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### Nano drug Delivery System and their Applications

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**Abstract:** Nano-medicine and nano delivery systems are a relatively new but rapidly developing science where materials in the nanoscale range are employed to serve as means of diagnostic tools or to deliver therapeutic agents to specific targeted sites in a controlled manner. Nanotechnology offers multiple benefits in treating chronic human diseases by site-specific, and target-oriented delivery of precise medicines

The most advanced technology for delivering the drugs to various sites in the body is nanotechnology. The nano-size of particles possesses a trans cellular mechanism in delivering the drug to the target sites. Many diseases can be treated effectively through this delivery using nano-capsules, nano-spheres, noisome dendrimers, polymeric micelles, liposomes, solid lipid nanoparticles (NPs), carbon nanotubes, fullerenes, polymeric-based NPs, and paramagnetic NPs with a size ranging from 1 nm to 500 nm.

**Keywords:** Nano Drug Delivery Systems (NDDS), Nanoparticles, Targeted Drug Delivery, Controlled Drug Release, Nanomedicine, Drug Delivery Applications

### 1. INTRODUCTION

Nano drug delivery systems (NDDS) are advanced pharmaceutical technologies that use nano-metric carriers (typically **1–100 nm**) to deliver therapeutic agents specifically to their site of action. By manipulating materials-at the atomic level, these systems overcome the fundamental limitations of conventional medicine, such as poor solubility, non-specific distribution, and rapid degradation Nano word originated from the Latin word which implies dwarf ideal size range offered by nanotechnology refers to the one-thousandth millionth of a particular unit. Thus nanometer is one thousand millionth of a meter (1nm= 10<sup>-9</sup>nm). The branch of nanotechnology is the science that deals with the processes that occur at a molecular level and of nano-length scale size. Nanotechnology offers drugs within the nanometer size range which enhances and reinforces the performance in a variety of dosage forms. Various advantages of nano sizing include decreased fed/fasted variability, decreased patient-to-patient variability, enhanced solubility, increased oral bioavailability, increased rate of dissolution, increased

surface area, less amount of dose required, and more rapid onset of therapeutic action. Polymeric nano particles are colloidal particles composed of a biocompatible or biodegradable lipid matrix. These are transport carrier compartment for drugs or other active molecules of non- liposomal character having size ranging from 10-1000nm(1 $\mu$ m). This bioactive are entrapped in the polymer matrix as particulates enmeshed or solid solutions or may be bound to the particle surface by adsorption or chemically. The nanoparticles loaded bioactive could not only deliver drugs to specific organs but delivery rate in addition could be controlled as being bystanders, burst, controlled, pulsatile or modulated. Depending on the process used for the preparation, two types of nanoparticles can be obtained nano-spheres or nano-capsules. Nano-spheres may be defined as solid core spherical particulates, which are nano-metric in size, they contain drug embedded within the matrix or adsorbed on to the surface, nano-capsules are vesicular system in which drug is essentially encapsulated within the central volume surrounded by an embryonic continuous polymeric sheet. In nano-capsules, the active drug is mainly encapsulated in solution systems.

## 2. Types of nano- Based drug Delivery Systems

The term “NDDS” refers to a broad range of nano materials that have been created to enable the controlled and targeted release of medications. Due to their variations in composition , structure, and mode of action, these materials can be used in a variety of therapeutic contexts.

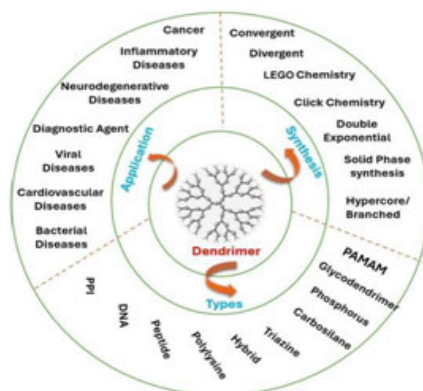


*DIFFERENT NANO-BASED DRUG DELIVERY SYSTEMS*

### 2.1.DENDRIMERS

Dendrimers are hyper branched globular shaped particles having a unique three-dimensional architecture. They can provide perfect control over molecular structure for a nano sized based drug delivery system due to their multiple functional surface groups. Dendrimers are highly branched tree- shaped macromolecules that have several benefits for drug delivery. By adhering to the ligands on their surface by straight forward ionic contact or chemical conjugation to the delivery system, dendrimers demonstrate the potential to transport pharmaceuticals to the target

region via a passive mechanism by improving penetration retention and active targeting.



