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# A RECENT TRENDS IN NANOPARTICULATE DRUG DELIVERY SYSTEM: MANUFRACTING ASPECTS, EVALUATION PARAMENTERS

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## *ABSTRACT*

The fields of nanomedicine and nano-delivery systems are relatively young and are undergoing fast development. These fields make use of materials at the nanoscale for the purpose of delivering diagnostic devices and medicinal medications in a controlled and targeted manner. When it comes to the treatment of chronic disorders, nanotechnology offers substantial advantages because of its capacity to accurately and specifically distribute therapeutic molecules to particular locations. Nanomedicine is now being used for a broad variety of purposes, including the development of biological, immunotherapeutic, and chemotherapeutic medications for the treatment of a variety of medical conditions.

This in-depth study provides a summary of recent advancements in the disciplines of nanomedicines and nano-based drug delivery systems, which is updated to reflect the most recent breakthroughs in these areas. The purpose of this study is to conduct an in-depth analysis of the use of nanomaterials for the purpose of identifying disease marker molecules. This enables selective sickness identification and enhances the effectiveness of both new and existing drugs, including natural goods. In addition to this, the study delves into the potential and challenges that are associated with the process of bringing nanomedicines derived from natural or synthetic sources to genuine clinical applications. In addition, the study offers insights into the changes that are now taking place in the area of nanomedicine as well as possible possibilities for the future. Nanotechnology, nanomedicines, nano drug delivery systems (NDDSs), and NDDS targeting method are some of the acronyms that are often used.

## I. INTRODUCTION

The purposeful engineering and manipulation of particulate matter into a physical state that is between 1 nanometer and 100 nm is what is known as nanotechnology. This physical state may then be rearranged or reassembled into nano-systems that have greater function [1]. A growing number of studies are being conducted to study the possible applications of nanoparticles and nanomaterials in the field of medicine. In the realm of application, the topic of medication delivery stands out as a particularly fascinating and promising area of study. One of these ground-breaking inventions is the nano drug delivery system, which takes use of nanotechnology to enhance the efficiency of medication administration, increase the effectiveness of therapy, and reduce the number of unwanted effects [2].

According to the definition provided by the World Health Organization (WHO), a drug delivery system (DDS) is "a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body" [3]. The increased drug bioavailability that these systems provide is achieved by enhancing the drug's solubility and stability, which ultimately results in the enhancement of therapeutic effectiveness. Because of their capacity to transport drugs to particular tissues, cells, or subcellular compartments, they are able to limit the effects that are not intended for them and lessen the toxicity that is released into the system [4].

According to Grand View Research[5,] it is estimated that the worldwide market for nano medication delivery would reach a spectacular $126.8 billion by the year 2026. This increase is expected to occur at a compound annual growth rate (CAGR) of 14.1% between the respective years 2021 and 2026. There is a possibility that this exponential growth might be attributed to the several advantages that nano drug delivery methods provide, including enhanced bioavailability, longer drug release, targeted administration to specific cells or tissues, and the ability to bypass biological barriers [6].

Nano drug delivery systems are very helpful in achieving sustained and regulated drug release, which enables therapies to be administered for longer periods of time, decrease the frequency of dose, and enhance patient compliance. The ability to overcome biological barriers, such as the blood-brain barrier, is another significant benefit, since it enables medications to reach locations that were previously inaccessible [7]. Additionally, nano drug delivery systems provide the possibility of combination therapy, which is a kind of treatment in which various medications or therapeutic agents may be encapsulated inside a single nanoparticle. This allows for the promotion of synergistic effects and tailored treatment techniques [8]. In general, the employment of nano drug delivery systems has a great deal of promise in terms of improving treatment results, reducing unwanted effects, and advancing the area of precision medicine [9].

Both organic and inorganic nanocarriers are used in the delivery of drugs using nanotechnology. Examples of organic nanocarriers include virus-based nanoparticles, solid liquid nanoparticles, dendrimers, polymeric nanoparticles, and polymeric micelles. Dendrimers in particular are also included in this category. As an example of an inorganic nanoparticle, carbon nanotubes and mesoporous silica nanoparticles are both viable options. As an example, liposomes, which are a sort of nano drug delivery system, have been the subject of a great deal of research [10]. Doxil, a liposomal preparation of doxorubicin, was approved for the treatment of ovarian cancer and AIDS-related Kaposi's sarcoma [11]. This was due to the fact that it demonstrated enhanced effectiveness and lower cardiotoxicity in comparison to the free medication.

