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Basics of Nanomedicine: Applications, Challenges in Drug Delivery and Hazards

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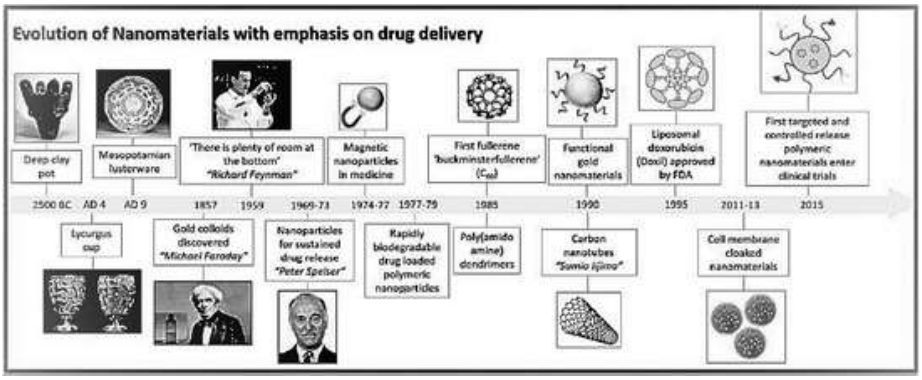
ABSTRACT

Future of Nanotechnology holds immense promise, with a huge potential to revolutionize various sectors like medicine, Imaging, Manufacturing and energy. It involves manipulating materials at the atomic and molecular level to create new structures and devices with unique properties and functionalities. While still in its early stages, nanotechnology is poised to address global challenges like disease, resource scarcity, pollution and other complex problems. In the field of Pharmacy Nanoparticles are revolutionising the drug delivery mechanisms, and have shown substantial efficacy in clinical studies. In medicine its uses are immense , from drug delivery to imaging and medical devices. Recent developments in nanomedicine have led to significant innovations, including nanomedicines based on natural products, carbon dots , nanorobots, dendrimers, liposomes, micelles, and metal-based nanoparticles, these advancements brings unique properties that enhance drug delivery, targeting specific tissues, and also therapeutic efficacy. Nanotechnology's potential to treat chronic disease through targeted tissues drug delivery mechanism is remarkable, but there are significant challenges and limitations that must be addressed to fully understand its use and benefits. The recent breakthroughs in nanomaterial-based nanodrug delivery mechanisms are still exploring the challenges and outlook for future advancements in nanomedicine. There is a need for continued research to overcome existing hurdles, such as optimizing drug formulations for oral drug delivery and to learn hazards associated, There is a promising future of nanomedicine in the health care sector and is set to spread rapidly.

Keywords: Nanotechnology, Nanoparticle, Nanomedicine, Drug delivery, Cancer Therapy, Tissue Engineering, Pharmaceuticals

1. Introduction



Medication, is any substance that is used or intended to use to modify or to explore physiological systems or pathological states for the benefit of the recipient. It is a substance which has chemical as well as physiological effects on human body. These effects may be beneficial (i.e. 1. To kill bacteria ,virus etc. 2. To provide supplementation 3. To manipulate enzymes, hormones etc.). A medicine is composed of two components, an active component and inactive component. There is a chemical substance present in the drug which causes the physiological effect is called active ingredient of a drug. There are some binders, filler, lubricants etc, which has no physiological effect on the body are called inactive ingredient. Mostly Drugs acts by binding to enzymes, by activation or inhibition of hormones, by affecting the

function or properties of proteins. These medications may be Natural products extracted from plants or may be synthesized artificially and are used to cure almost all the disease, abnormalities and always helped mankind to fight against infectious disease and epidemics. The use of drugs by humans has evolved with time, that's may be to improve health, also with patterns shifting from medicinal purposes to cultural rituals to recreational use and, in some cases, addiction. Although , in recent times there is a rise of sophisticated, science-based medicines, which are impacting society by improving health, increasing longevity, and raising the standards in healthcare practices. This evolution is marked by key advancements in pharmaceutical sector and innovation in other health care sectors as well. Inspite of all these advancements drug dosage forms are facing the problem of its efficacy, bioavailability,