### ***DENDRIMER APPLICATIONS SYNTHESIS METHODS AND TYPES***

#### ***1. Nanoparticles***

Nano particles are among the most widely studied types of NDDS. They can be composed of various materials, including lipids, polymers, metals, and ceramics, and can range in size from 1 to 1000 nanometers. Due to their small size, nano particles can easily penetrate biological barriers, such as the blood–brain barrier or tumor vasculature and deliver drugs to targeted areas with high specificity. Moreover, nano particles can be engineered to release their payload in response to external stimuli such as pH, temperature, or enzyme activity, enabling controlled release over time.

#### ***2. Liposomes***

A potential class of drug delivery methods, liposomes improve the safety and therapeutic effectiveness of a variety of pharmacological drugs. The Greek words “lipos”, which means fat, and “soma”, which means body, are the roots of the word “liposome”. Liposomes deliver the drugs into cells by fusion or endocytosis mechanisms to provide controlled drug release, which is protected from degradation by plasma enzymes and has reduced side effects. Moreover, liposomes can be easily modified by coating the surface or attaching different specific surface biomarkers PEG, antibodies, and peptides to reach cancer cells by active targeting. Liposomes’ efficacy in treating cancer has prompted much research, and their unique properties such as their high entrapment efficiency of active ingredients, accessibility, and scalability in production make them intriguing drug delivery systems (DDS).

#### ***3. Solid lipid nanoparticles (SLNs)***

SLNs which are in the size range of 10–1000 nm, are attracting major attention as a novel colloidal drug carrier with the potential to overcome limitations in drug delivery including poor drug loading capacity, size problems, unstable properties, uncontrolled drug release associated with polymeric nano particle, dendrimers and liposomes. SLNs offer unique properties such as

small size, large surface area, high drug loading and entrapment efficiency, low toxicity, excellent physical stability, controlled drug release, protection of drugs from degradation, and avoidance of the use of organic solvents.

The structure of SLNs based on lipids that are solid at room temperature. The lipid structure of SLNs is important to determine whether or not a loaded molecule can be strongly encapsulated within a delivery system. Therefore, the lipids that form the SLNs core structure could be important for high-rate drug loading. Additionally, most lipids that form the structures of SLNs are biodegradable, so SLNs show excellent biocompatibility and have less toxic effects. When the use of SLNs is investigated, it seems that SLNs have often been selected for lipophilic and hydrophilic drug compatibility with lipids that do not have toxic effects as carriers. However, in recent years, increasing attention has also been paid to the coating of SLNs in order to load lipophobic and hydrophilic drugs in the lipid structure and also to provide gene delivery.

#### 4. *Micelles*

Micelles are self-assembled nanoparticles that are created when amphiphilic molecules group together in aqueous fluids. Poorly water-soluble medications can be encapsulated within the hydrophobic core of micelles, increasing their stability and solubility.

Micelles have been investigated for both passive and active targeting techniques and are especially helpful for the administration of hydrophobic medications, such as anti-cancer medicines. Ghezzi *et al.* reported that micelles are perfect for controlled release in certain conditions because of their capacity to react to variations in pH, temperature, or the presence of specific enzymes. By adding ligands on their surface, micelles may be made to target certain cells or tissues, increasing drug delivery accuracy and minimizing adverse effects. Micelles are most commonly administered *via* intravenous (i.v.) injection/infusion (mostly used for chemotherapy), although oral and topical (ocular, nasal, buccal) administration have also been shown to have highly intriguing outcomes in terms of enhanced drug bioavailability. Micelles reduce the systemic toxicity of medications by directing drug distribution to certain tissues or cells. This can lower the frequency of dosing and result in a longer-lasting therapeutic impact. Sun *et al.* reported that for the effective administration of topical ocular medications, PBA-CS-VE nano micelles are a muco-adhesive solution with improved trans corneal permeability and extended preocular retention. In order to support gene therapy, micelles can also be employed to transport nucleic acids, such as DNA or RNA. Micelles are useful for treating chronic illnesses with extended pharmacological activity because of their controlled release characteristics. It can be difficult to produce micelle-based medication delivery devices on a large scale. One important area of research is ensuring that micelles stay intact in the body until they arrive at their destination. Micelle-based formulations need to be thoroughly tested for safety and effectiveness, just like any other novel drug delivery method. Micelles are often used and recognized colloidal particles in drug administration, and bCN micelles constitute a flexible, biocompatible oral drug delivery platform. Use of micelles is a promising drug delivery method, and research is being done to improve their stability, functioning, and targeting abilities.