In spite of the fact that they have a lot of promise, nano drug delivery systems are confronted with a number of obstacles that need to be overcome before they can be successfully implemented via clinical applications [12]. Nano drug delivery technologies face extra hurdles, particularly with regard to their stability and stored state. The complicated manufacturing and scaling up procedures that are required in maintaining the constant

quality, repeatability, and scalability of nanoparticles provide a substantial challenge [13]. The establishment of uniform procedures for evaluating safety, effectiveness, and quality is very necessary in order to facilitate regulatory approval and market entrance. As a last point of consideration, the expensive cost that is linked with nano medication delivery devices prevents their broad use. Increasing accessibility requires both the development of manufacturing techniques that are efficient in terms of cost and the consideration of economic feasibility [14].

## II. TYPES OF THE NDDSS

Liposomes, dendrimers, carbon nanomaterials, fullerenes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers, nanoshells, quantum dots, superparamagnetic nanoparticles, and other types of nanoparticles are just examples of the many different morphologies that nanoparticles may take [15]. The following is a discussion of the many morphologies of nanoparticles that may be used as drug delivery systems, along with their significance and the difficulties that they provide:

### 2.1. Lipsomes

In the process of self-assembly, amphiphilic phospholipids come together to create liposomes, which are colloidal particles that are surrounded by lipid bilayers. The diameters of these particles range from 25 nm to 200 nm, and they are often used in the administration of drugs, especially that which targets cancer cells. Liposomes were first discovered in 1965, and pharmaceutical companies have been using them as delivery vehicles for drugs since 1971 [16]. The hydrophobic effect is the driving force behind the creation of their bilayer structure. When polyethylene glycol (PEG) is added to the surface of liposomes, they are able to avoid being photographed by the reticuloendothelial system. The liposomal medicine Doxil was the first nanotechnology product for cancer therapy to get approval from the Food and Drug Administration. Liposomes have the ability to carry biological macromolecules such as DNA as well as smaller molecules, which is a significant benefit [17].

#### 2.1.1. Types of liposomes

When it comes to the delivery of drugs, liposomes are used extensively in the cosmetics and pharmaceutical sectors worldwide. A membrane-like structure, drug stability, enhanced biodistribution, and compatibility with both hydrophilic and hydrophobic medicines are some of the benefits that they provide with regard to drug delivery [18]. To categorize liposomes, there are four different types:

1) Traditional liposomes are made up of an aqueous core and a lipid bilayer that have the potential to include neutral, cationic, or anionic cholesterol as well as phospholipids. Under these circumstances, the lipid bilayer and the aqueous space are both capable of being filled with compounds that are either hydrophobic or hydrophilic.

2) The surface of the liposome is coated with polyethylene glycol (PEG) in order to achieve steric equilibrium. This sort of liposome is referred to as this type.

3) Ligands are coupled to the surface of the liposome or to the end of PEG chains that have been attached in the past. This sort of liposome is known as the ligand-targeted type. Peptides, carbohydrates, and antibodies are all examples of ligand substance.

4) The fourth form of liposome is referred to as a theragnostic liposome, and it is a combination of the first three types of liposomes. Additionally, it typically has a medicinal, imaging, and targeting component [19]. It also frequently includes a nanoparticle.

Thin layer hydration, mechanical agitation, solvent evaporation, solvent injection, and surfactant solubilization are all components of the standard manufacturing process [20].

### 2.1.2. Liposome as drug delivery systems

The use of liposomes in the delivery of medication to malignant and tumor tissues has been the subject of much study because to the extraordinary properties that they possess. The two primary strategies that have been used for this purpose are passive targeting and active targeting, as seen in Figure 1[21].

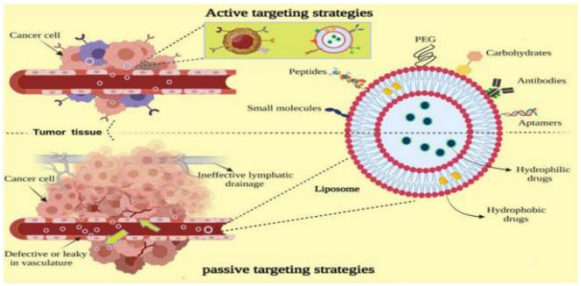


Figure 1.Passive targeting and active targeting.