toxicity, biocompatibility, side-effects and inactivity. These factors hinders the drug development and delivery. In last decades, highly sophisticated engineered nanomaterials have been explored to find solutions for these problems. In recent years we have witnessed unprecedented growth in research and development in the field of nanotechnology. Nanoparticles are also highly attractive subject these days in the field of medicine, because of their unique feature, such as surface to mass ratio is much higher than that of other particles. Nanoparticles have a relatively larger which can bind, absorb, and carry other compounds i.e. drugs, proteins, probes etc. It is important to mention that Nanoparticles whose dimensions are >100 nm are needed for loading a sufficient amount of drug. In addition, for drug delivery not only engineered particles may be used as carrier, but also the drug itself may be formulated at a nanoscale, and then function as its own "carrier". Composition of nanoparticles may vary, i.e. biological origin like phospholipids, lipids, lactic acid, dextran and chemical origin like polymer , silica, carbon. Nanoparticles are used for drug targeting to a specific intended diseased site. Here we will understand the medical applications of nanomedicine and its hazards.

2. Development of Nanomedicine

2.1 *Traditionally Drugs are developed on the basis of its delivery system i.e Oral ingestion, intramuscular or intravascular injection. Systemic blood circulation is responsible for distribution of drug in human body. But there are some problems with this system. (a) only a small amount of drug component is reaching the target organ (b) sometimes some part of the drug reaches other organs as well and as a result there will be some adverse effects. (c) low solubility of drug (d) low bio-availability of drug, i.e. a fraction of drug dose available for systemic circulation.*

Example, if a drug is given through intravenous Bio-availability is 100% but if given through other routes then Bio-availability will be less. (e) low efficacy – i.e. maximum response achieved from an applied dose of a drug. So if the affinity of a drug for a target is low then efficacy will be decreased. (f) fast excretion – if elimination of a drug is fast then effectiveness will decrease. (h) need of drug accumulation- i.e. in case of cancer therapy, there is a need of accumulation of a specific amount of drug.

2.2 Lack of optimum accumulation of drug is associated with chemotherapeutic agents for cancer treatment.

To overcome these issues and problems associated with traditional drug formulations and delivery system, development of Nanomedicine is required.

2.3 Nanoparticles as Nanomedicine, and drug delivery.

Nanoparticles used in Nanomedicine should be seen in a scale of nanometre , (10-1000 nm). Aim for research of nanoparticles in the field of medicine:
1. Delivery of drug should be more target specific.

2. Bio-availability as per requirement.
3. Efficacy as per requirement
4. Reduction in toxicity while maintaining therapeutic effects.
5. Greater safety then traditional drug delivery systems.
6. Faster development of newer safer drugs.

2.4 Find an appropriate carrier as drug delivery system:

Pre-requisite for design of new materials are as follows,

1. Drug incorporation and release
2. Stability of formula and shelf life
3. Biocompatibility
4. distribution and targeting

2.5 Table-1

Recapitulation of Nanoparticles and their applications in Health sector

(*Borm and Muller-Schulte 2006)*

Particle class	**Materials used**	**Applications**
Natural materials	1. Dextran 2. Gelatine 3. starch 4. liposomes	For drug delivery And for Gene delivery

	5. chitosan	
Polymer carriers	1. polycaprolactones 2. polylactic acid 3. polycaprolactone	For drug delivery and Gene delivery
Dendrimers	Branched polymers	For drug delivery
Ferrofluids	SPIONS USPIONS	In Imaging (MRI)
Fullerenes	Carbon based carriers	Photodynamic and drug delivery
Quantum dots	Cd/Zn -selenides	Imaging
Various	Silica	Gene delivery

In the above table, these are the possibilities for the preparation of nanomaterials used as Pharmaceutical carrier system. But so far none of the material is fulfilling the parameters mentioned above. The aims for nanoparticle entrapment of drugs are either enhanced delivery to, or uptake by, target cells and/or a reduction in the toxicity of the free drug to non-target organs. Both situations will result in an increase of therapeutic index.

