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REVIEW ARTICLE

Nanomedicine Drug Delivery System

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ABSTRACT

Nanotechnology is an emerging technology seeking to exploit distinct technological advances of controlling the structure of materials at a reduced dimensional scale approaching individual molecules and their organised aggregates or supramolecular structures. These technological innovations, referred to as nanomedicines by the National Institutes of Health (Bethesda, MD, USA), have the potential to turn molecular discoveries arising from genomics and proteomics into widespread benefit for patients. Nanomedicine is a large subject area and includes nanoparticles that act as biological mimetics (e.g., functionalized carbon nanotubes) "nanomachines" (e.g., those made from interchangeable DNA parts and DNA scaffolds such as octahedron and stick cube), nanofibers and polymeric nanoparticles. The rapidly increasing new field of nanotechnology, opened up by rapid advances in science and technology, creates myriad new opportunities for advancing medical science and disease treatment in human health care. This article presents a brief review of nanomedicines with an emphasis on its various aspects associated i.e. introduction, background, objective, advances, physiological principles of nanomedicine. The article also reveals the concept of nanotoxicology from nanomedicines and non-medical nanoparticles.

Keywords: Nanotechnology, nanomedicine, nanoparticulate.

1. INTRODUCTION:

Nanotechnology is the science and technology that measures, manipulates, and manufactures at the atomic, molecular, and supramolecular levels, aimed at creating materials, devices, and systems with fundamentally new molecular organizations, properties, and functions. It is the evaluation and next generation of science, technology, informatics, and electronics being miniaturized for new product development. Many believe it will affect nearly all sectors of the economy in a relatively short amount of time. Nanomedicine is one portion of research and development in the field of nanotechnology.[1] Nanotechnology has incorporated advances in a variety of diverse scientific disciplines including molecular biology, chemistry, genomics, physics, material science, and medicine.[2]

Nanomedicine is the medicinal diligence of nanotechnology (is the branch of engineering that deals with things smaller than 100 nanometers (especially with the manipulation of individual molecules)). The range of Nanomedicine from medical applications of nano-materials (is a field that takes a materials science-based approach to nanotechnology. It studies materials with morphological features on the nanoscale, and especially those that have special properties stemming from their nanoscale dimensions) to nano-electronic ((physics) the use of nanotechnology to create electronic components) biosensor (is an analytical device for the detection of an analyte that combines a biological component with a physicochemical detector component). The range can also be possible for future applications of molecular nanotechnology (a technology based on the ability to build

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structures to complex, atomic specifications by means of mechanosynthesis).[3]

Nanomedicine relates to medical research and intervention on the nanoscale. It involves the monitoring, repair, construction, and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures.[4] These areas included synthesis and use of nanostructures, applications of nanotechnology to therapy, biomimetic nanostructures, biological nanostructures, the electronic-biology interface, devices for early detection of disease, tools for the study of single molecules, and tissue engineering [5].

Nanomedical approaches to drug delivery center on developing nanoscale particles or molecules to improve drug bioavailability. Bioavailability refers to the presence of drug molecules where they are needed in the body and where they will do the most good. Drug delivery focuses on maximizing bioavailability both at specific places in the body and over a period of time. This can potentially be achieved by molecular targeting by nanoengineered devices.[6-7]

Current problems for nanomedicine involve understanding the issues related to toxicity and environmental in Nanomedicine seeks to deliver a valuable set of research tools and clinically useful devices in the near future.[8] The National Nanotechnology Initiative expects new commercial applications in the pharmaceutical industry that may include advanced drug delivery systems, new therapies, and in vivo imaging. Neuro-electronic interfaces and other nanoelectronics-based sensors are another active goal of research. Further down the line, the speculative field of molecular nanotechnology believes that cell repair machines could revolutionize medicine and the medical field.[9]

The sort of materials that could be called nanomedicines can include proteins, polymers, dendrimers, micelles, liposomes, emulsions,nanoparticles and nanocapsules. Nanomaterials are also used in diagnostics, e.g. colloids for radio pharmacy and as contrast agents in magnetic resonance imaging. New developments in nanomaterials are now producing small and ultra-small paramagnetic iron oxide particles (USPIOs) and investigating quantum dots for this field. In general, nanomaterials of this size are not able to penetrate membranes readily, and consequently are mostly dependent on the anatomy and physiology of the body to determine their distribution.[9,10]