### 5. Polymeric nanoparticles

Usually, manmade or natural polymers make up polymeric nanoparticles. Poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), chitosan, and polyethylene glycol (PEG) are typical examples. Their usual diameters range from 10 nm to 1000 nm, which enable them to be both large enough to encapsulate a sizable quantity of medicine and tiny enough to pass through blood arteries and infiltrate tissues. While hydrophilic medications can be attached to the surface or integrated into the shell, hydrophobic pharmaceuticals can be enclosed within the core of the nanoparticle. It is possible to design polymers to regulate the encapsulated drug's release. This may occur as a result of drug diffusion over time or deterioration of the polymer matrix. These biodegradable polymer-based nanoparticles are becoming more and more popular due to their biocompatibility and adjustable drug release patterns. Selvam *et al.* reported that when paired with polyethylene-glycol (PEG), hydroxyapatite (HAp) provides increased osteoblastic potential, fracture toughness, mechanical characteristics, biocompatibility, and Young's modulus. Because of their adaptability, polymeric nanoparticles may be customized for certain therapeutic uses, such as gene therapy or cancer treatment. By shielding the antigens and guaranteeing their gradual release, polymeric nanoparticles can be used to deliver antigens in vaccinations, enhancing the immune response. Proteins or peptides that the body's enzymes could ordinarily break down can be delivered *via* polymers. Even while polymers like PLGA are biocompatible, some of their breakdown products might be harmful at larger doses or if they build up in particular organs. Polyethylene glycol (PLGA) NPs were used by Park *et al.* to encapsulate adriamycin. In order to generate multifunctional carriers with improved capabilities, researchers are investigating hybrid systems that mix polymeric nanoparticles with other drug delivery methods (such as liposomes or micelles). The extremely hydrophobic curcumin was encapsulated in PLGA NPs by Szymusiak *et al.*, which enhanced oral absorption and reduced the dosage of the medication required to produce similar amounts in mice's plasma and nervous system tissue following oral treatment by around twice-as compared to unencapsulated curcumin.

### 3. Importance of nanoparticles in drug delivery

When drugs are loaded into nano particles through physical encapsulation, adsorption or chemical conjugation, the pharmacokinetics and therapeutic index of the drugs can be significantly improved in contrast to the free drug counterparts. Many advantages of nano particle-based drug delivery have been recognized, including improving serum solubility of the drugs, prolonging the systemic circulation lifetime, releasing drugs at a sustained and controlled manner, preferentially delivering drugs to the tissues and cells of interest, and concurrently delivering multiple therapeutic agents to the same cells for combination therapy. Nano structures, biomaterials and nano particles have unique physicochemical properties such as ultra small and controllable size, large surface area to mass ratio, high reactivity, and functionalizable structure. Biological membranes and access cells, tissues and organs are eligible for entrance of nanoparticles. These cells are not crossed by the larger-size particles easily, i.e. by conventional medicine.

### **Advantages of nanoparticles**

- Relatively simple preparation.
- Specific medication delivery.
- They have the ability to incorporate both hydrophilic and hydrophobic drug molecules.
- No part of it involves higher manufacturing costs which may in turn lead to increase in the cost of formulation.
- They have low encapsulation efficacy.
- The system can be administered via different routes including oral, nasal, parenteral, etc.
- Effective size and size dispersion control.
- The medicine in the capsule is well protected.
- They have longer clearance time.
- Drug retention at the site of action.
- They are capable of being stored for a period of up to one year and hence have longer shelf stability
- Enhanced therapeutic effectiveness.
- Enhanced bioavailability and Dose equivalence
- In an aquatic environment, active substances dissolve more quickly with increased surface area.
- Greater bioavailability is typically correlated with faster dissolution.
- Tiner drug
- Less variation between fed and fasting states.
- Reduced toxicity

### **Disadvantages of Nanoparticles**

- It involves higher manufacturing costs which may in turn lead to increase in the cost of formulation.
- They have low encapsulation efficacy.
- Water soluble drugs can be rapidly leaked out in the presence of blood components.