2.6 Table-2 Material under consideration and researched in last decade:

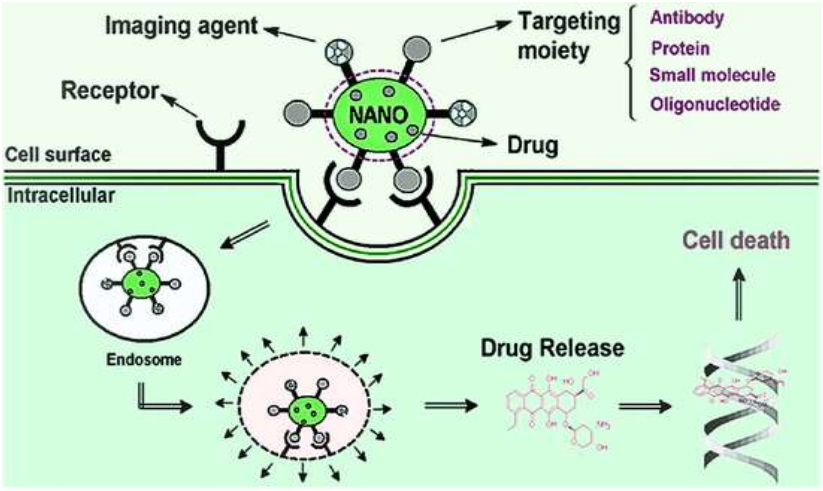
1. Cetyl alcohol/ Polysorbate
2. Gelatin
3. Hydrogel
4. Poly-alkyl-cyano-acrylate
5. Poly-D,L-lactic -co-glycolic acid
6. Solid lipid formulations
7. Chitosan
8. Gold
9. poly-ethylene glycol/ poly-e-caprolactone

3. Mechanism of Action of Nanomedicine delivery system

There is body's immune system which will recognise and act against the nanomedicine, so nanomedicine should be designed in such a way that it can avoid the immune system. Some nanoparticles are developed and used for drug formulations which increase efficacy, safety, tolerability of incorporated drug. Nanoparticles based formulations have shown remarkable improvements in: 1. Controlled release 2. High solubility 3. Improved pharmacokinetics and pharmacodynamics. Some other properties like Particle size, surface charge and shape playa an important role in creating effective nanomedicine delivery system.

3.1 Binding to receptors site :

Fig-1



3.1.1. Active Targeting:

Ligand-Receptor Interaction:

Nanoparticles are engineered with targeting ligands (e.g., antibodies, peptides, aptamers) that bind to specific receptors on target cells.

Examples of Ligands and Receptors:

Antibodies: Can be designed to target specific antigens on cancer cells.

Peptides: Short amino acid sequences that can bind to receptors like transferrin or folate receptors.

Aptamers: Short, single-stranded DNA or RNA molecules that can bind to specific proteins.

Folate: Binds to folate receptors, often overexpressed in cancer cells.

Transferrin: Binds to transferrin receptors, involved in iron transport, and can be exploited for targeted delivery.

Receptor-Mediated Endocytosis:

Binding of the ligand to its receptor initiates the process of endocytosis, where the cell internalizes the nanoparticle and its attached drug.

3.1.2. Enhanced Drug Delivery:

Increased Specificity:

Active targeting ensures that the drug is delivered primarily to the intended target cells, minimizing off-target effects and reducing systemic toxicity.

Improved Drug Concentration:

By concentrating the drug at the target site, active targeting can enhance the therapeutic effect and potentially reduce the required dosage.

Overcoming Barriers:

Nanoparticles can be designed to overcome biological barriers, such as the blood-brain barrier, to reach previously inaccessible areas.

3.2 Particle size: Particle size and size distribution are the important characteristics because these will determine the chemical and physical properties of nanomaterials. The hydrodynamic size and size distribution determine the in vivo distribution, biological fate, toxicity, and targeting ability of these nanomaterials for drug delivery system. Due to extremely small size these have high mobility and as a result these are capable of higher cellular uptake.

3.3 Charge on the surface*:* It is expressed and measured in terms of zeta potential which reflects the electrical potential of particle that may be affected by its composition and the medium in which it is dispersed. Drug molecules can be loaded via a number of processes such as covalent conjunction, hydrophobic interaction, charge -charge interaction etc. By manipulation zeta potential attachment or adsorption of charged molecule can be determined on the surface of nanoparticle.

3.4 Drug loading: when a drug is incorporated on a nanomaterials, this process is called drug loading. Best nanoparticle is that which has high drug loading capacity. If a drug has high loading capacity then it will minimise the drug doses.

3.5 Drug targeting: If the drug is targeted to a specific site then outcomes will be fruitful. Example, drug (nanomedicine) targeting the tumour will improve the chemotherapy. Enhanced permeability and retention enables selective localization in tumour spontaneously due to fenestrated blood vessels as in case of drug loaded liposome (doxorubicin-liposome complex). It has been shown to effectively improve selective localization in human tumours

in vivo of small-molecule drugs such as doxorubicin as demonstrated by nanosized liposomes target tumours spontaneously because of the fenestrated blood vessels. This is due to enhanced permeability and subsequent drug retention.

