composites are metal nanoparticles, together with silver, iron oxide, or gold nanoparticles, covered with hydrophilic polymers. Their major application has been as theranostics. Only recently, Hirsch *et al*,[20] developed gold nanoshell, which provided tunable emission light for bioimaging. Importantly, is the reality that, gold nanoparticles may be detected by means of x-ray and emit thermal electricity by excitation making it very beneficial for clinical imaging and thermal remedy (theranostics). In a related report, Corot *et al*,[21] developed super paramagnetic iron oxide nanoparticles for magnetic resonance imaging (MRI) of the whole body. Mechanistically, those nanoparticles are mainly engulfed via monocyte or macrophage after intravenous management. However, uptake of notable paramagnetic iron oxide by means of macrophage does no longer induce activation of close by cells making it suitable for analysis of inflammatory or degenerative sicknesses.

NANOPARTICULATE IN DRUG DELIVERY SYSTEM

Nanoparticles for the reason of drug delivery are described as submicron (< 1μm) colloidal debris. This definition consists of monolithic nanoparticles (Nano spheres) wherein the drug is adsorbed, dissolved, or dispersed for the duration of the matrix and Nano capsules wherein the drug is restrained to an aqueous or oily center surrounded through a shell-like wall. Instead, the drug may be covalently attached to the floor or into the matrix.

Nanoparticles are made from biocompatible and biodegradable materials comprehensive of polymers, either natural (e.g., gelatin, egg whites) or manufactured (e.g., polylactides, poly alkyl cyanoacrylates), or strong lipids. Inside the frame, the drug loaded in nanoparticles is generally launched from the matrix through diffusion, swelling, erosion, or degradation

The subsequent are a number of the essential technological blessings of nanoparticles as drug carriers: high stability (i.e., lengthy shelf life); excessive carrier capacity (i.e., many drug molecules may be included within the particle matrix); feasibility of incorporation of both hydrophilic and hydrophobic materials; and feasibility of variable routes of management, inclusive of oral administration and inhalation. These providers also can be designed to permit controlled (sustained) drug release from the matrix.

Drug release from nanoparticles[22]

The nanoparticle is coated by polymer, which releases the drug by controlled diffusion or erosion from the core across the polymeric membrane or matrix. The membrane coating acts as a barrier to

launch, consequently, the solubility and diffusivity of drug in polymer membrane becomes the figuring out issue in drug release. Furthermore release rate also can be tormented by ionic interplay between the drug and addition of auxillary ingredients. While the drug is worried in interplay with auxillary substances to form a much less water soluble complicated, then the drug launch may be very sluggish with almost no burst release effect.

To create a success nanoparticulate system, each drug delivery and polymer biodegradation are critical consideration factors. In general, drug release rate depends on solubility of drug, desorption of the surface bound/ adsorbed drug, drug diffusion through the nanoparticle matrix, nanoparticle matrix erosion/degradation and combination of erosion/diffusion process. Thus solubility, diffusion and biodegradation of the matrix materials govern the release process.

Classification of Nanoparticles

Nanoparticles are mainly classified in to three types.

1. One dimension Nano particles: one dimensional system (thin film) has been used for decades. Thin flim (sizes 1- 100 nm) or monolayer is presently basic place in the field of sun powered cells offering, distinctive innovative applications, for example, substance and natural sensors, data stockpiling frameworks, magneto-optic and optical gadget, fiber-optic frameworks.
2. Two dimension nanoparticles: Carbon nanotubes.
3. Three dimension nanoparticles: Dendrimers, Quantum Dots, Fullerenes (Carbon 60), (QDs).