-Their small size and large surface area can lead to particle-particle aggregation making physical handling of nanoparticles difficult in dry and liquid forms.

-They may trigger immune response and allergic reaction.

-They may involve use of harsh toxic solvents in the preparation process.

-Toxicity concerns with the widespread usage of polyvinyl alcohol as a detergent.

-Limited ability to aim.

-It is not feasible to stop therapy.

-Cytotoxicity .

-Pulmonary inflammatory disease and lung cancer risk

-Inflammation of the alveoli.

-The interference with autonomic balance caused by nanoparticles, which has an immediate impact on vascular and cardiac function

### **Action Mechanism of Nano Drug Delivery Systems**

Nano particles can be used to enhance drug delivery. In an effort to improve the effectiveness, safety, and tolerance of ingested medications, several nanoparticle formulations have been used in drug research. High solubility, controlled release, and better pharmacokinetic and pharmacodynamic features have all been demonstrated by formulations based on nano particles.

Effective nanoparticle delivery systems can be made using a variety of processes, and particle size, surface charge, and shape ..

#### **Particle size:**

The most crucial aspects of nano materials are their particle size and size distribution, which affect their chemical and physical properties. They have the ability to control medication loading, release, and stability.

According to reports, nanomaterials have an advantage over micro-scale particles because of their tiny size and high mobility, which allows for greater cellular uptake and makes them appropriate for a variety of cellular and intracellular targets.

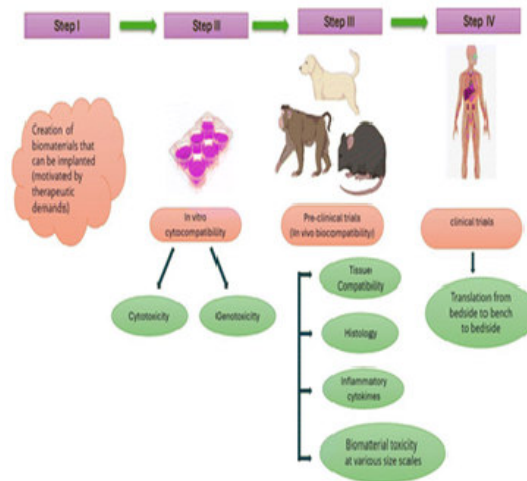
#### **Surface Charge:**

Surface charge is typically expressed and evaluated in terms of a nano material's zeta potential, which represents the electrical potential of particles and is impacted by both the composition-

of the particle and the media in which it is disseminated. According to reports, zeta potentials with values below 30m Vary stable in suspension and help keep particles from aggregating. Nonmaterial surface charge is essential for drug loading. Several techniques, including covalent conjugation, hydrophobic contact, charge-charge interaction, and encapsulation, can be used to load drugs. The nature of the medication and the nature of the target molecule both influence how molecules are loaded, which also changes the surface charge. It is possible to identify the attachment or adsorption of charged molecules to a nanoparticle's surface by adjusting the zeta potential.

## Loading drugs

Medication loading is the process of incorporating a drug on or in nano materials. The best drug delivery system for nano particles should be able to load large amounts of medication without aggregating. High medication loading capacity can reduce dosage or administration. Dispersibility is required for the medications to be delivered smoothly and effectively. Drug loading can be done in a variety of ways, but the effectiveness of drug loading and entrapment depends on the drug's solubility in the nanoparticles, the dispersion medium, the size and composition of the nano materials, the drug's molecular weight (MW), its solubility, the interaction between the drug and the body.



## Analyzing biomaterials' toxicity and biocompatibility

### Scalability and manufacturing

Ensuring consistency in the size, shape, and medication loading of nano particles is one of the primary challenges. Transitioning from laboratory success to commercial

production is a significant hurdle. NDSS require precise control over **particle size, morphology, and drug-loading efficiency**. Minor deviations in the manufacturing process can drastically alter the drug's safety and efficacy. Furthermore, high production costs and the

complexity of maintaining batch-to-batch consistency often deter large-scale industrial adoption.