2. BACKGROUND

The development of a wide spectrum of nanoscale technologies is beginning to change the foundations of disease diagnosis, treatment, and prevention. These technological innovations, referred to as nanomedicines by the National Institutes of Health (Bethesda, MD, USA), have the potential to turn molecular discoveries arising from genomics and proteomics into widespread benefit for patients. Nanomedicine is a large subject area and includes nanoparticles that act as biological mimetics (e.g., functionalized carbon nanotubes), "nanomachines" (e.g., those made from interchangeable DNA parts and DNA scaffolds such as octahedron and stick cube), nanofibers and polymeric nanoconstructs as biomaterials (e.g., molecular self-assembly and nanofibers of peptides and peptide-amphiphiles for tissue engineering, shape-memory polymers as molecular switches, nanoporous membranes), and nanoscale microfabrication-based devices (e.g., silicon microchips for drug release and micromachined hollow needles and two-dimensional needle arrays from single crystal silicon), sensors and laboratory diagnostics. Furthermore, there is a vast array of intriguing nanoscale particulate technologies capable of targeting different cells and extracellular elements in the body to deliver drugs, genetic materials, and diagnostic agents specifically to these locations. Indeed, research into the rational delivery and targeting of pharmaceutical, therapeutic, and diagnostic agents via intravenous and interstitial routes of administration with nanosized particles is at the forefront of projects in nanomedicine. This article critically evaluates key aspects of nanoparticulate design and engineering, as well as recent breakthroughs and advances in cellular and intracelluar targeting with such nanoscale delivery technologies after parenteral administration, including the advantage of the nanometer scale size range, biological behavior, and safety profile.[11]

Five overlapping subthemes of Nanomedicine include;

(i) Analytical techniques and ex-vivo diagnostic tools fabricated using nanoscience;

(ii) Nanoimaging (from subcellular events to diseases in patients);

(iii) Underpinning chemistry and engineering that is generating nanomaterials and nanodevices;

iv) Nanomedicines administered to treat disease, including biologically active therapeutics and drug delivery systems; and

(v) Translation from bench to clinic, including industrial scale-up, validation and regulation, and evaluation of safety and efficacy.[12-13]

How nanomedicine works?

Nanomedicine as we know is the appliction which has diverse dimensions. Many intelligent and effiecient instruments are helping dcotors for the cure of diseases. It works at a molecular or atomic scale; it designs the medical apparatus at extremely small scale to provide speed and high performance with low maintainace. Many devices such as bio sensor, nao electronic instruments,

pace makers, monitoring apparatus and advanced ECG machines, all these teriffic machines are the invention of nanomedicine. The most advanced form of nanomedicine uses the nanorobots and nano instruments as surgeons. These kinds of machines might repair damaged cells, or get into the cells and replace or assist damaged intracellular structures at individual stage.

Nanomachines could be used to monitor people with severe illnesses

Nanomedicine is a new interdisciplinary paradigm emerging from the timely convergence of two parallel recent developments. The tremendous advancements in genetic engineering and molecular biology has led to molecular basis of diseases and nanotechnology which offer a powerful means to control molecular interactions. Nanomedicine can significantly affect millions of individuals around the world with acute and chronic diseases including cancer, cardiovascular disease and infectious diseases.

The field of nanomedicine offers ever more breathless promises of new diagnoses and cures as well as ways of improving human performance.

It is a multidisciplinary field undergoing exponential growth with broad applications among all divisions of science.[14]

3. OBJECTIVES OF NANOMEDICINE

The prime objective of nanomedicine drug delivery includes;

- Developing systems that improve the solubility and bioavailability of hydrophobic drugs
- Designing delivery vehicles that can improve the circulatory presence of drugs, e.g. of protein-based drugs which are difficult to administer orally due to their breakdown in the alimentary canal before they reach their therapeutic site
- Reducing toxicity: much lower doses of highly targeted drugs means less systemic toxicity
- Designing mechanisms to target drugs to specific cells or tissues
- Increasing specificity: it will become possible to target individual pathogens or bio molecules
- Developing delivery systems for slow release to maintain a level therapeutic dose.
- Developing novel nanostructures that can be used in specific applications, e.g. ocular, wound management, cancer therapy, neurology, orthopaedics.[15]

4. ADVANTAGES OF NANOMEDICINE

The advantages of nanomedicine drug delivery are as follows;