Carbon Nanotubes[23]

A number of properties result from the regular formation of carbon atoms in graphene cylinders. Carbon nanotubes are a monstrous tube shaped gigantic particle comprising of a hexagonal game plan of sp2 hybridized carbon iotas (C-C separate is around 1.4 Å). The mass of CNTs comprises of single or numerous layers of graphene sheets, of which those framed by moving up of single sheet are called single-walled carbon nanotubes (SWCNTs) and those shaped by moving up of in excess of one sheet are called multi-walled CNTs (MWCNTs). Both SWCNTS and MWCNTS are capped at each ends of the tubes in a hemispherical arrangement of carbon networks referred to as fullerenes warped up by means of the graphene sheet (Figure No.1). the interlayer separation of the graphene layers of MWCNTS measures about zero.34 nm on common, each forming an individual tube, with all of the tubes having a larger outer diameter (2.5 to 100 nm) than SWCNTS (0.6 to 2.4 nm). SWCNTs have a superior characterized divider, while MWCNTs will probably have auxiliary deformities, bringing about a less steady nanostructure. In the medical field, three main attributes of CNTs have been exploited:

- Their small size.
- Their high surface area to volume ratio.
- Their ability to contain chemicals.

Carbon nanotubes can be produced small enough to pass through holes in tumours or to transport DNA .The large surface to volume ratio provides a good platform for efficient transportation of chemicals and for the reactions needed for ultra-sensitive glucose detection.

Dendrimers[24]

Dendrimers are hyper-fanned, globular, monodisperse, 3 dimensional nanoscale manufactured ppidendrimer polymers, having altogether portrayed length, frame and chiral dendrimer positive sub-atomic weight [Figure No.2]. Dendrimers show off characteristics features of both molecular chemistry and polymer chemistry. Atomic science like habitations are a direct result of their well ordered controlled union even as it shows polymer science like homes as it is comprised of peptide dendrimer monomers. A structure of dendrimers have 3 unmistakable units specifically,

1. A Central core unit
2. Generations i.e. branches, which are radically attached to the central core. Generation play an important role in physical chemical properties.

3. Terminal functional group attached to the outermost series of branches. Terminal functional group plays an important role in the properties of the dendrimers.

Quantum dots

Semiconductor nanocrystals, additionally known as quantum dots (QDS), have grown to be a necessary tool in biomedical research, especially for multiplexed, quantitative and long-term fluorescence imaging and detection. The basic rationale for using QDs arises from their unique and fascinating optical properties that are not generally available for individual molecules or bulk semiconductor solids. (Figure No.3). In comparison with conventional organic dyes and fluorescent proteins, QDs have distinctive characteristics such as size-tunable light emission, improved signal brightness, resistance against photo bleaching and simultaneous excitation of multiple fluorescence colors. Recent advances in nanoparticle surface chemistry have led to the development of polymer-encapsulated probes that are highly fluorescent and stable under complex biological conditions. This new generation of water-soluble QDs solved the problems of quantum yield decrease, chemical sensitivity and short shelf-life previously encountered by the ligand exchange based QD solublization method. As a result, these particles, linked with bioaffinity molecules, have raised new opportunities for ultrasensitive and multicolor imaging of molecular targets in living cells and animal models[25].

Fullerenes

Fullerenes are molecules composed entirely of carbon with spherical (buckyballs), ellipsoid, tubular (nanotubes) or a combination shape (nanobuds). They consist of hexagonal and pentagonal (sometimes also heptagonal) rings, with the latter necessary for the curvature of the molecule. (Figure No.4). Each carbon is sp2 hybridized and it is connected to other carbon atoms by one double bond and two single bonds. The smallest fullerene in which no two pentagons share an edge is C60, and as such it is the most common. The structure of C60 is that of a truncated icosahedron. Each vertex is replaced by a five-membered ring - a pentagon. This process also converts each of the twenty former triangular faces into six-membered rings - hexagons, with a carbon atom at the corners of each hexagon and a bond along each edge. Since the atomic strain tends to be focused inside the 5-membered rings which can be at risk for conclusion, structures that maintain a strategic distance from adjoining (side-sharing) pentagons are particularly solid. It turns out that C60 and C70 are the smallest carbon clusters for which this can be achieved. They behave chemically and physically as electron-deficient alkenes rather than electron rich aromatic systems. They are soluble in organic solvents and they can easily accept electrons. Fullerenes modification by the addition of hydroxyl groups (fullerenols), can increase their solubility in water.