### **Over coming biological barriers**

The blood–brain barrier, cellular membranes, and the extracellular matrix are just a few of the biological barriers that nano particles must be able to get through. The blood–brain barrier (BBB) is a highly selective permeability barrier that separates the brain's tissue from its blood arteries. It keeps big molecules out of the brain, including the majority of medications. The lipid bilayer membrane that envelops each cell in the body serves as a selective barrier to keep undesirable things out. To overcome this obstacle, nano particles must be engineered with certain properties, such as proper size, charge, and surface changes. Some tactics include employing “smart” nano particles that can react to

changes in the brain's microenvironment, such as pH shifts, or targeting ligands, such as transferrin or antibodies, that can attach to receptors on the BBB's endothelial cells. Mucus layers serve as physical barrier to keep infections and external objects out of the body and are found on numerous epithelial surfaces, including the lungs, gastrointestinal system, and eyes. Cellular absorption can be improved by employing cationic particles or by covering the nanoparticles with lipids or deliver Herceptin to the target site for several weeks with just a single dose. Due to the improved retention of Herceptin within the tumor, the hydrogel-based drug delivery is more efficient than conventional subcutaneous and intravenous delivery modes, thus making it a better anti-tumor agent .Nanoparticles can be modified in several ways to prolong circulation, enhance drug localization, increase drug efficacy and potentially decrease the development of multi drug resistance through the use of nanotechnologies.

### **Applications**

Recent developments in medication delivery using nanoparticles have shown their therapeutic promise in a number of domains.

#### **1.Cancer treatment**

In order to minimize harm to healthy organs, chemotherapeutic medicines have been delivered directly to tumor cells using nanoparticles. Furthermore, the creation of theranostic nanoparticles, which combine therapy and diagnosis, has been made easier by their capacity to transport imaging agents. Currently, a lot of clinical and preclinical research is being conducted on the topic of targeting macrophages in the development of cancer therapies. . Staggering numbers of individuals suffer from cancer worldwide, highlighting the need for an accurate detection method and novel drug delivery system that is more specific, efficient and exhibits minimal side effects. Anticancer treatments are often regarded as superior if the therapeutic agent can reach the specific target site without resulting in any side effects. Chemical modifications of the surface of nanoparticle carriers may improve this required targeted delivery. One of the best examples of modifications at the surface of nanoparticles is the incorporation of PEG or polyethylene oxide. These modifications enhance not only the

specificity of drug uptake, but also the tumour targeting ability. Incorporating PEG avoids the detection of nanoparticles as foreign objects by the body's immune system, thus allowing them to circulate in the bloodstream until they reach the tumour. Additionally, the application of hydrogel in breast cancer is a prime example of this innovative technology. Herceptin is a type of monoclonal antibody used in breast cancer treatment by targeting human epidermal growth factor receptor 2 (HER2) on cancer cells. A vitamin E based hydrogel has thus been developed that can deliver Herceptin to the target site for several weeks with just a single dose. Due to the improved retention of Herceptin within the tumour, the hydrogel based drug delivery is more efficient than conventional subcutaneous and intravenous delivery modes, thus making it a better antitumour agent. Nanoparticles can be modified in several ways to prolong circulation, enhance drug localisation, increase drug efficacy and potentially decrease the development of multidrug resistance through the use of nanotechnologies.

***Examples of FDA approved nanomedicines***

<b>Clinical Agent</b>	<b>Formulation</b>	<b>Applications</b>
<b>Eligard</b>	Leuprolide acetate and polymer (PLGA)	Prostate cancer
<b>Genexol-PM</b>	mPEG-PLA micelle loaded with paclitaxel	Metastatic breast cancer
<b>Doxil / Caelyx</b>	Liposomal doxorubicin	Ovarian cancer, breast cancer, Kaposi's sarcoma, multiple myeloma
<b>Onivyde</b>	Liposomal irinotecan	Pancreatic cancer
<b>Abraxane</b>	Albumin-stabilized nanoparticle paclitaxel	Metastatic breast cancer
<b>Myocet</b>	Liposomal doxorubicin	Metastatic breast cancer (combination therapy)

**2. Drug Delivery Approach in Skin Diseases**

Skin diseases are follicular and cutaneous. These dermatological diseases are treated nowadays with nanotechnology. Nanoparticle delivery for cutaneous disease treatment is preferred, with minor side effects. The conventionally used creams, gels, and ointments are insufficient for delivering drugs due to low penetration in skin tissues. To address this, polymeric, lipid, and surfactant nanocarriers are used. The polymeric micelles enhance drug penetration into the skin tissue to treat skin cancer. As in this reported study, chitosan polymeric NPs, liposomes, and gold nanoparticles can treat atopic dermatitis by improving drug penetration into the dermal and epidermal layers. Gold nanoparticles are extremely small in size and can penetrate easily

and effectively with very low toxicity and no skin damage. As such, they are used widely in nanocarrier formulations for skin diseases.