1. Regenerative medicine
   The aim of regenerative medicine is to repair, or more accurately help the body itself, to repair and replace lost or damaged tissue rather than to just destroy or remove damaged or diseased tissue, or to replace it with non-biological materials.[16,17]
2. The pathophysiological condition and anatomical changes of diseased or inflamed tissues offers many advantages for the delivery of various nanotechnological products. Drug targeting can be achieved by taking advantage of the distinct pathophysiological features of diseased tissues. Actually, the physiology of diseased tissues may be altered in a variety of physiological conditions and can be exploited for passively targeting of drugs. Thus, it exploits the anatomical differences between normal and diseased tissues to achieve site-specific and targeted delivery of drugs.[18]
3. Nanotechnological products have an advantage over other normal drugs. An ideal targeting system should have long circulating time, it should be present at appropriate concentrations at the target site, and it should not lose its activity or therapeutic efficacy while in circulation.
4. Various nanosystems, as a result of their larger size, are accumulated at higher concentrations than normal drugs .[19]
5. In addition, the increased vascular permeability coupled with an mpaired lymphatic drainage in tumors allows an enhanced permeability and retention effect of the nanosystems in the tumors or inflamed tissues.[20]
6. Nanosystem also presents an excellent opportunity for passive targeting of drugs to the macrophages present in the liver and spleen. Thus, this natural system can be used for targeting drugs for intracellular infections.
7. The therapeutic value of many promising drugs for the treatment of various neurological disorders is diminished by the presence of the blood-brain barrier. The blood-brain barrier is a unique membrane that tightly segregates the brain from the circulating blood. Thus, drug delivery to this organ is a challenge, because the brain benefits from very efficient protection. Nanotechnology offers a solution for using the numerous chemical entities for treating brain disorders that are not clinically useful because of the presence of the blood-brain barrier. Nanoparticles can be effectively used to deliver relevant drugs to the brain.
   Drug loading onto nanoparticles modifies cell and tissue distribution and leads to a more selective delivery of biologically active compounds to improve drug efficacy and reduces drug toxicity. Thus, various nanosystems can be successfully used as new drug carriers for brain delivery.[20]
8. Artificial antibodies.
   Nanomedicine was the first to conceptualize the artificial red and white blood cells and later on it successfully showed the positive results. Cancer

patients are now treated by injecting artificial red blood cells to balance the human body blood level. Artificial antibodies, white & red blood cells and antiviral nanorobots could be considered as successful applications of nanomedicine.[20]

9. Nanomedicine has also helped doctors to better understand the phenomenal changes in the human nervous systems. Fixed nanomachines could be inserted in the nervous system of the human body to monitor pulse rate, brain activity, and other important functions.
10. Antibiotics to the lower airways by aerosol administration has potential advantages that deposition to the alveolar site of the infection can reach high local concentration and therefore inhaled drugs can reduce the occurrence of serious systemic adverse effects by dose reduction. Given the central role of antibiotic and antiviral treatment in numerous respiratory diseases and the multitude of clinical studies concerning sytemical and topical antibiotic.[16]
11. It directly penetrates into the tumor cells ant cause distruction of tumor cell. Drugs having solubility problem can formulate in nanomedicine form.[10]
12. Encapsulation in nanocarriers could achieve delivery of the reagents (imaging and therapeutic drugs) to the sites of action in the body, while minimizing systemic toxicity and enzymatic degradation. These functional systems have the potential to become a general solution in drug delivery.[21]

5. PHYSIOLOGICAL PRINCIPLES FOR NANOMEDICINES

Nanomaterials have been investigated as potential medicines for several decades. Consequently, a great deal of work has been conducted on how to exploit constructs of this size range in a beneficial way. Similarly, a number of the consequences from the use of these materials have already been considered. Nanomaterials do behave differently to low-molecular-weight drugs, the biological properties of nanomaterials being mainly dependent on relevant physiology and anatomy, which are reviewed in this article. Biodistribution, movement of materials through tissues, phagocytosis, opsonization and endocytosis of nanosized materials are all likely to have an impact on potential toxicity.[22]

6. NANOTOXICOLOGY FROM NANOMEDICINES

Nanoparticles may overcome solubility or stability issues for the drug and minimize drug-induced side effects. But there could be significant toxicity issues associated with the nanocarriers themselves. Also highly intensive, media-driven debate could be expected with the introduction of nanodevices, similar to the genetically modified food debate, similar to the genetically modified food debate. The impact on human health has been assessed in the United Kingdom as part of a document published by the Office of Science and Technology. This independent article produced by the Royal Society and Royal Academy of Engineering represents an exhaustive discussion on the potential exposure to nanoparticles. It raises concerns that nanoparticles, because of their size and ability to pass across cellular membranes, represent a potential biohazard. The issue of toxicity becomes even more serious for intravenously injected nanoparticles, as size partly determines tissue distribution. The report compares nanotechnology development with asbestos fibers, which caused wide spread health and safety concerns.[11, 23]

