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Smart Nanomaterials for Targeted Drug Delivery: Properties, Functionalization and Biomedical Applications

Aastha Sharma[1]; Ashita Garg[1]; Samjeet Singh Thakur[2,*]

Abstract

Targeted drug delivery has become an important area of research in modern pharmaceutical and biomedical sciences. Traditional drug delivery methods often suffer from several limitations such as poor bioavailability, non-specific distribution of drugs and undesirable side effects caused by the exposure of healthy tissues to therapeutic agents. In recent years, nanotechnology has provided innovative solutions to overcome these challenges through the development of smart nanomaterials capable of delivering drugs directly to specific sites in the body. These nanomaterials possess unique physicochemical properties such as small size, high surface area, and the ability to respond to different biological stimuli. The objective is to examine the role of smart nanomaterials in targeted drug delivery and to discuss their mechanisms, types, applications, and recent research developments. Various smart nanocarriers including liposome, polymeric nanoparticles, dendrimers, gold nanoparticles and magnetic nanoparticles have shown significant potential in improving the efficiency and selectivity of drug delivery systems. These materials can be designed to respond to internal stimuli such as pH, enzymes, and redox conditions or external stimuli such as temperature, light and magnetic fields, enabling controlled and site-specific drug release. Recent studies indicate that smart nanomaterials significantly enhance therapeutic efficacy while minimizing systemic toxicity. They have demonstrated promising applications in the treatment of cancer, neurological disorders, and infectious diseases by enabling precise drug targeting and controlled release. Despite certain challenges related to toxicity, stability, and large-scale production, the development of smart nanomaterials represents a major advancement in modern medicine. Overall, the integration of nanotechnology with drug delivery systems has a potential to revolutionize therapeutic strategies and contribute to the development of safer, more effective, and personalized treatment approaches in the future.

Keywords: Targeted drug delivery, nanotechnology, smart nanomaterials, nanocarriers, controlled drug release, stimuli-responsive, therapeutic efficacy, systemic toxicity.

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INTRODUCTION

The field of drug delivery has changed a lot over the past few decades with emergence of nanotechnology. Traditional drug administration methods often suffer from limitations such as poor solubility, rapid degradation, lack of selectivity, and systematic side effects. To overcome these challenges, researchers began exploring nanoscale materials capable of carrying therapeutic agents directly to specific sites in the body. This led to the development of smart nanomaterials, which are particles designed to respond to biological or external stimuli and release drugs in a controlled and targeted manner [1, 2].

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Smart nanomaterials include systems such as liposomes, polymeric nanoparticles, dendrimers, and metallic nanoparticles, all of which can be functionalized to interact selectivity with diseased tissues. Their small size and modifiable surface properties allow them tocirculate through the body, cross biological barriers, and deliver drugs with improved precision compared to conventional formulations [3].

The importance of smart nanomaterials lies in their ability to enhance therapeutic efficacy while minimizing harmful side effects. By encapsulating drugs within nanoscale carriers, it becomes possible to protect the active compound from premature degradation, improve its solubility and control its release rate. Targeted drug delivery ensures that a higher concentration of the drug reaches the diseased tissue while reducing exposure to healthy cells, thereby lowering toxicity and improving patient safety [4].

These systems also support both passive targeting, through phenomena such as enhanced permeability and retention in tumor tissues, and active targeting, where ligands attach to the nanoparticle surface bind specifically to receptors on target cells. Such precision has made smart nanomaterials a promising platform for treating complex diseases particularly cancer, tuberculosis and neurological disorders as shown in Figure 1 [4].

Conventional drug delivery often fails because medicine breaks down before reaching the target. The success of lipid nanoparticle-based vaccines and ongoing research in nanocarrier- mediated chemotherapy has demonstrated the practical feasibility of the systems in clinical settings as chronic diseases and drug resistance continue to rise globally, conventional treatmentstrategies are proving insufficient, increasing the need for smarter and more efficient drug delivery approaches [5].

Modern research is focusing not only on delivering drugs but also on integrating diagnostic and therapeutic functions into a single platform, a concept known as theranostics. Smart nanomaterials are at the center of this development because of their tunable properties, such as physical, chemical, and biological [6].

Despite the promising potential of smart nanomaterials, several challenges still limit their widespread clinical application. Issues such as long-term toxicity, immune system interactions, large scale manufacturing and regulatory approval remain significant barriers. Some nanoparticles may accumulate in organs like the liver and spleen, leading to possible toxicity and biocompatibility concerns. In addition, variability in targeting efficiency and the complexity of designing stimuli responsive systems make their translation from laboratory research to real world therapy difficult.

Therefore, there is strong need for continued research to develop safer, more efficient, clinically reliable smart nanomaterials-based drug delivery systems. Addressing these challenges is essential to fully realize the potential of nanotechnology in improving therapeutic outcomes and shaping the future of modern medicine [7, 8].



Figure 1. Genetically targeted delivery [8].

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History & Evolution of Nanotechnology in Drug Delivery

Drug delivery systems in the early days were primarily limited to conventional dosage forms such as tablets, capsules, and injections. These methods often resulted in nonspecific distribution of drug throughout the body, leading to reduced therapeutic efficiency and increased side effects. The development of liposomes in the 1960s marked the first major step towards nanoscale drug carriers, demonstrating that drugs can be encapsulated within microscopic vesicles and protected from degradation. This marked the beginning of nanoscale drug delivery systems [9].

During the 1980s and 1990s, significant progress was made with the introduction of polymeric nanoparticles, dendrimers, and metallic nanoparticles. These carriers offered improved stability, higher drug loading capacity, and better control over drug release. Researchers increasingly focused on designing systems that could overcome biological barriers and enhance drug bioavailability [10].

In the early 2000s, drug delivery systems evolved into smart nanomaterials capable of responding to specific external or internal stimuli such as pH, temperature, enzymes and magnetic fields. This development enabled more controlled and site-specific drug release. At the time, the concept of Targeted drug delivery gained importance, as scientists began modifying nanoparticle surfaceswith ligands, antibodies, and other molecules that allow them to recognize and bind to specific cells or tissues [11].

In the last decade, the field has witnessed the emergence of multifunctional nanocarriers that integrate both diagnostic and therapeutic capabilities into a single nanoparticle platform led to the development of theranostic nanomaterials. These advanced systems represent a major milestone in nanomedicine, as they enable real-time monitoring of treatment along with precise drug delivery. Overall, the evolution of nanotechnology in drug delivery reflects a continuous shift from simple drug carriers to highly sophisticated, responsive, and targeted systems designed to improve treatment outcomes [12].

BASICS OF NANOTECHNOLOGY AND SMART NANOMATERIALS

Nanotechnology refers to the science of working with small things, typically in the size range of 1-100 nanometers. At this scale, materials exhibit physical, chemical, and biological properties that are significantly different from those observed in their bulk form. This unique behavior arises due to large fraction of atoms present on the surface of nanoparticles, which enhances their reactivity and interaction with surrounding environments [13].

Nanomaterials can be fabricated in different shapes such as spheres, rods, tubes and sheets and they may be composed of organic, inorganic or hybrid materials. Their small size allows them to penetrate biological barriers, circulate to the bloodstream, and interact at the cellular and molecular levels, making them highly suitable for biomedical applications including drug delivery, imaging, and diagnostics. According to recent research, the ability of nanoparticles to cross cellular membranes and accumulate in target tissues is a key factor that makes them effective carriers for therapeutic agents, especially in cancer treatment and targeted therapy [14].

Some key characteristics of nanomaterials include extremely small particle size and large surface-to-volume ratio, which significantly increases their surface energy and interaction with biological molecules. Tunable surface chemistry through functionalization allows nanoparticles to be modified with ligands, antibodies and polymers, enabling targeted delivery and improved biocompatibility. In addition, nanomaterials exhibit enhanced mechanical and optical, and electrical properties compared to bulk materials. These properties have been widely reported in recent studies, where functionalized nanoparticles showed improved stability, controlled drug release, and higher therapeutic efficiency [15].

These characteristics make nanomaterials particularly valuable in designing advanced therapeutic systems that require precision and controlled interactions within biological systems. Recent advancements highlight that smart nanomaterials can be engineered to respond to specific stimuli such

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as pH, temperature, redox conditions, and enzymes, allowing site-specific drug release. Such responsiveness improves treatment outcomes while minimizing systemic toxicity, which remains a major limitation of conventional drug delivery systems [16].

Unique Properties of Nanomaterials

Nanomaterials exhibit several distinctive properties that make them highly effective for biomedical pharmaceutical applications. Some of the unique properties include: High surface area-to-volume ratio, which allows greater drug loading and enhanced interaction with biological tissues; Size- dependent physical and chemical behavior, resulting in unique optical, magnetic, and electrical properties compared to bulk materials; Ease of surface functionalization, enabling attachment of polymers, antibodies, or targeting ligands for improved stability and specificity; Ability to cross biological barriers, such as cell membranes and the blood-brain barrier, due to their extremely small size; Improved solubility and bioavailability of poorly water- soluble drugs when incorporated into nanoscale carriers [17].

Advanced Physicochemical Characteristics:

The high surface-to-volume ratio of nanomaterials is a fundamental driver of their reactivity, as a significant fraction of the atoms are located on the particle surface, leading to an increase in surface energy and altered thermodynamic properties. In drug delivery contexts, this enables a high density of therapeutic payloads and the simultaneous conjugation of multiple functional moieties, such as polyethylene glycol (PEG) for “stealth” properties and specific ligands for receptor-mediated endocytosis. Furthermore, the quantum confinement effect observed in semiconductor nanoparticles (quantum dots) and the surface Plasmon resonance (SPR) in noble metal nanoparticles allow for sophisticated bioimaging and photothermal therapeutic interventions that are unattainable with conventional molecular agents [18].