### **3. Drug Delivery Approach in Bone Diseases**

Bone diseases includes bone defects due to many pathological factors, such as fracture, trauma, osteoporosis, arthritis, infections, and many other diseases. In fact, bone regeneration as a disease treatment is a very complex process, due to which nanomaterials and biological materials are fused to repair bones effectively. The combination of biomaterial and nanomaterial has reduced bone implantation through the development of bone bioscaffolds.

### **4. Treatment of cardiovascular diseases**

Cardiovascular diseases are another field where the properties of nanoparticles may be leveraged. Cardiovascular diseases are the leading cause of death globally, and the rates are increasing alarmingly, due to an increase in sedentary lifestyles. Common examples of cardiovascular diseases that affect several individuals includes stroke, hypertension and restriction or blockage of blood circulation in a specific area. These diseases are the most common causes of prolonged disability and death. Nanotechnologies offer novel avenues for therapeutic and diagnostic strategies for management of cardiovascular diseases. Gold and silica nanoparticles have been developed to improve NO supply for possible application in cardiovascular diseases, where low NO bioavailability occurs. Drug delivery via liposomes has been proven to be effective for prevention of platelet aggregation, atherosclerosis and thrombosis. Prostaglandin E1 (PGE1) exhibits a wide range of pharmacological properties, including vasodilation, inhibition of platelet aggregation, leukocyte adhesion, as well as exhibiting an antiinflammatory effect. Liposomal drug delivery of PGE1 (Liprostin™), is currently undergoing phase III clinical trials for the treatment of various cardiovascular diseases, such as restenosis following angioplasty. Additionally, the use of liposomes carrying the thrombolytic drug urokinase has also been assessed; cyclic arginylglycylaspartic acid (cRGD) peptide liposomes encapsulated with urokinase can selectively bind to the GPIIb/IIIa receptors, and this improves the thrombolytic efficacy of urokinase by almost 4fold over free urokinase.

Efficacy and effectiveness of the conventional thrombolytic drugs can also be advanced via novel nanotherapeutic approaches. Drugs can be selectively targeted to vascular blockage sites through mechanical activation within blood vessels based on the high fluid shear strains present within them. *In vivo* and *in vitro* studies have been encouraging, thus validating this approach for use in lysis of blood clots, using a significantly lower amount of thrombolytic drug.

One example of this technology is the use of dendrimers. Dendrimers have been used in several diseases as a means of delivering therapeutic agents. Plasminogen activator (rtPA) has been successfully attached to dendrimers producing an alternative drug delivery system, allowing for refinement of the rtPA dendrimer complex concentration throughout the duration of treatment using different dilution proportions of each part of the complex. Another potential role of nanoparticles is to decrease haemorrhaging.

## 5. Gene delivery

Because nanoparticles can transfer nucleic acids (DNA, RNA, and siRNA) directly to target cells, they are increasingly being used in gene therapy, offering promise for genetic diseases and customized treatment.

## Conclusion

Nano-based drug delivery systems represent a transformative advancement in modern therapeutics, offering precise, controlled, and efficient drug delivery. Drug delivery made possible by nanotechnology has a promising future in pharmaceuticals. The drug delivery industry is significantly impacted by the development of nanotechnology, with effects on nearly all routes of

administration, including oral and injectable. The current pharmaceutical industry is frequently characterised by inadequate bio-availability, which all too frequently leads to greater patient expenses and ineffective therapy, but more critically, increased risks of toxicity. Since nanotechnology concentrates on the extremely small, it is ideally suited to develop systems that can more effectively deliver medications to the body's tiniest regions. Drugs delivered via nanotechnology can also pass through cell membranes, which is crucial for the anticipated expansion of genetic medicine over the coming years. Nanotechnology-enabled medication delivery could result in decreased drug toxicity, lower treatment costs, higher bioavailability, and an extension of the commercial life of unique drugs for both doctors and patients.

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