The change in the physicochemical and structural properties of manufactured nanomaterials with a decrease in size could be responsible for a number of material interactions that could lead to toxicological effects. Several nanomaterials characteristics can culminate in reactive oxygen species (ROS) generation, which is currently the best-developed paradigm for nanoparticle toxicity (Table 1).[22]

Experimental NM effects	Possible pathophysiological outcomes
ROS generation	Protein, DNA and membrane injury, oxidative stress
Oxidative stress	Phase II enzyme induction, inflammation, mitochondrial perturbation
Mitochondrial perturbation	Inner membrane damage, permeability transition pore opening, energy failure, apoptosis, apo-necrosis, cytotoxicity
Inflammation	Tissue infiltration with inflammatory cells, fibrosis, granulomas, atherogenesis, acute phase protein expression (e.g., C-reactive protein)
Uptake by reticulo-endothelial system	Asymptomatic sequestration and storage in liver, spleen, lymph nodes, possible organ enlargement and dysfunction
Protein denaturation, degradation	Loss of enzyme activity, auto-antigenicity
Nuclear uptake	DNA damage, nucleoprotein clumping, autoantigens
Uptake in neuronal tissue	Brain and peripheral nervous system injury
Perturbation of phagocytic function, "particle overload," mediator release	Chronic inflammation, fibrosis, granulomas, interference in clearance of infectious agents
Endothelial dysfunction, effects on blood clotting	Atherogenesis, thrombosis, stroke, myocardial infarction
Generation of neoantigens, breakdown in immune tolerance	Autoimmunity, adjuvant effects
Altered cell cycle regulation	Proliferation, cell cycle arrest,

	senescence
DNA damage	Mutagenesis, metaplasia, carcinogenesis

Table 1. Nanomedicines effects as the basis for pathophysiology and toxicity

6.1 Health and safety issues

A large proportion of the atoms that make up a nanoparticles because of their small size, are exposed to the exterior of the particle and may participate in many chemical processes. It may lead to the adverse consequences due to exposure in to the environment. Studies in human showed that deposition of nanoparticle in the lungs increases with decreasing particle size and the toxicity of inhaled insoluble nanomaterials increases with decreases particle size and increasing particle surface area. Certain classes of nanoparticle could be responsible for destructive inflammatory processes in the lungs eg. Carbon black nanoparticle may induce a type-II alveolar epithelial cell line to release pro-inflammatory mediators.

Nanotechnology changes the properties of substance eg. Carbon as fullerens and nanotubes an attractive candidate for applications but also make them dangerous, when expose to environment. The measure for safety needs to be taken on environmental concern with the use of nanotechnology. Nanomedicine have potential to cross blood brain barrier may cause harm to the patient. The verichip corporation has declared the availability of the world first and only patented, FDA – cleared radiofrequency identification implantable microchip, with this ethical question arises about patient own personal detail which is available to other. Privacy and confidentiality of the patients may be affected. The protection and maintenance of health information of the patient is the ethical issue, and while using nanotechnology in medical field ensuring privacy and confidentiality is of utmost importance.[20]

6.2 Cell death and altered gene expression

Recent evidence is drawing attention to some of the above questions, but investigation in this avenue of research is scant. For example, though much has been made of the promise of cadmium selenide QDs in imaging, little is known about their metabolism and potential deleterious effects. However, cadmium selenide QDs are lethal to cells under UV irradiation, as this releases highly toxic cadmium ions. Some polymeric micelles depending on the nature of their monomer constituents can induce cell death via apoptosis or necrosis, or both. Differential gene expression has been reported in certain cells after cisplatin delivery with polymeric micelles when compared with that of free cisplatin treatment.[11]