Biological Interaction and Transport Kinetics:

At the nano-bio interface, the adsorption of biological macromolecules –primarily proteins- onto the high energy surface of nanomaterials results in the formation of a “protein corona” This biological coating dictates the physiological identity of the nanoparticle, influencing its circulation half-life, cellular uptake mechanisms, and eventual biodistribution. Nanoscale carriers can exploit the Enhanced Permeability and Retention (EPR) effect, characterized by leaky vasculature and impaired lymphatic drainage in neoplastic tissues, to achieve passive targeting. Additionally, the ability to engineer the surface charge and hydrophobicity allows these materials to bypass the reticuloendothelial system (RES), thereby optimizing the pharmacokinetic profile and reducing systemic toxicity of encapsulated potent pharmacological agents [19].

These properties collectively make nanomaterials highly suitable for designing advanced and efficient drug delivery systems.

CLASSIFICATION OF NANOMATERIALS USED IN DRUG DELIVERY

Nanomaterials used in targeted drug delivery are broadly classified into organic, inorganic, and hybrid nanomaterials based on their composition and natural properties. Each class offers specific advantages in terms of drug loading, stability, targeting capability, and biocompatibility as shown in Figure 2.

Organic Nanomaterials

Organic nanomaterials are primarily composed of biodegradable and biocompatible materials such as lipids, polymers, and proteins. Because of their biological compatibility and low toxicity, they are widely used in pharmaceutical applications.

The primary advantage of these organic systems lies in their high biocompatibility and inherent biodegradability, which minimizes the long-term systemic toxicity often associated with synthetic

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implants in Figure 3. Furthermore, their chemical versatility allows for precise modifications, enabling researchers to encapsulate a wide variety of therapeutic agents – ranging from hydrophobic small molecules to sensitive genetic material – while protecting them from premature degradation in the physiological environment [20, 21].

Liposomes

Liposomes are spherical vesicles composed of one or more phospholipids bilayers surrounding an aqueous core. They are among the earliest and most extensively studied nanocarriers for drug delivery due to their unique structural similarity to biological membranes, which significantly improves cellular uptake through endocytosis or fusion. A critical feature of liposomes is their amphiphilic nature; the aqueous core allows for the encapsulation of hydrophilic drugs, while the lipid bilayer provides a reservoir for hydrophobic molecules. This dual-loading capacity, combined with their ability to reduce drug toxicity and improve pharmacokinetics by altering the biodistribution of potent drugs, has led to several clinically approved formulations. In modern oncology, liposomes have been successfully utilized in vaccine delivery and chemotherapy, providing a sustained release profile that enhances therapeutic efficacy. At the molecular level, the performance of these liposomal bilayers is governed by the structural organic chemistry of their constituent phospholipids, primarily dipalmitoyl phosphatidylcholine (DPPC) and dioleoyl phosphatidylethanolamine (DOPE) To optimize pharmacokinetics, surface functionalization via covalent PEGylation is performed given in Figure 4.

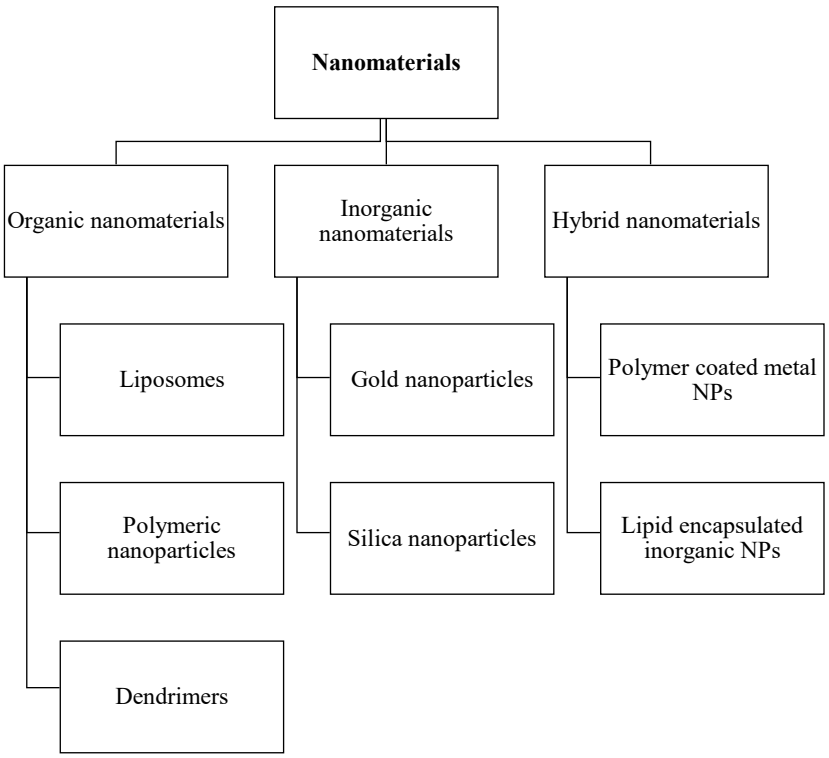


Figure 2. Classification of nanomaterials used in drug delivery.

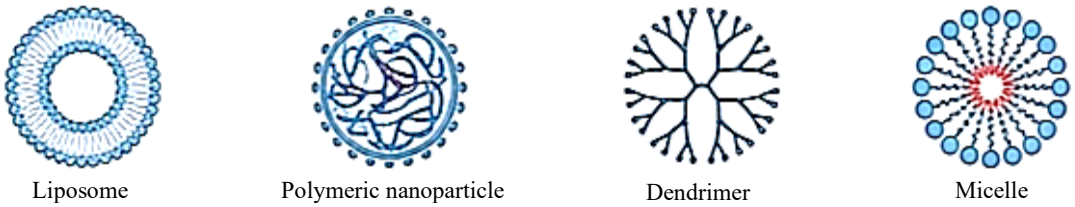


Figure 3. Organic nanomaterials design [22].

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The hydrophilic ether linkages (-o-) of the repeating polyethylene glycol chains from dynamic hydrogen bonds with surrounding water molecules. This creates a dense sterile hydration layer that sterically hinders the absorption of serum opsonin's, effectively preventing clearance by the reticuloendothelial system (RES) [23, 24].

Polymeric Nanoparticles

Polymeric nanoparticles are solid colloidal particles made from natural or synthetic polymers such as PLGA, chitosan, or PEG. They are designed to either encapsulate drugs within their matrix or adsorb them onto their surface for controlled delivery. Recent review studies highlight polymeric nanoparticles as one of the most versatile platforms because their mechanical and chemical properties can be tuned to meet specific needs. These systems provide a controlled and sustained drug release mechanism, protecting sensitive proteins and nucleic acids from enzymatic degradation within the bloodstream. By functionalizing the polymer surface with PEG (polyethylene glycol), these nanoparticles can achieve "stealth" properties, avoiding detection by the immune system and increasing the circulation time of the drug [26].

Dendrimers

Dendrimers are highly branched, tree like macromolecules with a well-defined three-dimensional structure consisting of a central core, repeating branching units, and multiple functional groups on the surface. This unique structure provides a high drug loading capacity due to internal cavities created by the branching, while the surface groups allow for the simultaneous attachment of targeting ligands and imaging agents. The monodisperse nature of dendrimers ensures precise control over size and surface chemistry, which is vital for reproducible drug delivery. Dendrimers have shown significant potential in delivering anticancer drugs and diagnostic molecules due to their uniform size and multifunctional surface. Allows them to exploit the EPR effect, accumulating more effectively in tumor tissues than in healthy cells. A premier example of a highly defined organic architecture in this class is the Poly (amidoamine) (PAMAM) dendrimers. The synthetic preparation of PAMAM relies on the iterative, divergent organic steps starting from an ethylenediamine core. The outward growth involves an initial repetitive Michael addition of methyl acrylate to the primary amine functional groups, followed by an exhaustive amination of the resulting ester groups with an excess of ethylenediamine as shown in Figure 5. Each successive iteration yields a specific macromolecular generation (G_O, G_1, G_2……), doubling the surface primary amine density and creating well defined internal hydrophobic cavities ideal for guest-host drug encapsulation [27, 28].

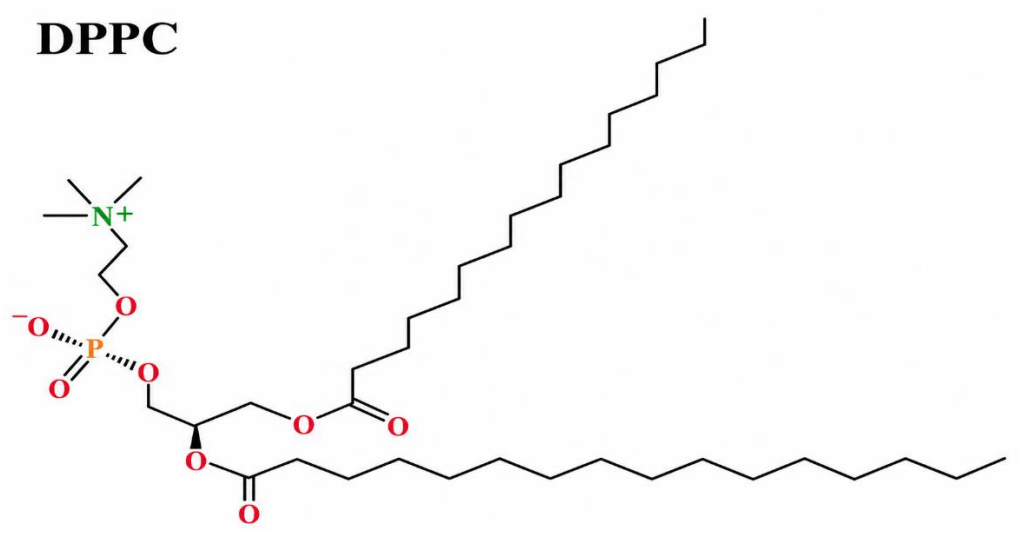


Figure 4. Structure of dipalmitoyl phosphatidylcholine (DPPC) [25].