Fullerenes are effective antioxidants, reacting comfortably and at a excessive price with loose radicals, which might be frequently the motive of mobile harm or loss of life. They carry on like "radical sponges," as they can wipe up and kill at least 20 free radicals reliable with fullerene particle. The most interesting property for medical use is their antioxidant activity and their sensing/detecting ability, and the most interesting potential application of fullerenes in nanopharmacology is the development of targeted drug delivery systems[26].

Properties of nanoparticles

Some of the residences of nanoparticles that are essential for utility in drug shipping consist of easy, low priced production method that is simple to scale up. The delivering strategy rejects natural solvents or possibly dangerous components. All the components of the system should be commercially to be had, safe, low-cost, non-poisonous and biodegradable. The nanoparticles should be solid with recognize to length, floor morphology, length distribution and other important bodily and chemically.

Synthesis of Nanoparticles for Drug Delivery

Two methods are used for Synthesizing nanoparticles for pharmaceutical purposes

1. Bottom up process, for example, pyrolysis, idle gas build-up, solvothermal response, sol-gel creation and organized media in which hydrophobic compound, for example, liposomes are utilized as bases to mount the medication.
2. Top down process such as attrition / milling in which the drug is chiseled down to form a nanoparticle.

To conquer those boundaries, superior nanoparticles for drug transport were evolved to enable the spatially and temporally managed release of drugs in response to specific stimuli at ailment websites. Moreover, the managed self-assembly of organic and inorganic substances might also allow their use in theranostic packages. This review affords a top level view of a current advanced nanoparticulate gadget that may be used as a capability drug shipping service and makes a speciality of the capability packages of nanoparticles in numerous biomedical fields for human health care. A novel process for synthesis of polymericnanoparticles for use in drug delivery applications using the electro spraying technique. The technologyis standardized for synthesis of natural polymer based nanoparticles such as chitosan-gelatin based nanoparticles

- Nanocarriers
- Ligands
- Solid Lipid Nanoparticles
- Polymeric Nanoparticles
- Dendrimer Nanocarriers
- Silica materials
- Carbon Nanocarriers

Future opportunities and challenges

Nanoparticles provide large benefits regarding drug targeting, delivery and release and with their additional capability to combine diagnosis and therapy, turn out to be one of the important equipment in nanomedicine. The main goals are to improve their stability within the biological environment, to mediate the bio-distribution of lively compounds, improve drug loading, focused on, delivery, launch, and interplay with organic limitations. The cytotoxicity of nanoparticles or their debasement stock remains an essential issue, and upgrades in biocompatibility clearly are a noteworthy trouble of future research[27-29].