6.3 Cell death and gene therapy

A very clear warning is evident from the poor success in human gene therapy with viruses. Although, viral vectors are extremely efficient delivery systems for nucleic acids, they can induce severe immunotoxicity as well as inadvertent gene expression changes after random integration into the host genome. These issues have generated a surge in design and engineering of synthetic polycationic nonviral gene transfer systems. However, the polycationic nature of the gene-delivery vehicles can induce immediate or delayed cytotoxicity by mechanisms involving necrosis as well as apoptosis. Necrosis may occur as a result of membrane destabilization or pore formation after interaction between the cationic components of the delivery system with cell surface proteoglycans and negatively charged proteins in cytoskeleton, such as actin. In the case of Jurkat T cells the apoptotic mechanism appears to be due to polycation-mediated release of Bcl-2-sensitive proteins such as cytochrome *c* from the mitochondrial intermembrane space and altered mitochondrial functions. However, different cationic materials, and depending on their molecular weights and polydispersity, may initiate apoptosis at different times and by different mechanisms or modes. The effect of these materials on cell death may depend on cell nature, mitochondrial content and the extent mitochondrial heterogeneity. Nevertheless, cytotoxic gene-delivery systems may compromise transcription and translation processes and potentially limit protein expression. In protocols, which attempt to restore gene function, for instance in metabolic disorders, such toxicity issues take on even greater importance. In addition to these, cDNA microarray expression profiling studies have recently revealed marked changes in the expression of cell proliferation, differentiation and proapoptotic genes in human epithelial cells, after treatment with cationic formulation. This raises further concern as to whether such delivery systems could adversely influence the desired effects of the delivered genetic agents. For instance cationic carriers may exacerbate, attenuate or even mask the effects of delivered nucleic acids. Thus, gene transfer/therapy represents an important area where smart macromolecular design and engineering is critical to achieving a successful outcome in the near future and could benefit through recent advances in high-throughput approaches to polymer design and screening . Such approaches may lead to understanding of the molecular basis of interaction between cationic polymers and mitochondrial and nuclear membrane as well as cationic polymers and BCL-2 family of proteins comprising inhibitors and inducers of apoptosis.

6.4 Pseudoallergy and idiosyncratic reactions

Finally, another potential pitfall associated with nanocarrier infusion into human subjects is the generation of non-IgE-mediated signs of hypersensitivity. These reactions are idiosyncratic and are believed to be secondary to complement activation, and presumably are

a reflection of an individual's immune cell sensitivity to complement-derived mediators. Hypersensitivity can be ameliorated by slowing the rate of infusion or by patient premedication, and often fails to appear on repeat administration of the nanocarrier. Idiosyncratic reactions occur after infusion of stealth systems, such as poly(ethylene glycol)-grafted liposomes. Refined surface engineering may eventually eliminate such side effects, for example by better polymer design, linkage modification, controlling the conformation and packing of grafted polymers and/or by introducing complement regulatory proteins or inhibitors on to the nanoparticle surface . However, the ultimate goal is to understand the molecular mechanism of complement activation-related pseudoallergy, which operates in a small population of individuals. Future developments in immunogenomics and predictive gene-derived toxicogenomic may eventually provide new methods for assessing an individual's sensitivity to nanomedicines and hence reduce the risk of immune-mediated side effects.[11]

6.5 Cytotoxicity

Recently, it was shown that differently shaped poly(3,4-ethylene-dioxythiophene) (PEDT) nanoparticles possessing similar diameters, which were fabricated by chemical oxidization polymerization using sodium bis (2-ethylhexyl) sulfosuccinate (AOT) reverse micelles as the template, affected cell viabilities and inflammatory responses to particles tested, PEDT-1 (with lowest aspect ratio) induced a greater degree of cytotoxicity, apoptosis, and reactive oxygen species production in human lung fibroblast IMR90 and mouse alveolar macrophage J774A.1 cell lines. Although these results suggest that particle shape may play a role in affecting cell viabilities possibly through biological interactions, more systemic studies on the effects of nanoparticle shapes for cell viability are required to verify if the findings can indeed be broadly extrapolated to other materials and particle shapes. Extensive and systematic bio-evaluations of drug carrier candidates are required to yield greater insights on the shape requirements for specific drug delivery applications. Coupled with the rapid development of synthetic tools that can yield morphologically well-de.ned biodegradable and/or biocompatible polymeric nanostructures, an improved understanding of the shape effects on biological processes is expected to give rise to a new generation of innovative drug carriers with significantly enhanced drug delivery outcomes for the clinics.

6.6 Implications for Nanotoxicology from Non-medical nanoparticles

Non-medical nanoparticles, which may be found in atmospheric pollution or produced in industrial processes, are unlikely to have these advantages, and their toxicology will be largely determined by the materials they are composed of and their surface characteristics. The latter will determine where they eventually accumulate. Many airborne nanoparticles are likely to have a hydrophobic surface and will therefore be prone to accumulation in the spleen and liver. However, a number of industrially produced nanomaterials do need to be treated to prevent aggregation, and such stabilized materials are likely to behave in a similar manner to the stabilized nanomedicines designed to circulate in the vasculature. Whichever path is followed, whether involving stabilized or unstabilized particles, there are potentially toxic consequences predictable from physiology and anatomy.[9]

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