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Inorganic Nanomaterials

Inorganic nanomaterials are composed of metals, metal oxides, or ceramic materials. They are known for their high structural stability, unique optical properties, and ease of functionalization, which makes them suitable for both drug delivery and imaging applications. These materials possess high chemical and thermal stability compared to their organic counterparts, and they exhibit tunable optical, magnetic, and electronic properties that are not found in biological molecules. This makes them ideal candidates for theranostic application where a single nanoparticle serves both a diagnostic role (imaging) and a therapeutic role (drug delivery) [30].

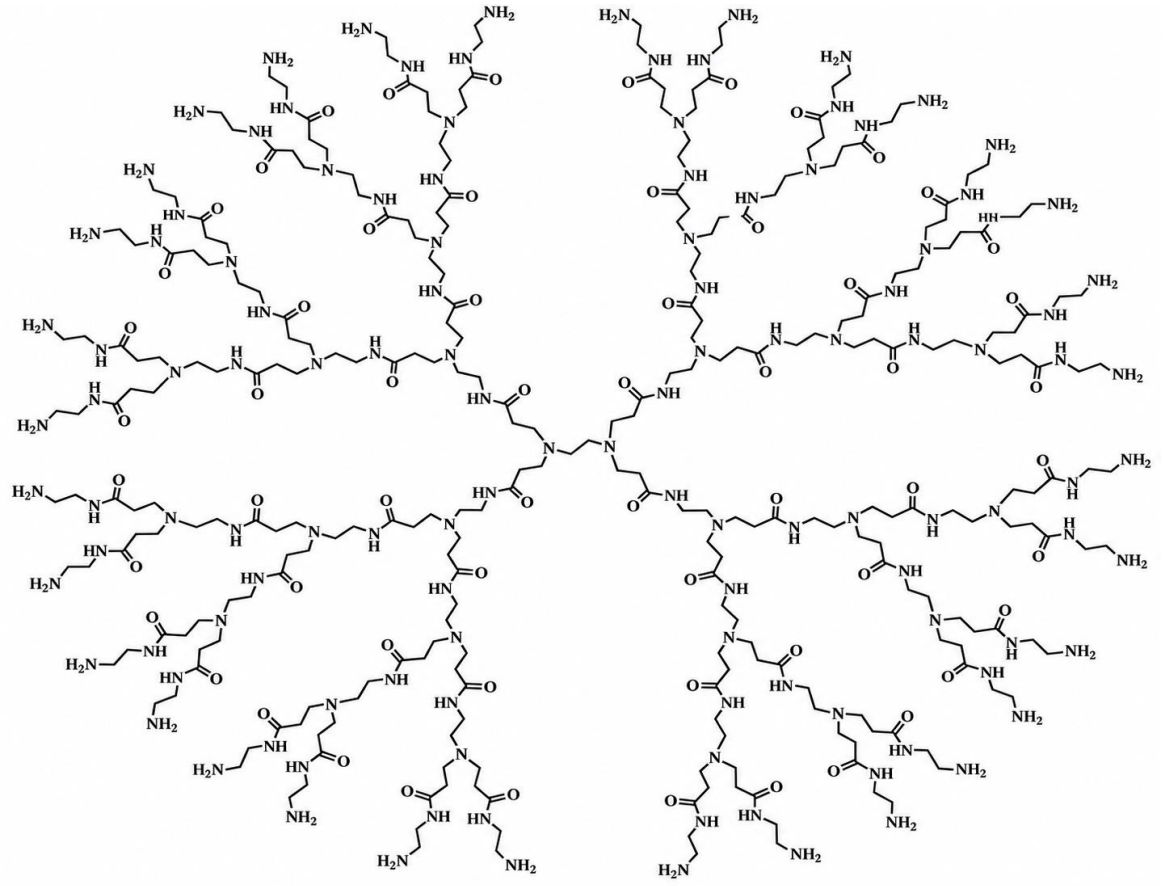


Figure 5. G3Poly (amidoamine) (PAMAM) dendrimers [29].

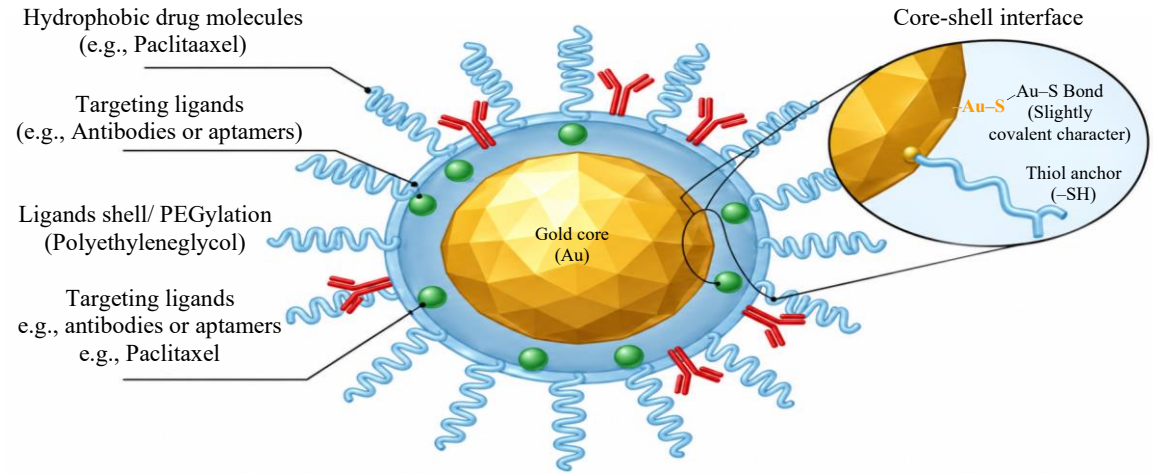


Figure 6. Functionalized gold nanoparticle designed for targeted drug delivery [31].

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Gold Nanoparticles

Gold nanoparticles (AuNPs) are widely studied due to their excellent biocompatibility and the phenomenon of Surface Plasmon resonance (SPR). This optical property allows AuNPs to convert light into heat, making them particularly useful in photothermal therapy for targeted cancer treatment. Beyond therapy, their surface can be easily modified with thiol-containing molecules, antibodies and drugs to ensure site-specific delivery as in Figure 6. Gold nanoparticles can also be engineered to release their cargo in response to external stimuli such as light or temperature changes, providing a "smart" drug delivery system that minimizes off-target effects and enhances the concentration of the drug at the tumor site [32].

Silica Nanoparticles

Silica nanoparticles, especially mesoporous silica nanoparticles (MSNs), are extensively used because of their highly porous structure and large internal surface area. These pores allow for an exceptionally high drug-loading capacity, while the pore size can be controlled to regulate the release rate of the encapsulated molecules. The robust chemical stability of the silica framework ensures that the particles remain intact until they reach the target site, and the surface silanol groups provide a versatile handle for easy functionalization. The structural framework of mesoporous silica nanoparticles (MSNs) is engineered through controlled sol-gel organic chemistry. This involves the base catalyzed hydrolysis and subsequent condensation of silicon alkoxide precursors, predominantly tetraethyl orthosilicate (TEOS), in the presence of structure directing micellar template such as cetyltrimethylammonium bromide (CTAB). Post synthesis calcination reveals a dense matrix of surface silanol groups(≡Si-OH) as in Figure 7. These groups serve as reactive inorganic handles for covalent surface modification through silanization reactions using organosilane coupling agents like (3-aminopropyl)triethoxysilane (APTES), transitioning the surface to an amine-terminated monolayer available for bioconjugations [33, 34].

Hybrid Nanomaterials

Hybrid nanomaterials are formed by combining organic and inorganic components into a single system. This approach aims to integrate the advantages of both material types while minimizing their individual limitations. In these systems organic components typically provide biocompatibility and flexibility, and a shield against immune recognition, while inorganic components contribute mechanical strength, imaging capability, and controlled release tiggers. Hybrid nanocarriers can be designed as polymer-coated metal nanoparticles, liposome-encapsulated inorganic nanoparticles, or core-shell structures with organic shells and inorganic cores shows in Figure 8. Because of these synergistic advantages, hybrid nanomaterials are increasinglybeing explored as next-generation platforms for theranostic applications, where diagnosis and treatment are integrated into a single, highly efficient system [35].

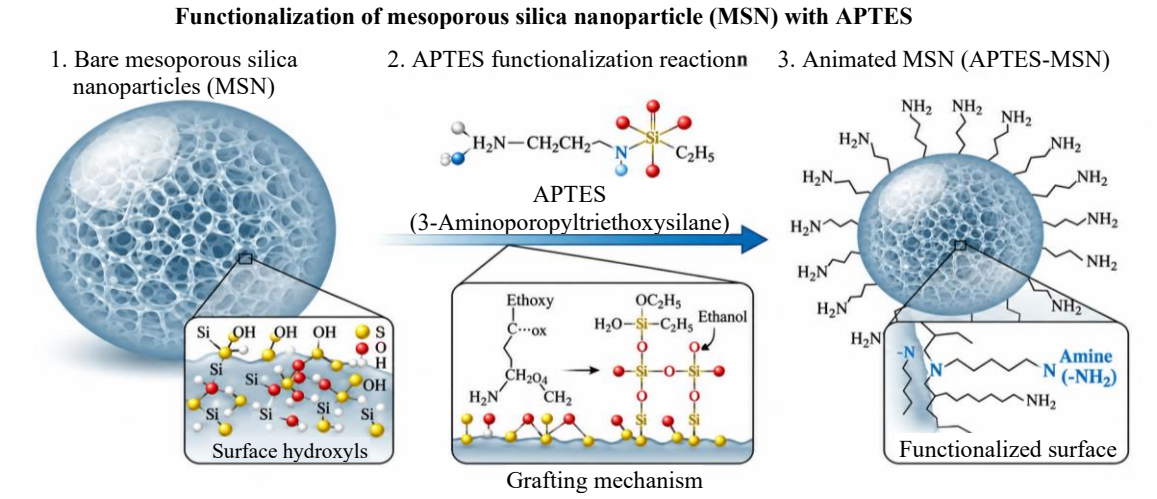


Figure 7. Structure and synthesis of APTES silica nanoparticle [36].