3.6 Drug release: The process of diffusing or dissolution drug in the body, which is loaded into nanoparticle, is known as drug release while biodegradation refers to collapsing the drug delivery system inside the body. Both drug release and biodegradation are important to consider when developing a nanoparticle drug delivery system. The ability of nanoparticles to pass through the blood brain barrier is an important advantage for drug delivery systems for effective treatments[45]. However, the efficacy of nanoparticles toward the treatment of neurological disorders, like brain tumour, stroke, and Alzheimer's disease, have been largely constrained in spite of the advances and breakthroughs in nanotechnology-based medical approaches. Targeting of drugs to the central nervous system remains for the future success and development of nanotechnology-based diagnostics and therapeutics in neurology.

4. Toxicity of nanomaterials used as Drug Delivery System.

In nanomaterials due to high surface to volume ratio and quantum size effect, nanomaterials exhibit unique properties as compared to bulk materials. Nanomaterials have shown toxicity which is unusual and not seen with bulk materials. Even Gold which remains inert at bulk is highly active at nanometric scale.

However there is a limited data available on the fate of nanomaterials inside the living cells and their toxic effect. Nanoparticles are usually smaller in size, comparable to large biological molecules such as enzymes, receptors, of a size about 100 to 10,000 times smaller than human cells. However, the greater surface area to volume ratio of these particles causes their higher chemical reactivity and results in increased production of reactive oxygen species (ROS). Reactive Oxygen Species (ROS) formation is one of the mechanisms of nanoparticles toxicity which could cause oxidative stress, inflammation and consequent damages to the proteins, cell membrane and DNA. Due to these adverse effects in-vitro analysis is must for nanomaterials to be used as nanomedicine.

Table-3 Toxicity by few nanoparticles

Nanoparticles	**Test Organ/Species**	**Toxic effects**
Zn0 nanoparticles	*Pulmonary Adenocarcinoma cell line LTEP-a-2*	cytotoxicity on human pulmonary adenocarcinoma cell lines LTEP-a-2
Ti02 nanoparticles	*Peripheral blood* *Mononuclear cells*	suppressed IDO activity and IFN-C production
Silver nanoparticles	*Colon carcinoma cells*	oxidative stress and cytotoxicity
Nickel oxide nanoparticle	*Pulmonary epithelial cell lines BEAS-2B & A549*	inflammation and genotoxic effect in lung epithelial cells
Fullerenol nanoparticles	*Cultured human lung fibroblasts*	*cytotoxicity and genotoxicity*
Silver nanoparticles	*Human umbilical vein endothelial cells*	*endothelial cell injury and dysfunction*
Titanium oxide, zinc oxide, magnesium oxide, Gold, Silver nanoparticles	*Suspensions of Balb/c Skin cells*	cytotoxicity
Metal oxide nanoparticles **CeO2, TiO2, AlO3**	*Human peripheral blood lymphocytes*	*induced changes in the expression levels of adhesion molecules and the c-x-c chemokines receptors type-4 in these cells, T-cell proliferation upon cell exposure to TiO2 and AL2O3*

4.1 Mechanism of toxicity caused by Nanoparticles:

Nanoparticles may show physiochemical reaction, which leads to free radical formation or ROS including superoxide radicals anions and hydroxyl radicals, this may activate the oxidative enzymatic pathways, it results in oxidative stress. In general, there are several sources for oxidative stress. (a) Oxidant-generating properties of particles themselves as well as their ability to stimulate generation of ROS as a part of cellular response to nanoparticles, (b) Transition metal-based nanoparticles or transition metal contaminants used as catalysts during the production of non-metal nanoparticles, (c) Relatively stable free radical intermediates present on reactive surfaces of particles, (d) Redox active groups resulting from functionalization of nanoparticles, (e) Small NPs have a higher probability to be internalized by passive uptake than large ones, (f) Under otherwise identical conditions, small nanoparticles are more likely to cause toxic cellular responses. Increasing evidence suggests that the special physicochemical

properties of nanomaterials pose potential risks to human health. Therefore it is necessary to understand how cells respond to nanomaterials and through what mechanisms.

4.2 Interaction of nanoparticles with human body cells

Route through which nanoparticles can enter the human body are (a) inhalation (b) ingestion (c) dermal invasions. After entering the human body these nanoparticles interacts with a number of biochemicals such as Sugars, Proteins and Lipids. These are dissolved in the body fluids like interstitial fluid between cells, lymph or blood. There is immediate coating of nanoparticles takes place and thus the newly formed structure is called "protein corona" that determines the biological fate of nanoparticles. It has been suggested that the final corona reflects its own prior history. The size of nanoparticles has a strong effect on their interactions with living cells, influencing uptake efficiency, internalization pathway selection, intracellular localization and cytotoxicity.