The surface of liposomes may be functionalized to provide stealth by the process of PEGylation. Additionally, liposomes can be functionalized to improve receptor-mediated endocytosis through the use of targeted ligands like as antibodies, peptides, proteins, carbohydrates, Aptamer, and a variety of other small molecules. In living organisms, the half-life of liposomal circulation is extended by PEGylation. It is possible to encapsulate medications into the aqueous lumen, integrate them into the lipid bilayer, or conjugate them to the surface of the liposome, depending on whether the pharmaceuticals are hydrophobic or hydrophilic [22].

The physical characteristics of the tumor and the amount of nanomaterials present are taken into consideration when passive targeting is performed. An excessive quantity of angiogenesis is caused by cancer cells' over expression of vascular endothelial growth factor (VEGF), which induces the expansion of blood vessels. With liposomes of the appropriate size, it is possible for them to circulate in the circulation for a longer period of time, which enables the nanosystem of the anti-tumor medicine to concentrate on the tumor tissue. Vein holes in tumor tissue are much larger than those in normal tissue [23].

Because of abnormalities in the lymphatic system, nanoparticle retention durations increase when a drug delivery system comes into contact with malignant tissue. This is something that is inconceivable for a drug molecule of such a small size [24].

Additional coating of the nanoparticle with a biocompatible polyethylene glycol (PEG) polymer is required for this procedure. This coating not only enables the nanoparticle to circumvent the reticuloendothelial (RES) system, but it also extends the amount of time that

blood circulates inside the circulatory system. PEG achieves this effect by protecting lipsomes from opsonization [25].

Photosensitizing medicines are activated by light in the process of photodynamic therapy (PDT), which results in the production of reactive oxygen species (ROS) or singlet oxygen, both of which are capable of destroying malignancies. PDT was first used for the treatment of bladder cancer; however, since then, research has been conducted to investigate its potential application in other types of cancer [26]. Nanocarriers have the capacity to boost photodynamic therapy (PDT) by enhancing the bioavailability and stability of photosensitizers. This is accomplished by encapsulating the photosensitizers. On the other hand, because of the limited light penetration, PDT is only effective on cancers that are located on the surface. Nanocarriers are able to overcome a number of limitations, including limited bioavailability, hydrophobic side effects, large dose needs, and self-aggregation in aqueous conditions. In terms of increasing the efficacy of PDT, they show potential [27].

As a result of their amphiphilic and non-ionic structure, liposomes are very adaptable drug carriers. They are able to transport medications that are soluble in water as well as those that are lipid-soluble [28]. Researchers have the capacity to control the permeability, stiffness, size, and surface functionalization of these materials in order to develop drug delivery systems that are both sustained and targeted [29]. Drug oxidation may be avoided by the use of liposomal delivery, which also fulfills the need for biodegradable drug delivery [30].

However, despite their many advantages, structures based on liposomes have a number of limitations that prohibit them from being widely used in clinical settings. Among the most significant obstacles are their physical and chemical stability, limited solubility in aqueous solutions, short half-life in the body, high manufacturing costs, and allergic responses to certain liposomal compounds [31].

### 2.2. Carbon nanomaterials

Carbon, the fundamental component of DNA, is what gave rise to all life on Earth. Owing to its distinct electron configuration (1s2, 2s2, and 2p), it exists in several forms[32]. Its ability to bind almost any element gives it a broad variety of technological applications, such as the transportation of synthetic compounds and medications[33].

Based on structural differences, CBNs are separated into graphene, mesoporous carbon, nanodiamonds, fullerenes, and carbon nanotubes. These materials exhibit improved immunogenicity, biocompatibility, and drug-loading capacity[34]. Functionalized CBNs have been used to produce biocompatible scaffolds and nanomedicines. They have been studied for cancer treatment because of their excellent supramolecular stacking, high adsorption capacity, and photothermal conversion capacity[35]. Combining adaptive traits with chemical functionalization may enhance therapy.