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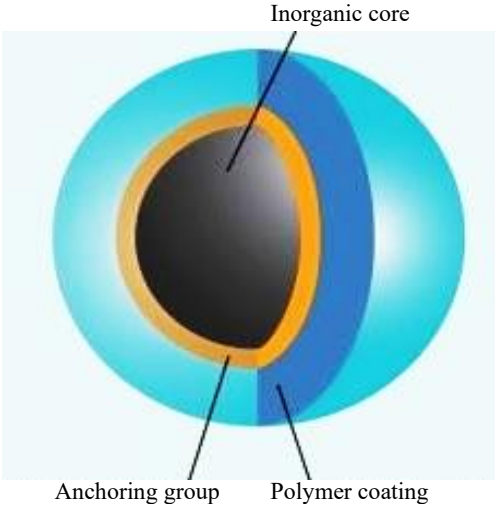


Figure 8. Polymer coating on core-shell material [37].

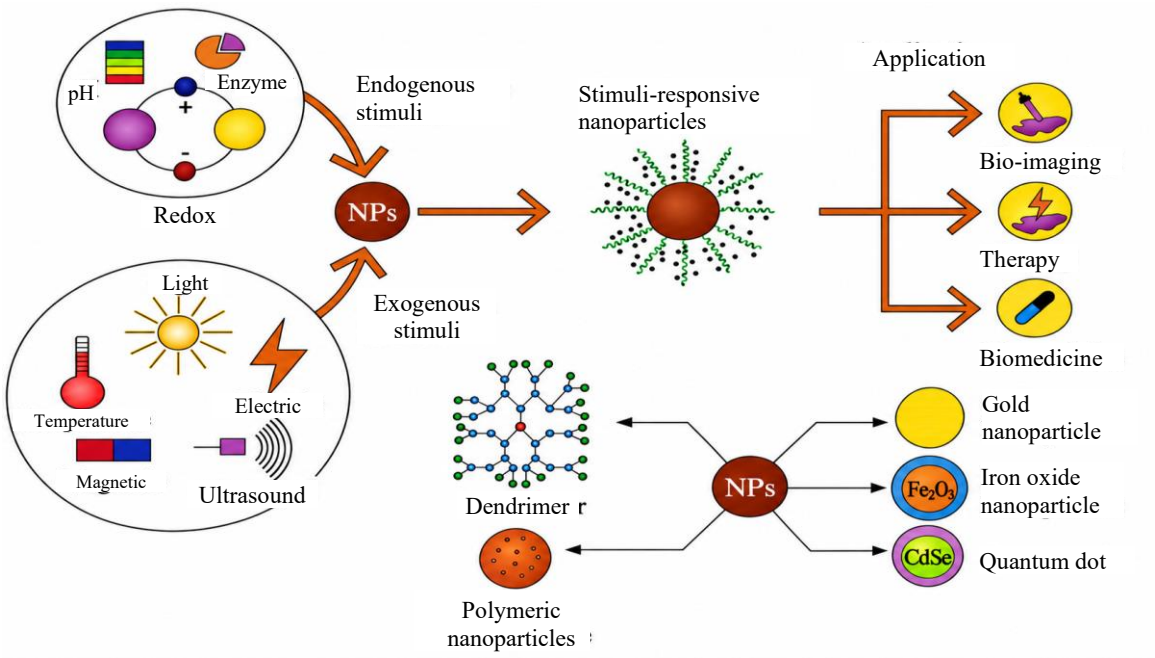


Figure 9. Overview on external and internal stimuli responsive drug delivery system [38].

STIMULI-RESPONSIVE NANOMATERIALS

Stimuli-responsive nanomaterials, often referred to as smart nanocarriers, are advanced drug delivery systems that can change their physical or chemical properties in response to specific environmental triggers. This behavior enables controlled and site-specific drug release, which helps in improving therapeutic efficiency while reducing systemic toxicity [39].

These systems are broadly classified based on the type of stimulus used to trigger drug release, including internal (endogenous) stimuli such as pH and temperature, and external (exogenous) stimuli such as magnetic fields, light, and ultrasound as shown in Figure 9.

pH-Responsive Systems

pH-responsive nanomaterials are designed to exploit the significant pH gradient that exists between healthy tissues and diseased environments such as tumors, inflamed tissues, or specific intracellular compartments like endosomes and lysosomes. Intumor microenvironments, the extracellular pH is

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typically slightly acidic (~ 6.5-6.8) due to the Warburg effect and lactic acid accumulation, while intracellular compartments may have even lower pH levels (~5.0-6.0). Smart nanocarriers utilize pH-sensitive polymers, linkers, or coatings that remain stable at normal physiological pH 7.4. However, upon entering an acidic environment, these materials undergo physical or chemical changes- such as swelling, degradation, or bond cleavage- which facilitates selective drug release. To achieve highly selective pH-induced payload release, organic linkers with specialized acid-labile dynamic covalent bonds are engineered into the nanocarrier backbones.

The hydrazone linker (›C=N-NH-) remains structurally stable under normal physiological circulation kinetics at the pH 7.4. However, upon cellular internalization into the acidic endosomal and lysosomal lumens (pH 5.0-6.0), the high hydronium ion concentration drives an acid catalyzed hydrolysis mechanism. This rapidly cleaves the carbon-nitrogen double bond, regenerating the native carbonyl and hydrazine precursors, thereby unlocking and releasing the active therapeutic agent. Alternatively, polymers containing tertiary amine monomers, such as poly (2-(dimethylamino) ethyl methacrylate) (PDMAEMA), undergo protonation at acidic pH. The generation of positive ammonium charges creates intense intra-chain electrostatic repulsion, causing the polymer matrix to swell from a hydrophobic coil to a hydrophilic expanded state, forcing drug expulsion [40, 41].

Temperature-Responsive Systems

Temperature-responsive nanomaterials are designed to respond to changes in temperature, either from natural physiological differences or extremely applied heat. These systems typically use thermo sensitive polymers that exhibit a phase transition at a specific temperature, known as the Lower critical solution temperature (LCST). Below this critical threshold, the polymer chains remain hydrated and stable; however, when the temperature rises above the LCST, the polymer structure collapses or undergoes a conformational change that triggers the release of the encapsulated drug. This reversible behavior is particularly useful in localized cancer treatment, where hyperthermia can be applied directly to tumor tissues to trigger targeted drug release while simultaneously sensitizing the cancer cells to the treatment.

Redox-responsive smart nanomaterials exploit the sharp chemical gradient of the tripeptide glutathione (GSH) between the extracellular matrix (~2–20 uM) and the intracellular cytosol (~2–10 mM), a variation up to a thousand-fold overexpressed in malignant cells. These carriers integrate covalent disulfide linkers (-S-S-) within their macromolecular framework. Upon entry into the reducing environment of the cytosol, the elevated level of reduced GSH triggers a thiolate-disulfide exchange reaction. The nucleophilic attack by the sulfhydryl group of GSH breaks the disulfide crosslinks into free thiols (-SH), inducing a catastrophic disassembly of the polymeric or micellar carrier to immediately release the internal payload [42, 43].

Magnetic-Responsive Systems

Magnetic-responsive nanomaterials typically incorporate magnetic nanoparticles, such assuper paramagnetic Iron oxide Nanoparticles (SPIONs), which can be manipulated using an external magnetic field. These systems enable two primary advantages: Magnetic targeting, where nanoparticles are guided byexternal magnets to a specific anatomical site, and Controlled drug release, triggered by alternating magnetic fields (AMF) that generate localized heat through Neel and Brownian relaxation. This approach offers non-invasive control over drug delivery, leading to an enhanced accumulation of therapeutic agents at the target site shows in Figure 10.

By concentrating the drug within the diseased tissue, these systems significantly reduce the exposure of healthy tissues to toxic drugs and are widely investigated for their potential in “theranostic” applications- combining diagnostic imaging with targeted therapy [44].

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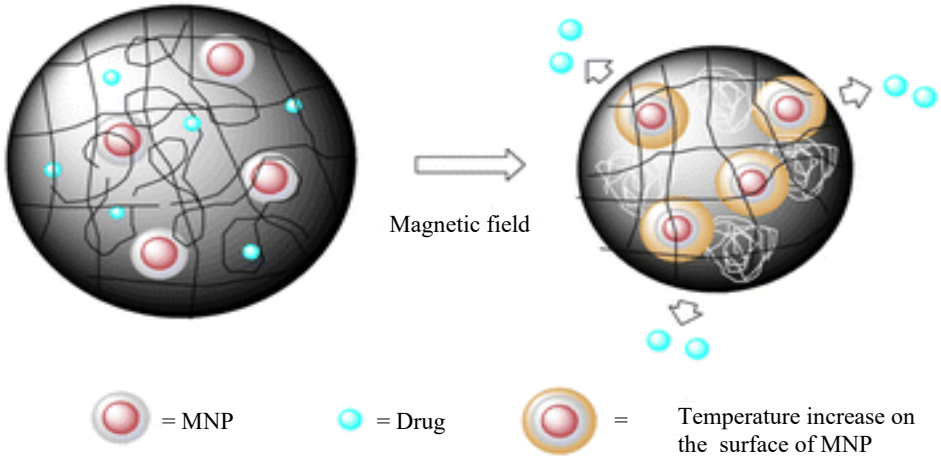


Figure 10. Magnetic field- triggered drug delivery [45].