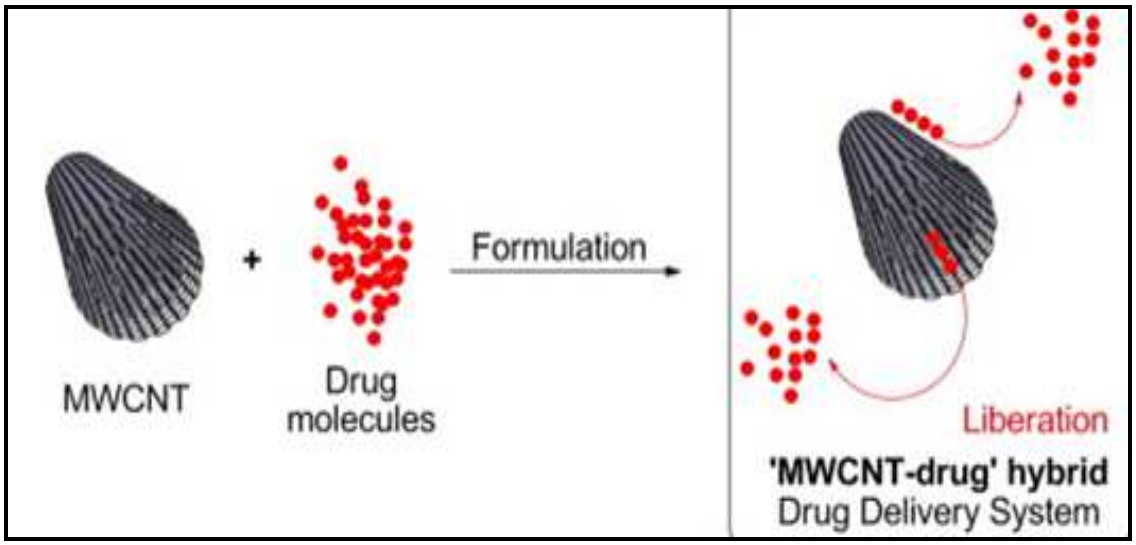

Figure No.1: Multi-walled CNTs (MWCNTs)