4.3 Nanoparticle and cardiovascular system

As we know ligand coated engineered nanoparticles are being studied and used as agents for molecular imaging or drug delivery tools. Cationic nanoparticles, including Gold and polystyrene have shown to cause Haemolysis and blood clotting. while normally anionic particles are non-toxic. Studies are still been conducted on this clotting and other cardiovascular toxic effects.

4.4. Nanoparticles and Brain

Nanoparticles can enter the Brain by two mechanisms:

1) Trans-synaptic transport: after inhalation through the olfactory epithelium.

This method is studied primarily with model particles (such as Carbon, Au, MnO2 in experimental inhalation models in rats.) Studied by, (Oberdorster et al 2004)

2) Blood-Brain-Barrier , studied by,(Kreuter 2001, Koziara et al 2006, Tiwari and Amiji 2006). studies suggest that the physiological barrier may limit the distribution of some proteins and viral particles after transvascular delivery to the brain, suggesting that the healthy BBB contains defence mechanisms protecting it from blood borne nanoparticle exposure. When nanoparticles with different surface characteristics were evaluated, neutral nanoparticles and low concentrations of anionic nanoparticles were found to have no effect on BBB integrity, whereas high concentrations of anionic nanoparticles and cationic nanoparticles were toxic for the BBB. Nanoparticles have been shown to induce the production of reactive oxygen species and oxidative stress. And this has been confirmed in the brain after inhalation of MnO_2 nanoparticles (Elder et al 2006). Oxidative stress has been implicated in the pathogenesis of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. Evidence for the involvement of ambient air nanoparticles in these effects is presented by studies in biopsies from city dwellers. Alzheimer's like pathology was demonstrated in brain sections by increased markers of inflammation and AB42-accumulation in frontal cortex and hippocampus in association with the presence of nanoparticles.

5. Nanoparticles as Medicine : Nanomedicine

Table-3. Time lines of cancer nanomedicine

1960	Liposome+d0x0rubin, for breast cancer treatment.
1976	1st controlled release polymer for proteins and other macromolecules
1980	1st targeted liposomes
1986	Discovery of EPR effects
1995	FDA approval of Liposomal Doxorubicin (DOXIL)
2002	Silicon hydrogel contact lenses
2010	IMLYGIC -for melanoma
2015	Nano chip for tumour targeting
2017	1st two drugs (Daunorubicin and cytarabine) contains nanomedicine
2019	Lipid nanoparticle mRNA cancer vaccine
2020	Emergence of Gold nanoparticles and quantum dots for therapy.

From last two decades we have a considerable amount of data on toxicity due to nanoparticles. In most studies the nanoparticles were used as a model for ambient air particle toxicity. One of the more general conclusions is that indeed there is a clear tendency for very small particles to be more toxic than

larger particles with the same chemical composition. For nanoformulations used in drug delivery the focus in most papers is mainly on obtained reduction of toxicity of the incorporated drug, whereas the possible toxicity of the carrier used is not considered. Especially possible residues of such a treatment may harbor potential local and/or systemic toxic responses. For medical applications certain routine assays need to be performed which will detect a number of potential hazards. However, it can be anticipated that not all hazards are at this moment known for the use of nanoparticles. For parenteral use interactions with blood components, systemic distribution and kinetics are of importance, when engineered NPs are being used as devices to target drugs to specific tissues, to increase their biological half time, or for imaging purposes. Each nanoparticle formulation should be tested on a case by case basis in the requisite ways focusing on their portal of entry. In the development of nanomedicine, testing procedures and protocols needs to be followed and a number of basic issues needs to be considered, which are as follows:

As there are some side effects by the traditional particles. e.g. inflammation. Nanoparticles may cause the same effects as traditional particles but they may be more potent because of greater surface area. Nanoparticles could cause new types of effects not previously seen with larger particles or bulk chemicals.