Light-Responsive Systems

Light–responsive nanomaterials release their therapeutic cargo when exposed to specific wavelength of light, ranging from ultraviolet (UV), and visible to near- infrared (NIR) radiation. In these systems, nanoparticles are functionalized with photosensitive molecules or coatings that react to light exposure by undergoing bond cleavage, structural changes or photothermal heat generation. The primary advantage of light responsive systems is the high level of spatial and temporal control they offer, as drug release can be triggered exclusively at the illuminated site. While UV- light is often used for surface level treatments, near infrared light is particularly valued in clinical applications because it can penetrate deeper into biological tissues with minimal absorption by water or hemoglobin, allowing for the treatment of more deeply situated tumors through minimally invasive procedures [45, 46].

METHODOLOGY & DRUG LOADING

The successful application of smart nanomaterials in targeted drug delivery largely depends on how these nanocarriers are designed, synthesized and modified. Proper design ensures optimal particle size, high drug loading efficiency, stability in biological environments, and precise targeting capability. Recent research emphasizes that careful control over synthesis, drug incorporation, and surface modification is essential for achieving safe and effective nanocarrier systems.

Methods of nanoparticle synthesis

Nanoparticles used in drug delivery can be synthesized using a variety of physical, chemical, and biological methods. The choice of synthesis method affects particle size, shape, surface characteristics, and overall performance of the Nanocarrier.

Chemical Methods

Chemical synthesis remains the most versatile approach for developing polymeric nanoparticles, primarily through techniques such as solvent evaporation process, a polymer is dissolved in an organic solvent, emulsified into an aqueous phase, and the solvent is subsequently evaporated to precipitate the particles. Nanoprecipitation (or solvent displacement) relies on the rapid diffusion of a semi- polar solvent into an aqueous medium, causing the immediate interfacial deposition of the polymer as in Figure 11. These methods are widely favored because they allow researchers to exert precise control over the internal morphology of the particle and the efficiency with which a drug is encapsulated within the matrix [47, 48].

Physical Methods

Physical methods such as high-pressure homogenization, milling, and spray drying utilize mechanical energy rather than chemical reactions to achieve nanostructure. High-pressure homogenization involves forcing fluid through a narrow gap at high velocities, using shear forces to

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break down bulk materials into sub-micron droplets shows in Figure 12. While these techniques are highly scalable and useful for producing large quantities of nanoparticles for industrial applications, they often face challenges regarding "polydispersity" sometimes leading to a broader particle size distribution that requires additional filtration to ensure uniformity [49–51].

Biological or Green Synthesis

Advancing towards more sustainable chemistry, Biological or green synthesis utilizes the natural reductive capacity of plant extracts, bacteria, or fungi to convert metal ions into stable nanoparticles. These biological agents act as both reducing and stabilizing agents, eliminating the need for toxic surfactants or harsh organic solvents. This approach is not only environmentally friendly but also inherently produces nanoparticles with higher biocompatibility, as the biological molecules often form a "corona" around the particle that particle that reduces its toxicity in vivo [52].

Drug Loading Techniques

Drug loading is a critical step in nanoparticle preparation, as it determines how much therapeutic agent can be carried and how effectively it can be released at the target site. The selection of loading method depends heavily on the solubility of the drug and the desired pharmacokinetic profile as in Figure 13.

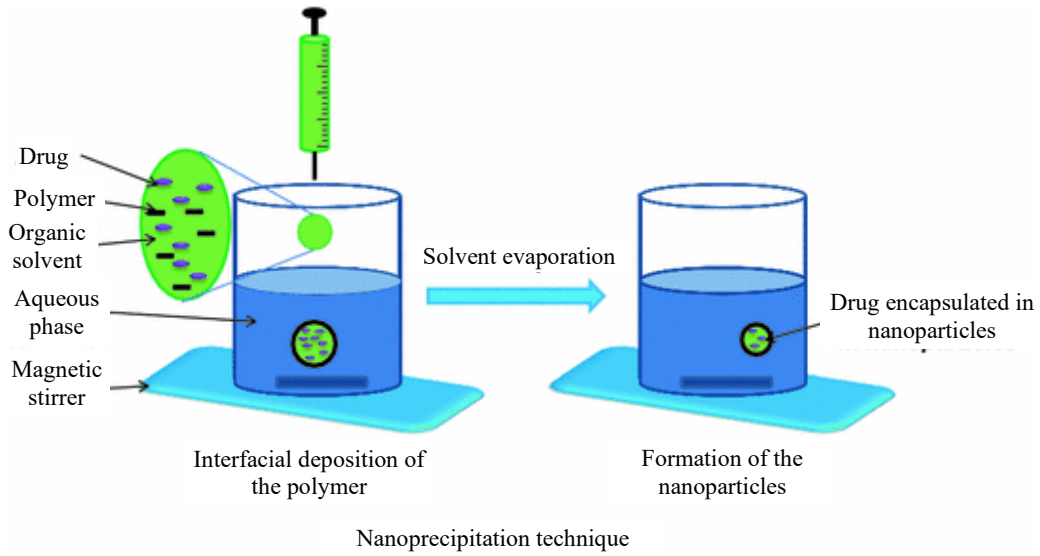


Figure 11: Nanoprecipitation technique [49].



Figure 12. High pressure homogenizer [53].

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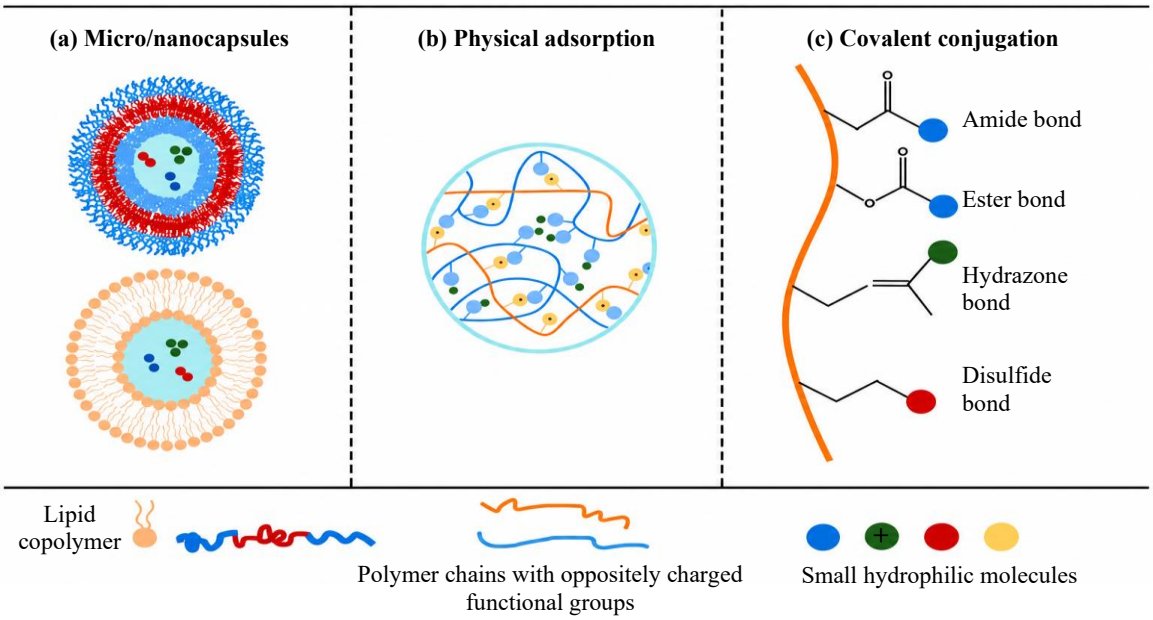


Figure 13. Different drug loading techniques [54].

Encapsulation or Incorporation

In the **e**ncapsulation method, the drug is physically trapped within the nanoparticle matrix or core during the actual formation of the particle. By integrating the therapeutic agent at the moment of synthesis—often through oil-in-water emulsions, the drug becomes an intrinsic part of the nanostructure. This technique generally provides the highest loading efficiency and offers a superior protective barrier for sensitive drugs (like proteins or RNA) against enzymatic degradation in the bloodstream [54, 55].

Adsorption or Absorption

Conversely, adsorption involves attaching the drug to the surface of pre-formed nanoparticles through physical interactions such as hydrogen bonding, van der Waals forces, or electrostatic attraction. While this method is significantly simpler to execute and avoids the harsh conditions sometimes found during particle synthesis, it typically results in a "burst release" profile. Because the drug is located on the periphery rather than the core, it can be released more rapidly upon contact with biological fluids [56].

Covalent Conjugation

Covalent conjugation represents a more permanent chemical bond where the drug is linked directly to the nanoparticle surface or the polymer backbone via biodegradable spacers. This method offers the most sophisticated level of control, allowing for a sustained and triggered release that only occurs when specific chemical bonds are cleaved by enzymes or pH changes at the target site. The predominant synthetic strategy for establishing these covalent linkers relies on EDC/NHS carbodiimide coupling chemistry. In this mechanism, 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) acts as an activating agent by reacting with a carboxylic acid moiety to form a highly reactive, transient O-acylisourea intermediate. To prevent rapid hydrolysis back to the carboxylic acid, N-hydroxy succinimide (NHS) is introduced to convert the intermediate into a semi-stable, amine-reactive NHS-ester. This activated ester undergoes a nucleophilic substitution when exposed to primary amines on the surface of target drugs or ligands, forming a highly stable, bio-orthogonal amide linkage [57, 58]. However, this requires meticulous molecular design to ensure that the chemical modification does not diminish the drug's original therapeutic activity.