### 2.3. Carbon nanotubes

Carbon nanotubes (CNTs) are cylinders or tubes that possess a unique combination of strength, elasticity, and stiffness. Single-walled nanotubes (SWCNTs) are one-dimensional hollow and cylindrical graphene sheets that are stretched and enfolded. They were produced

using sp2 hybridization. These carbon nanotubes (CNTs) may expand to hundreds of times their initial length, with a diameter of around 1 nm[36].

The electrical characteristics of multi-walled carbon nanotubes (MWCNTs) are more complex and are made up of many graphene sheet layers. These nanotubes vary in size from 5 nm to 50 nm[37].

When functional groups or therapeutic compounds are added, functionalized carbon nanotubes, or f-CNTs, exhibit enhanced solubility, biocompatibility, and decreased toxicity[38]. CNT surfaces may be modified via covalent and non-covalent methods, yet they may have an impact on mechanical strength[39].

Among the various varieties of carbon nanotubes, the prospective advantages of SWCNTs in metal nanoparticles, such as bulk medicine loading, structural flexibility, intrinsic stability, extended circulation duration, and bioavailability, have attracted attention[40]. The capacity of functionalized SWCNTs to entrap low molecular weight compounds and antibodies allows for higher drug loading. Additionally, it makes it possible to conjugate biological molecules without triggering an immune reaction. Chemotherapy often employs doxorubicin (DOX), yet it has drawbacks such as irreversible toxicity, limited barrier crossing capacity, and adverse effects. Since carbon nanotubes (CNTs) have a large surface area, stability, and cell membrane penetration, they may transport DOX efficiently while minimizing negative effects. Hyaluronic acid (HA) and amino-functionalized single-walled carbon nanotubes (NH2-SWCNTs) demonstrated quicker release of DOX in the surroundings of the tumor cells during the therapy of breast cancer. The structure of doxorubicin (DOX) is shown in Figure 2[41], and SWCNTs-DOX-HA enhanced breast cancer therapy by more successfully inducing apoptosis and reducing tumor cell proliferation than SWCNTs-DOX alone.

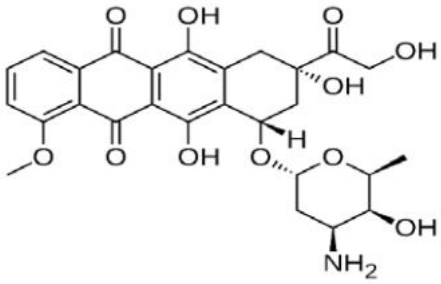


Figure 2. Structure of doxorubicin (DOX)

pH-sensitive SWCNT-folic acid (FA) conjugates reduced DOX adverse effects while exhibiting increased drug loading and anticancer effects. The pH-dependent release and cytotoxicity of FA-EDA-MWCNTs-DOX against breast cancer cells were shown.[42].

**2.4. Graphene**

Graphene is a single-layer carbon material with partly full sp2 orbits that has a high surface area, excellent optical clarity, excellent thermal conductivity, and robust mechanical strength. It functions as a semiconductor, interacting with electrons to produce new quasi-

particles. Ballistic transport without dispersion is made possible by graphenenanoribbons and quantum dots[43].

Graphene has a low solubility and strong electrical conductivity. Changes such as graphene oxide and layered graphene-oxide are possible using sol-gel chemistry. Polymer surface modification improves biocompatibility, and graphene and its derivatives have a wide range of uses in medicine and drug delivery[44]. In response to external and internal cues, graphene nanoparticles modulate medication release, enhancing absorption, removing obstacles, and reducing adverse effects[45].

Among grapheme nanomaterials, GOs have garnered a lot of interest because to the functional groups that are present on the side walls. Graphene was able to bind to DOX and camptothecin via hydrophobic contact and π-π stacking. GOs connect to the hydroxyl and amino groups of DOX more easily because of the hydroxyl and carboxyl groups on their surface[46].

The 4T1 cancer cell lines were used in the research to demonstrate that the electrochemical approach effectively demonstrated both cellular and carrier capacity. 5-fluorouracil loaded GO was developed based on pH-stimuli drug delivery, and Figure 3[47] depicts the structure of 5-fluorouracil.

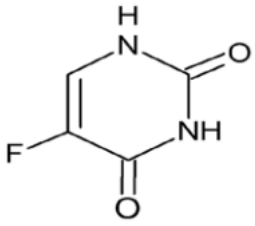


Figure 3.Chemical structure of 5-fluorouracil.