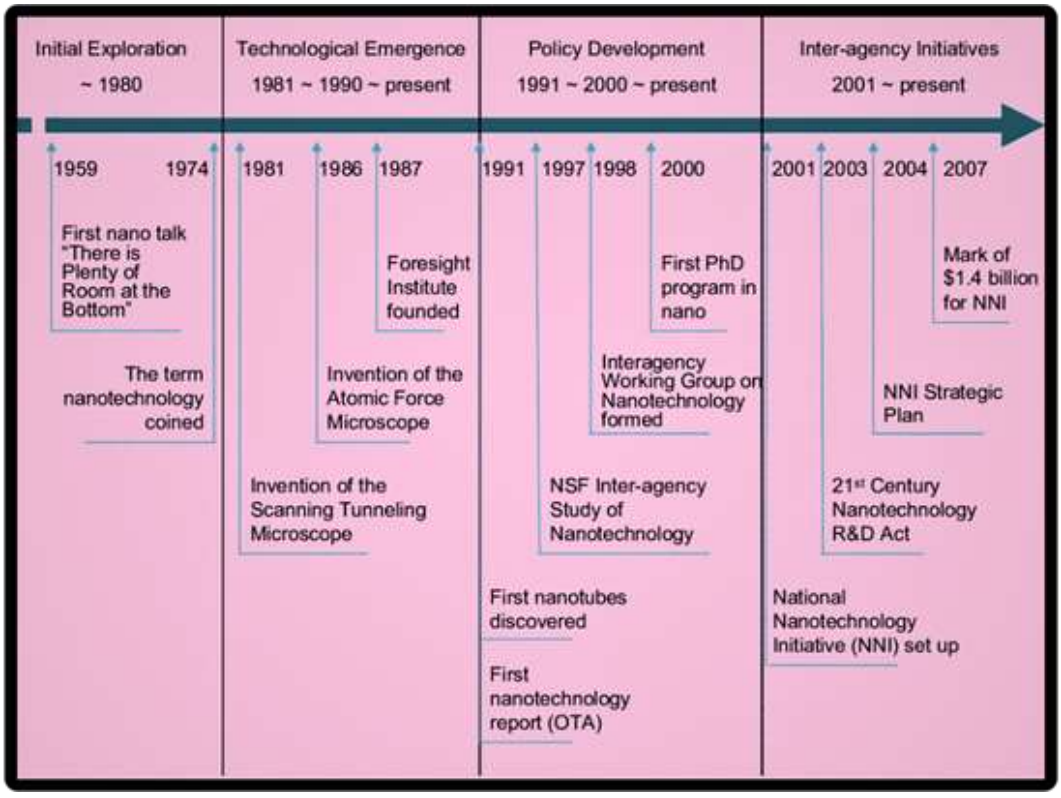
Can we extrapolate available data and concepts, which might be available from epidemiological studies of ultrafine particles.

Is our current regulation robust enough to handle risks of nanomaterials?

Should we use the precautionary principle in current regulatory testing? The precautionary principle (PP) is a highly debated issue in international politics and was first added in EU environmental regulation in the Maastricht treaty in Article 174 (e.g. Article 130r).

6. CONCLUSION

Discovering a new drug and mechanisms of delivery is challenging and important task of biochemistry and pharmacology. Today it may be challenging and complicated for discovering and understanding the applications of nanomedicine. But the use of Nanotechnology in pharmacology and more specifically drug delivery is set to spread rapidly. For decades pharmaceutical sciences have been using nanoparticles to reduce toxicity and side effects of drugs. Up to recently it was not realized that these carrier systems themselves may impose risks to the patient. The type of hazards that are introduced by using nanoparticles for drug delivery are beyond that posed by conventional hazards imposed by chemicals in delivery matrices. However, so far, the scientific paradigm for the possible (adverse) reactivity of nanoparticles is lacking and we have little understanding of the basics of the interaction of nanoparticles with living cells, organs and organisms. A conceptual understanding of biological responses to nanomaterials is needed to develop and apply safe nanomaterials in drug delivery in the future. Furthermore a close collaboration between those working in drug delivery and particle toxicology is necessary for the exchange of concepts, methods and know-how to move this issue ahead. Governments play a significant role in funding nanotechnology research, offering financial support through grants, dedicated research programs, and national initiatives aimed at fostering innovation. India is rapidly emerging as a key player in the global nanotechnology landscape, particularly in the field of healthcare.



The Indian government has established the NanoMission under the Department of Science and Technology to support nanotech research and commercialization, with an ten-year investment of ₹1000 crore (about USD 140 million). Governments are responsible for ensuring the safety and efficacy of nanomedicines through regulatory bodies like the FDA in the US. This includes establishing guidelines and standards for manufacturing, testing, and clinical trials. Governments must address the ethical implications of nanomedicine, such as patient privacy, data security, and equitable access to treatments.

Conflict of interest : Author declares no conflict of research interest.

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