Note: The effectiveness of these systems is highly sensitive to external variables; recent studies highlight that synthesis conditions such as temperature, solvent type, and mixing rate strongly influence nanoparticle morphology and long-term stability.

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MECHANISM OF TARGETED DRUG DELIVERY

Targeted drug delivery systems are designed to transport therapeutic agents specifically to diseased tissues while minimizing their distribution to healthy cells. This is achieved through different mechanisms that control how nanocarriers circulate, accumulate, and release drugs within the body as depicted in Figure 14.

Broadly, these mechanisms are classified into; Passive targeting, Active targeting, and Controlled drug release systems, which often work together to improve therapeuticoutcomes.

Passive Targeting and EPR Effect

Passive targeting is based on the natural physiological characteristics of diseased tissues, particularly tumors. This mechanism exploits the structural abnormalities of tumor vasculature; specifically, tumor tissues have leaky blood vessels with large gaps between endothelial cells, which allow nanoparticles to extravagate into the interstitial space. Furthermore, these tissues typically exhibit poor lymphatic drainage, which prevents efficient removal of macromolecules. As a result, nanoparticles tend toaccumulate in tumor tissues more than in normal tissues, a physiological phenomenon widely known in oncology research as the Enhanced Permeability and Retention (EPR) effect.

Key features of this approach include its inherent simplicity, as it does not require any surface modification of nanoparticles. Instead, the accumulation depends strictly on physical properties such as particle size (typically 10–200 nm), shape, and surface charge. This enables higher drug concentration at the disease site compared to free drugs, thereby improving the therapeutic index. However, the mechanism has limitations, including significant variability in EPR effect among patients and tumor types, as well as limited penetration into deep, dense tumor tissues as discussed in Figure 15. Passive targeting is considered the first step in drug delivery, often followed by active targeting for improved specificity [59–61].

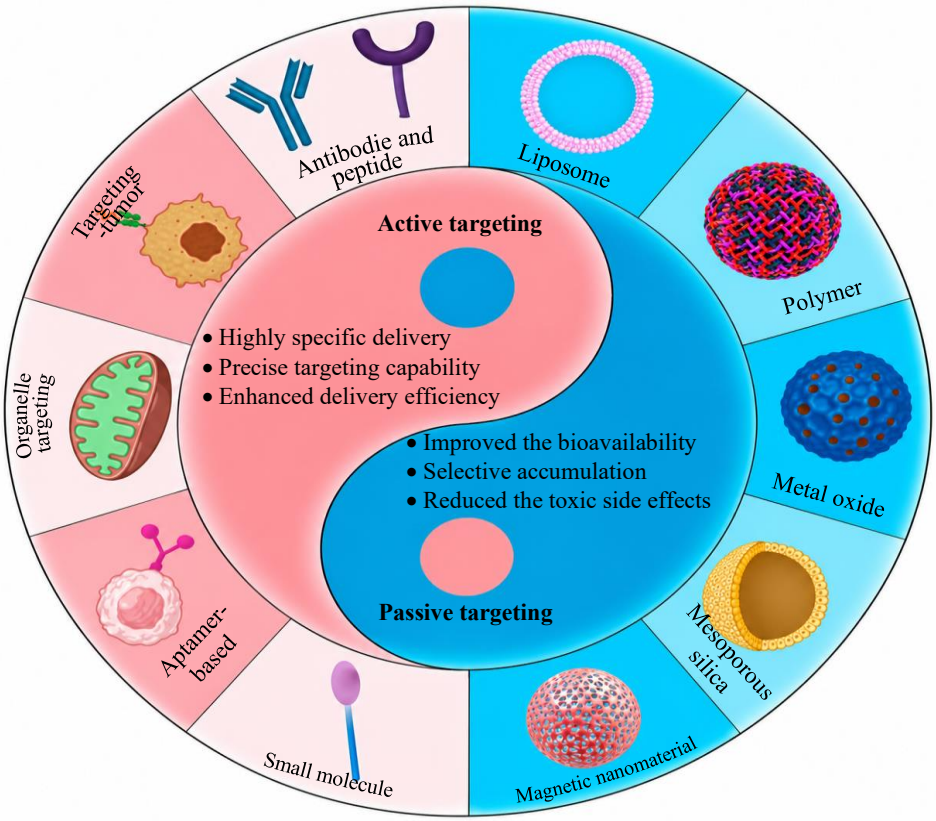


Figure 14. Active versus passive targeting strategies [59].

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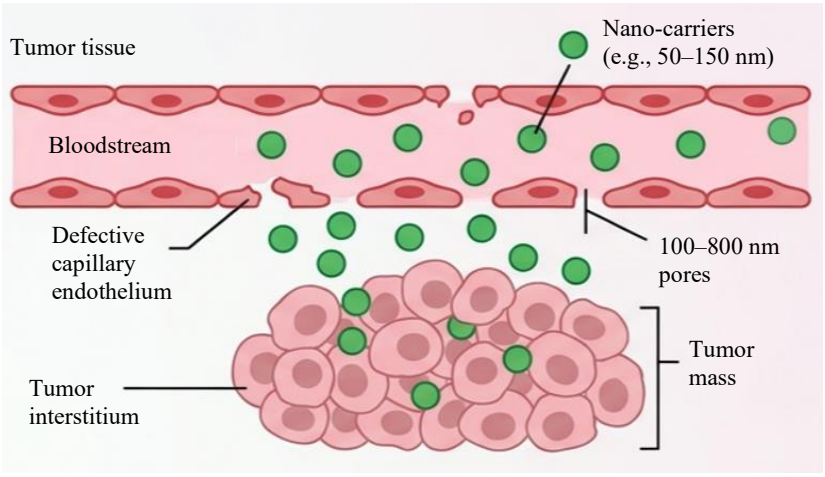


Figure 15. Enhanced Permeability and Retention (EPR) effect in cancer drug delivery [62].

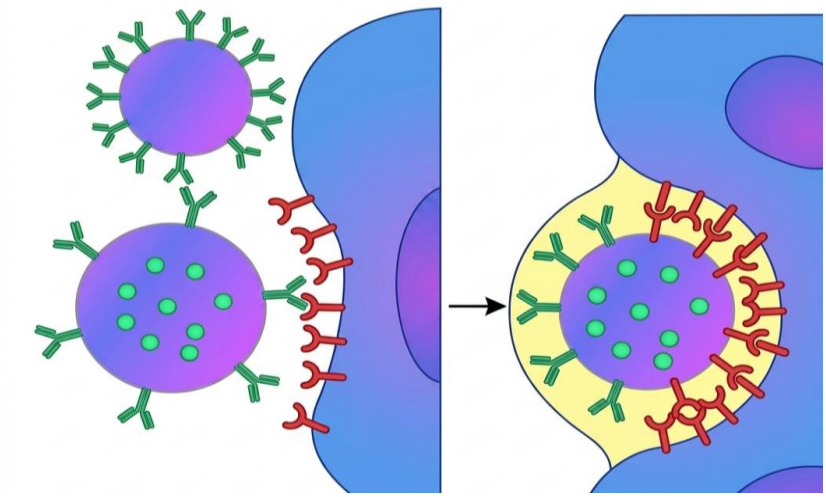


Figure 16. Active targeting of drug-loaded nanoparticles to a specific cell surface [63].

Active Targeting via Ligand-Receptor Interaction

Active targeting involves modifying the surface of nanocarriers with specific ligands that can recognize and bind to receptors overexpressed on diseased cells. In the mechanism, nanoparticles are functionalized with high affinity ligands such as antibodies**,** peptides, aptamersor small molecules like folicacid. These ligands bind selectively to specific receptors present on target cells acting like a "lock and key" system. From a physical organic chemistry perspective, this ligand-receptor recognition is governed by a cascade of highly coordinated, localized non-covalent intermolecular forces. Long-range electrostatic attractions guide the nanocarrier to the cell surface, where short-range spatially ordered hydrogen bonding networks, van der Waals forces, and hydrophobic interactions determine the thermodynamic binding affinity (K_d). When a ligand, such as folic acid, locks into overexpressed folate receptors, it alters the conformational free energy of the local plasma membrane, triggering the assembly of clathrin or caveolae pits to initiate receptor-mediated endocytosis shows in Figure 16. Once binding occurs, the nanoparticle is typically internalized into the cell via receptor-mediated endocytosis, ensuring that the drug payload is delivered directly into the intracellular environment [62, 64].

The primary advantage of active targeting includes significantly increased specificity toward diseased cells and enhanced cellular uptake of drug-loaded nanoparticles by ensuring the carrier only interacts with specific cellular markers, this method achieves a marked reduction in damage to healthy tissues. Active targeting significantly improves the efficiency of drug delivery, especially in cancer therapy where certain receptors are highly overexpressed on the surface of malignant cells.

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Controlled and Sustained Drug Release

Controlled drug release refers to the ability of nanocarriers to release their drug payload in a regulated manner over time or in response to specific stimuli. This ensures that the therapeutic agent is available at the required concentration for the necessary duration. The mechanism involves drugs that are either encapsulated, adsorbed, or chemically linked to nanoparticles, with release occurs through diffusion from the nanoparticle matrix, degradation of the carrier material or in response to internal such as pH or specific enzymes within the tumor microenvironment, or external, such as light, temperature, or magnetic fields[64, 65].