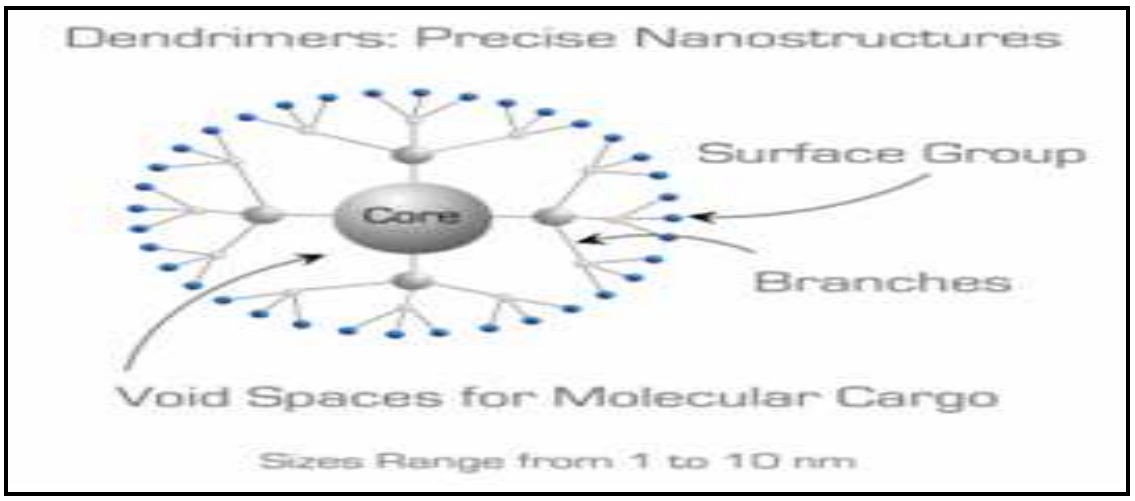

Figure No.2: Dendrimers

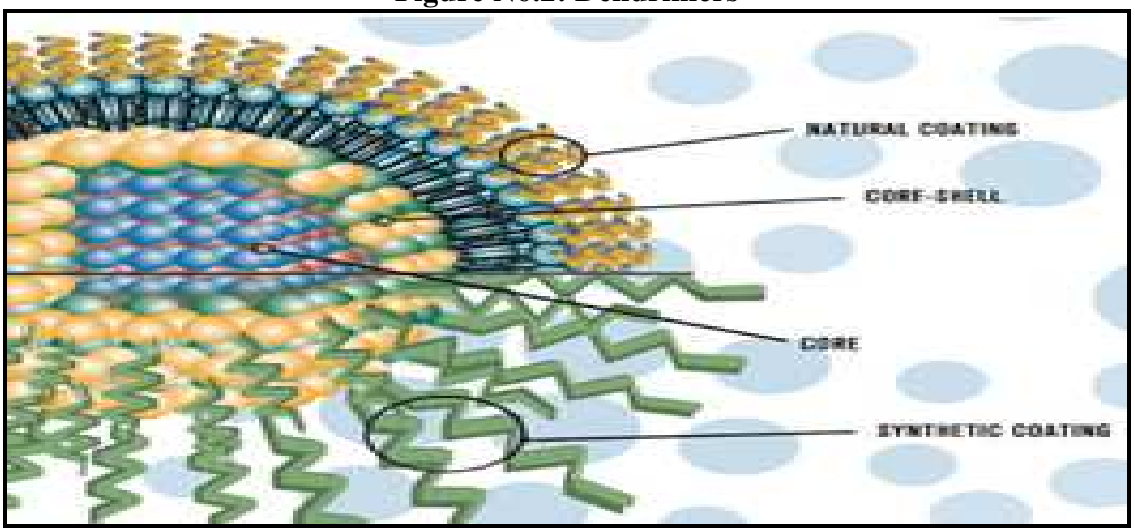

Figure No.3: Quantum Dots

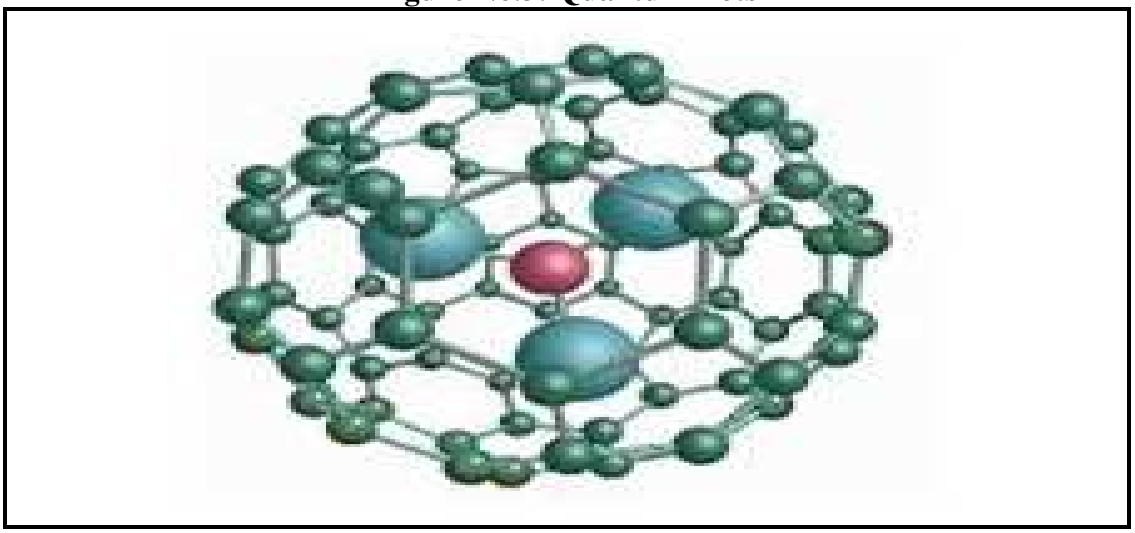

Figure No.4: Fullerenes

CONCLUSION

This new nano generation will to begin with maintain us healthy because of nanorobots with a view to restore each damage that we've got in our frame. Secondly it'll give scientists the ability to manipulate the combination of atoms in an item and to turn it into a lighter stronger and extra long lasting object than before, just by way of using carbon nanotubes which can be recognised to be one hundred times stronger than steel and similarly to that they may be very flexible. It includes minimal effort explore looked at that for disclosure of new substance element. Minimizing the drug usage would significantly reduce the efficient cost of drug which would give financial relief to the patients. Nanotechnology have the potential to substantially affect manufacturing process across a wide range of industries over the medium to long term. So, future research in this field is necessary for its application.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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