The anticancer agent's release was regulated by this formulation in the tumor's acidic pH of 5.8, but it was significantly decreased in the physiological pH of 7.4.

## III. MULTIFUNCTIONAL NANOPARTICLES AS NDDSS

Drug delivery methods may limit side effects by using metal nanoparticles since they directly target the affected organs.

### 3.1. Silver nanoparticles

Because of its antiviral, antifungal, and antioxidant qualities, silver is the precious metal with the greatest profit-orientedness when it comes to manufacturing NPs and nanoparticles. These are well-known because of their anti-bacterial, anti-viral, antifungal, and antioxidant activities, as well as their remarkably increased physicochemical qualities in comparison to the bulk material, including optical, thermal, electrical, and catalytic capabilities[48]. It has been shown that a range of cell types are vulnerable to the cytotoxicity of silver nanoparticles via necrosis and apoptosis. Furthermore, they demonstrate outcomes against adverse effects of traditional treatments, including oxidative stress to DNA, generation of reactive oxygen species (ROS), augmentation of lactate dehydrogenase (LDH) leakage, and suppression of stem cell differentiation[49].

### 3.2. Gold nanoparticles

Gold nanoparticles, or AuNPs, are strong radiosensitizers that are used in medical procedures including cancer therapy and medication administration[50]. Strong radiosensitizers used in medicine delivery and cancer therapy are gold nanoparticles, or AuNPs. Because Au NPs may control medication release by internal biological triggers or external light activation, they can transport a wide range of medicinal substances, recombinant proteins, vaccines, or nucleotides into their targets. The remarkable efficacy of AuNP-based medication delivery has garnered much interest [51].

## IV. TARGETING STRATEGY OF THE NDDSS

Active targeting and passive targeting are the two ways by which nanocarriers may deliver nanodrugs to their intended targets. In active targeting, we concentrate on certain markers that are exclusive to diseased cells—not healthy ones. For instance, we may use compounds that engage with the folate receptors that are overexpressed in diseased cells. One biomarker that may be actively addressed that is overexpressed in ovarian cancer is CA-125[52].

When it comes to passive targeting, polymer size matters. The location of sick cells may have a greater accumulation of larger polymers. This occurs as a result of the polymers' ability to enter the diseased region via blood vessel junctions with leaks. It's similar to using blood channel openings to transport medications to the desired location[53].

Figure 4 shows how to target nanoparticles (NPs) both passively and actively to increase the therapeutic effectiveness of anticancer medications. In Figure 4A, NPs are passively targeted to capitalize on the increased permeability and retention (EPR) effect; in Figure 4B, NPs are actively targeted to improve cellular absorption and accumulation of NPs by receptor-facilitated endocytosis[54].

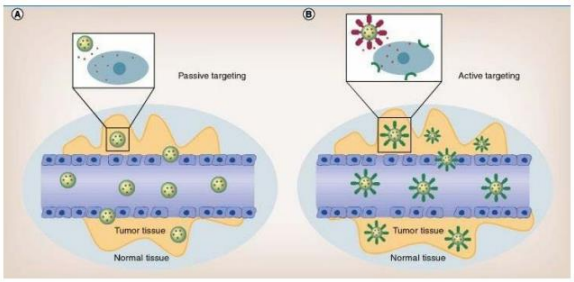


Figure 4.Passive and active targeting of nanoparticles (NPs) as a drug delivery system.

## V. APPLICATION OF NDDSS

Nano drug delivery systems have various applications in medical field. Some are given below:

### 5.1. AuNPs in cancer therapy

For gold nanoparticles to be used as therapeutics, it is essential to comprehend how they are biodistributed and accumulate in living systems. This can only be done with accurate characterization of the nanomaterials, a reliable animal model, a sizeable sample, and strong statistical analyses. AuNPs regulate damage to healthy cells and lessen the likelihood of

adverse outcomes[55]. AuNPs are a novel component in cancer therapy that display aggregation[56] and a size-dependent lethal effect on various cancer cells[57]. The anti-cancer action of AuNP is complicated and poorly understood. The positive charges are on AuNPs, but cancerous and healthy cell membranes include molecules that are negatively charged, such as lipids, which cause AuNPs to be absorbed and internalized[58]. Another mechanism by which AuNPs enter cells is endocytosis, which results in the accumulation of tiny AuNPs inside HeLacells[59].