Two primary types of release behavior characterize these systems: Sustained release, which involves the gradual and continuous release over an extended period to maintain steady-state levels, and triggered release, where the release is initiated by specific environmental conditions. The benefits of these systems are manifold; they maintain therapeutic drug concentration for longer durations, reduce the frequency of dosing, and minimize side effects due to controlled exposure. Controlled release systems are often integrated with passive and active targeting mechanisms to achieve maximum therapeutic efficiency. Together these mechanisms make nanocarrier-based drug delivery systems far more effective and safer than conventional drug administration methods.

APPLICATIONS/ THERAPEUTIC USES

Smart nanomaterials have emerged as powerful tools in modern medicine due to their ability to deliver drugs in a controlled, targeted, and efficient manner. Their applications extend across various fields, including cancer therapy, brain drug delivery, infectious disease treatment, and gene therapy. These systems improve drug bioavailability, reduce toxicity, and enhance therapeutic outcomes compared to conventional treatments.

Cancer Therapy

Cancer therapy is one of the most extensively studied and successful applications of smart nanomaterials. These materials are engineered to selectively accumulate in tumor tissues through passive mechanisms such as EPR effect and active targeting strategies. By enhancing the delivery of chemotherapeutic drugs directly to cancer cells, they significantly reduce the systemic exposure that typically causes damage to healthy tissues. Furthermore, nanomaterials improve the fundamental pharmacokinetic properties of oncological drugs, including their solubility, stability, and circulation time leading to better therapeutic efficiency.A major breakthrough in this field is the development of stimuli responsive systems; these carriers are designed to sense the unique tumor microenvironment-such as its specific pH levels, elevated temperatures, or internal enzymes –to enable controlled drug release exactly where it is needed. Beyond standard chemotherapy, these platforms are now integral to photo thermal therapy, immunotherapy, and high-resolution cancer imaging, offering a precision those traditional treatments simply cannot match [66].

Drug Delivery Across Blood-Brain Barrier

The blood-brain barrier (BBB) is a major challenge in treating neurological disorders because its highly selective semi-permeable border prevents most drugs from entering the brain. Smart nanomaterials help overcome this barrier through their unique nanoscale size,whichallows them to navigate tight junctions that larger molecules cannot cross. By utilizing surface functionalization with specific ligands, these carriers can facilitate receptor-mediated transport essentially “tricking” the barrier into allowing entry. The use of lipid based and polymeric nanoparticles is particularly effective here, as they can be designed to mimic natural biological molecules that the brain naturally accepts. Key applications in this domain include the treatment of brain tumors, the delivery of specialized drugs for Alzheimer’s and Parkinson’s diseases, and the targeted delivery of neuroprotective agents to prevent further neuronal damage as in Figure 17. Research consistently shows that these nanocarriers significantly enhance drug penetration into the brain while minimizing systemic toxicity that often complicates neurological care [67].

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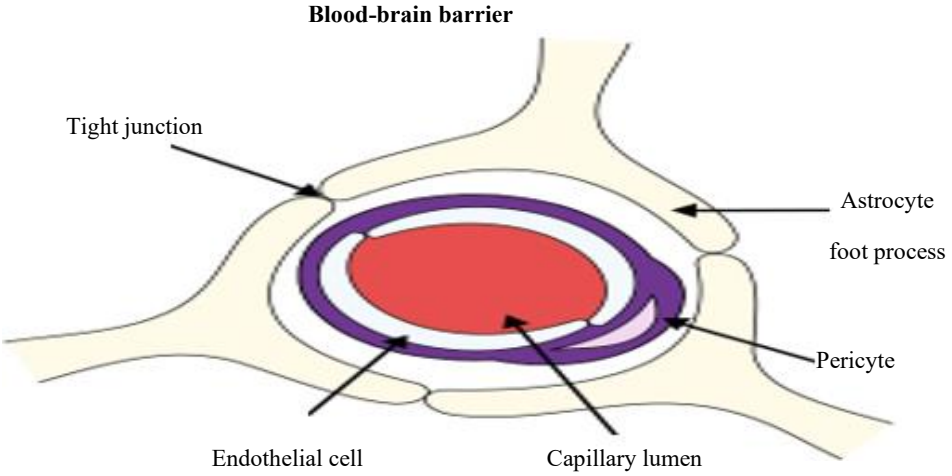


Figure 17. Anatomical diagram of the Blood-Brain Barrier (BBB) structure [68]

Treatment of Infectious Disease

In the fight against pathogens, smart nanomaterials are increasingly being explored for the treatment of infectious diseases due to their ability to improve drug delivery and overcome the growing threat of antimicrobial resistance. These nanocarriers enhance the stability and bioavailability of antimicrobial dugs, which are often degraded before they can reach the site of infection. By enabling targeted delivery to infected cells ortissues, they allow for a reduced required dosage, which in turn limits the risk of side effects.

This technology is proving vital in overcoming antibiotic resistance by improving intracellular drug delivery, ensuring that the medication reaches bacteria hiding within host cells. Current applications include advanced treatments for Tuberculosis, viral infections, and bacterial infections involving highly resistant strains.Recent studies highlight that nanotechnology-based delivery systems can significantly improve the effectiveness of existing antimicrobial therapies, breathing new life into older medications by changing how they are presented to the body [68, 69].

Gene delivery and vaccine delivery

Smart nanomaterials play a crucial role in gene therapy and vaccine delivery, especially for nucleic acid- based treatments that are notoriously fragile. Nanocarriers serve as a protective shield for DNA, RNA, and siRNA, preventing them from being degraded by the enzymes in the body before they reach their destination. They facilitate cellular uptake and the subsequent intracellular delivery of this genetic material, which is essential for “Turning off” disease causing genes or introducing healthy ones.

Commonly used nanocarriers in this field include liposomes, polymeric nanoparticles, lipid nanoparticles (LNPs), and dendrimers. These platforms are currently being applied to gene therapy for cancer and genetic disorders, as well as the production of m RNA vaccines and RNA interference (RNAi) therapies. Recent research emphasizes that smart nanomaterials have greatly improved the efficiency and safety of gene delivery systems, making them a key component of modern therapeutic strategies and a cornerstone of the next generation of personalized medicine [70].

ADVANTAGES & LIMITATIONS

Advantages of Smart Nanomaterials-Based Drug Delivery Systems

Smart nanomaterials offer several advantages over conventional drug delivery systems due to their ability to deliver drugs in a controlled and targeted manner. One of the most significant benefits is targeted drug delivery where nanocarriers selectively accumulate in diseased tissues, thereby reducing drug exposure to healthy cells and minimizing systemic side-effects. Furthermore, these systems provide improved drug bioavailability by enhancing solubility and stability of poorly water-soluble drugs and protecting them from premature degradation in the bloodstream [71].

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The capacity for controlled and sustained release enables a gradual or stimuli triggered discharge of the therapeutic agent, maintaining optimal therapeutic levels for longer durations without the need for frequent dosing. This site-specific delivery leads to reduced side effects and toxicity while ensuring enhanced cellular uptake as the nanoscale size allows for easier penetration into target cells and tissues. Additionally, the versatility and multifunctionality of these materials mean they can be engineered for simultaneous imaging, diagnosis, and therapy (known as theranostics). Perhaps most impressively, they possess the ability to overcome biological barriers, such as the blood brain barrier, which previously restricted the treatment of complex diseases like cancer and neurological disorders.

Limitations & Safety Concerns

Despite their potential, smart nanomaterials face several limitations that restrict their widespread clinical application. Many of these concerns arise from their unique physicochemical properties, which can interact unpredictably with biological systems.

Toxicity and Bioaccumulation

One of the major concerns associated with nanomaterials is their potential toxicity and accumulation in the body. Because of their small size, nanoparticles can easily cross biological membranes and interact with cellular components, leading to accumulation in vital organs such asthe liver, spleen, kidneys. Research indicates that toxic effects may arise due to generation of reactive oxygen species (ROS), which triggers oxidative stress, cellular damage, and the disruption of normal cellular processes. The severity of this toxicity depends heavily on particle size, shape, and surface charge, concentration and overall duration of exposure [72].

Immunological Responses

Nanomaterials can interact with the immune system in complex ways, sometimes leading to unintended immune responses. Upon entering the body, nanoparticles often undergo the formation of a “protein corona” on their surface which can lead to recognition by immune cells such as macrophages. Possible immune responses include inflammation, activation of specific immune pathways, allergic or hypersensitivity reactions. Furthermore, rapid clearance by immune system may significantly reduce the effectiveness of drug delivery and limit the circulation time of nanoparticles preventing them from reaching the target site in sufficient quantities. Recent research highlights that this response depends strongly on nanoparticle’s composition and surface properties [73].

Manufacturing and Cost Issues

Large scale production of smart nanomaterials presents several practical challenges that hinder clinical translation. Complex synthesis processes require precise control over size, shape and surface properties which often leads to a high production cost due to the need for expensive materials and advanced equipments. Furthermore, there are significant reproducibility issues, as maintaining consistency between different batches remains difficult in manufacturing environment.

Beyond the laboratory regulatory challenges persist due to lack of standardized guidelines for approval of nanomedicine products.Finally, scalability limitations mean that methods successful in a controlled laboratory setting may not be easily translated to an industrial scale. These technical and economic hurdles continue to slow down the commercialization of nanomaterial-based drug delivery systems despite their promising results in research studies [74].

RECENT ADVANCES

The landscape of smart nanomaterials is rapidly evolving, moving beyond simple carriers towards intelligent, multifunctional systems. Recent breakthroughs have focused on improving precision, integrating diagnostics with therapy, and leveraging computational tools to accelerate clinical translations.