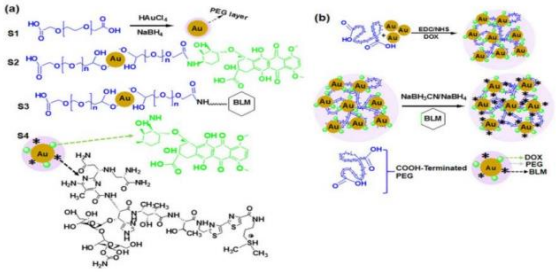

Figure 5. Synthesis of PEG-AuNPs NPs (a) the chemical composition of DOX and BLM and the procedures involved in conjugating them to the surface of S1; (b) a schematic depicting the production of S2, S3, and S4 NPs.

We focused on the development of the following gold nanoparticles-based drug delivery systems: AuNPs covered by PEG carrying carboxylic groups, PEG-AuNPs linked to DOX, PEG-AuNPs linked to BLM, and, finally PEG-AuNPs linked to both DOX and BLM (referred to as S1, S2, S3 and S4, correspondingly) as illustrated in Figure 5[59].

### 5.2. AgNPs as anti-viral agents

A significant problem for the pharmaceutical, medical, and biotechnological industries is the development of resistance by different viral pathogens against anti-viral drugs[60]. Because of their successful interactions with sulfhydra, amino, carboxyl, phosphate, and imidazole groups, AgNPs are well acknowledged to suppress viruses.

Due to their inhibitory efficiency against a variety of viruses, including hepatitis, coronavirus, influenza, herpes, recombinant respiratory syncytial virus, and human immunodeficiency virus, AgNPs have recently gained popularity as anti-viral medicines[61]. AgNPs were employed to create a nanoscale delivery system for the antiviral drug zanamivir, and surface-enriching AgNPs with amantadine to prevent H1N1 virus resistance as demonstrated in Figure 6[62].

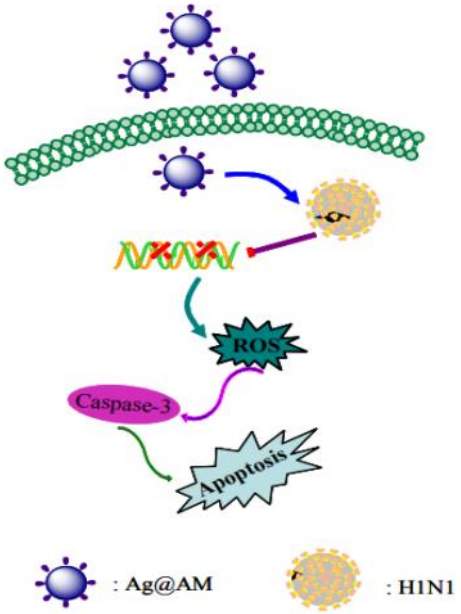


Figure 6.The reversal of H1N1 influenza virus-induced apoptosis by silver nanoparticles.

## CONCLUSION AND FUTURE PERSPECTIVES

The development and spread of nanotechnology for therapeutic and medical-related applications during the last two to three decades has created unique opportunities to develop medical diagnostics and treatments for human disorders. These opportunities have been made possible by the advancement of nanotechnology. The nanomaterials exhibit precise control over desired properties, as evidenced by their heightened solubility of various cargoes, capacity to combat diseases, regulated transmission, enhanced strength, increased distribution throughout the organism, ability to adjust to specific proportions, efficient transport across tissues and cells, and targeted delivery to desired locations. The creation of picture components and detectors with a better sensitivity for the purposes of analysis and identification is possible via the use of these kinds of approaches. A number of other issues still need to be overcome before this research might potentially result in the production of drugs that are beneficial for therapeutic purposes. One of the most significant challenges that must be overcome before this technology can be commercialized is the creation and evaluation of innovative methods for controlling the interactions that nanoparticles have with the body. In order to successfully transport nanomaterials to specific locations of the body, it is necessary to find a solution to the problem of preventing organs such as the liver and spleen from entrapping them. Through the manipulation of material characteristics at the nanoscale, it has become feasible to improve and modify technologies that are already in existence. There is thus the possibility that the promise of nanotechnology-based medicines might become a reality with appropriate time and research.

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