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Multifunctional and Theranostic Nanoparticles

One of the most significant recent shifts in nanomedicine is the development of theranostic platforms, which combine diagnostic imaging and therapeutic action into a single agent. Recent research has highlighted the use of Magnetic Mesoporous Nanoparticles (MMNPs) and gold nanoparticles (AuNPs) that serve as high contrast agents for MRI and CT scans while simultaneously delivering drug- payloads. These systems allow clinicians to monitor the accumulation of the drug at the target site in real time, ensuring that the treatment is reaching the intended area before activating the release as shows in Figure 18.

Additionally, advanced materials like Covalent Organic Frameworks (COFs) are being explored for their ordered π-conjugated backbones and tunable pore architectures. These features provide unique advantages for high drug loading and highly controlled release. By integrating multiple functions—such as photothermal therapy (PTT) and biosensing—into a single nanostructure, researchers are creating "all-in-one" solutions that can detect, treat, and monitor cancer progression with unprecedented sensitivity [75].

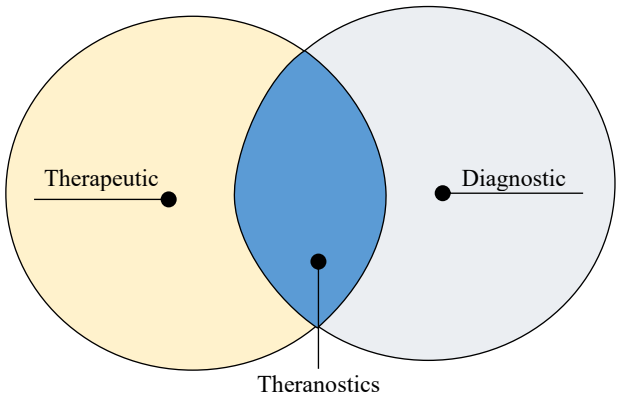


Figure 18. The concept of Theranostics [76].

Enhanced Lipid Nanoparticles (LNPs) for mRNA Delivery

The success of mRNA-based vaccines has sparked a new wave of innovation in Lipid Nanoparticles (LNPs). Recent studies from 2025 and 2026 have introduced "organ-selective" LNPs designed to bypass the liver, which is the default destination for most injected particles. By modifying the chemical structure of ionizable lipids—such as incorporating aromatic rings and bio reducible disulfide bonds—scientists have effectively guided nanoparticles specifically toward the lymph nodes or lungs.

This level of precision is revolutionary because it allows for lower dosing, which significantly reduces the risk of systemic inflammation and off-target side effects. Furthermore, new "SORT" (Selective Organ Targeting) methodologies enable researchers to predict exactly where an mRNA payload will be expressed simply by adjusting the ratio of internal lipid components. These advances are paving the way for highly effective, personalized vaccines and protein replacement therapies for rare genetic disorders [76, 77].

AI-Assisted Nanocarrier Design

The integration of artificial Intelligence (AI) and machine learning (ML) is transforming nanomedicine from a "trial-and-error" science into a predictive, data-driven discipline. Recent frameworks utilize deep learning models to analyze vast datasets of physicochemical properties—like size, surface charge, and hydrophobicity—to predict how a nanoparticle will behave in the human body before it is even synthesized in the lab.

Innovative tools like Generative Adversarial Networks (GANs) and Diffusion models are now being used to propose entirely new nanocarrier candidates with optimized release profiles. By bridging the

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gap between computational modeling and laboratory experiments, AI-assisted design reduces the time and cost of development. This approach is particularly impactful for complex brain disorders, where AI helps design particles that can more effectively navigate the blood-brain barrier, offering new hope for the treatment of Alzheimer's, Parkinson's, and glioblastoma [78].

Stimuli-Responsive "Smart" Gatekeepers

The latest generation of nanocarriers features highly sophisticated gate keeping mechanisms that respond to specific biological cues. While older systems reacted broadly to pH changes, newer research focuses on enzyme-responsive and dual-stimuli nanoparticles. These carriers remain completely locked while circulating in the blood but "unlock" only when they encounter a specific enzyme overexpressed in a tumor or a specific intracellular environment.

By utilizing biodegradable polymers like PLGA or chitosan functionalized with these sensitive molecular switches, researchers have achieved a near-zero "leaky" release during circulation. This ensures that toxic drugs are only exposed to the body at the precise moment of cellular internalization. These "smart" gatekeepers turn drug delivery into a highly synchronized biological event that mimics the body's own regulatory systems [79].

CHALLENGES &FUTURE PERSPECTIVES

While the field of smart nanomaterials is advancing significantly, the transition from successful laboratory experiments to everyday clinical use brings along a number of difficulties. Addressing these challenges requires a deep understanding of how synthetic materials interact with the complex physiological mechanism of the human body and a combined effort to standardize how these therapies are produced and regulated.

Major Challenges

Biological Complexity and Unpredictable Behavior

One of the biggest challenges is that nanocarriers often behave differently in the human body compared to controlled laboratory conditions. Their performance is highly dependent on factors such as biodistribution, interaction with various tissues, and the specific rate of drug release at the target site. Current research suggests that the results obtained in animal studies often fail to accurately predict human outcomes due to the inherent heterogeneity of tumors and the significant variability between individual patients. This "biological gap" complicates targeting efficiency, as a system that works perfectly in a mouse model may be recognized and cleared by a human's immune system before it can perform its task [80].

Toxicity and Safety Concerns

Safety remains the biggest concern, as nanoparticles may accumulate in vital organs such as the liver, spleen, and kidneys. Once these particles cross biological membranes, they can interact with cellular components in ways that are not yet fully understood. A major risk is the generation of Reactive Oxygen Species (ROS), which can lead to oxidative stress and irreversible cellular damage. Because the long-term effects of many nanomaterials are still not fully understood, safety evaluation remains incredibly complex. Researchers must account for variations in size, shape, and chemical composition, all of which can strongly affect the toxicity profile of a single carrier [81].

Regulatory & Manufacturing Hurdles

The path to clinical approval is further slowed by regulatory challenges and a lack of clear, standardized guidelines for nanomedicine. This uncertainty often leads to significant delays in clinical approval and increased development costs. On the industrial side, large-scale manufacturing issues present a bottleneck; scaling up from a small lab batch to mass production is difficult. Maintaining a uniform particle size, consistent drug loading, and reproducibility between batches requires advanced equipment and strict quality control that many current facilities are still developing [82].

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Future Perspectives and Emerging Trends

The future of drug delivery lies in creating systems that are not just "carriers" but are "intelligent partners" in the healing process. By focusing on biocompatibility and personalization, the next generation of nanomedicine aims to solve the very challenges we face today.

Development of Safer and Biodegradable Nanomaterials

The primary focus of upcoming research is the development of safer and biodegradable nanomaterials. By prioritizing biocompatible materials and biodegradable polymers, scientists aim to reduce long-term toxicity and ensure that the body can naturally break down and eliminate the carrier once the drug has been delivered. This shift is essential for reducing the risk of bioaccumulation and making these therapies viable for long-term treatment of chronic conditions [83].

Personalized and precision medicine

We are moving toward an era of personalized and precision medicine, where nanocarriers are tailored to the individual patient's characteristics and specific disease profiles. By integrating with biomarkers, these smart systems can be "programmed" for better targeting, ensuring that the treatment is uniquely suited to the genetic and physiological makeup of the person receiving it. This approach minimizes "trial-and-error" medicine and maximizes the chances of a successful recovery [84].

Advanced Multifunctional Systems and AI Integration

The development of theranostic nanocarriers is another emerging area, where a single particle can handle drug delivery, imaging, and real-time monitoring simultaneously. This is being further accelerated by the integration with Artificial Intelligence (AI). AI is now being used to predict nanoparticle behavior in biological systems, optimize drug formulations, and reduce the need for slow, expensive trial-and-error experimentation. By leveraging machine learning, we can design the "perfect" carrier for a specific drug much faster than ever before [85].

Emerging Technologies: Nanorobotics & Biomimicry

Looking further ahead, exciting innovations like nanorobotics for precise drug delivery and biomimicry—where nanoparticles are designed to mimic natural cells—are likely to appear soon. We are also seeing the rise of gene-editing delivery systems, such as those using CRISPR, and combination therapies that use multiple drugs within a single nanocarrier to attack diseases from multiple angles. Through stronger collaboration between researchers, clinicians, and regulatory authorities, these emerging technologies have the potential to fundamentally redefine how we treat the most challenging diseases of our time [86, 87].

CONCLUSION

In this report, we have comprehensively explored the rapidly evolving field of smart nanomaterials, beginning with a foundational overview of their transformative role in modern medicine. Through a detailed analysis of engineering methodologies, we compared the distinct advantages and trade-offs of chemical, physical, and biological synthesis techniques, alongside an examination of advanced drug-loading mechanisms—such as physical encapsulation and covalent bonding—that are critical for maintaining the structural integrity and stability of delicate therapeutic agents. Our investigation further highlighted the sophisticated transport mechanisms that drive precision medicine, specifically detailing how passive targeting via the Enhanced Permeability and Retention (EPR) effect works in tandem with active ligand-receptor interactions to selectively accumulate therapies at diseased sites. By mapping diverse clinical applications against current toxicological and biocompatibility limitations, we addressed the real-world challenges that remain, including manufacturing scalability, batch-to-batch reproducibility, and the sheer complexity of interacting with biological systems. Ultimately, this research underscores a pivotal shift toward next-generation, AI-driven, and highly personalized delivery networks. By combining smart materials that respond dynamically to physiological cues with predictive artificial intelligence, these systems promise to eliminate the historical guesswork of dosing, minimize systemic side effects, and fundamentally redefine the future of targeted therapy.

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