

Targeted Drug Delivery by Smart Nanocarriers: Design, Therapeutic and Their Translation Challenges

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ABSTRACT

Smart nanocarriers have become revolutionary delivery platforms in targeted drug delivery due to the critical vulnerabilities of traditional methods of therapeutic delivery, such as low bioavailability, non-specific delivery, and off-target toxicity. This review will discuss the rational design, therapeutic strategies and the translational issues of stimuli-responsive nanocarrier systems that are developed to obtain spatiotemporal control of drug release. The use of organic (liposomes, dendrimers, polymeric micelles), inorganic (gold, silver, iron oxide, graphene derivatives) and high-order hybrid (lipid-polymer hybrids, cell membrane-coated biomimetic systems) nanoparticles is discussed. Principles of nanocarrier design, such as the mechanics of physicochemical properties (size, shape, surface charge), targeting (passive EPR effect, active ligand-mediated recognition), and stimulus-responsive mechanisms (endogenous (pH, enzymes, redox)) or exogenous (temperature, light, magnetic field) stimuli are critically discussed. The therapeutic uses include oncology, where nanocarriers overcome the multidrug resistance and the tumor microenvironment, infectious disease, neurological diseases, cardiovascular diseases and inflammatory/autoimmune disorders. Although there has been considerable preclinical advancement and more than 4,000 clinical trials, there are still translational challenges, such as formation of protein corona, reticuloendothelial clearance, scale of manufacturing, regulatory complexity and issues related to immunogenicity. New paradigms, which combine artificial intelligence-based design, microfluidic organ-on-chip devices and patient-specific computational modeling, have the potential to overcome these obstacles. This review offers a platform upon which a rational design of future smart nanocarriers can be attained by integrating progress in nanomaterial engineering with biological and regulatory factors to achieve the potential of precision nanomedicine.

Keywords: Smart nanocarriers; Targeted drug delivery; Nanomedicine; Stimuli-responsive systems; Clinical translation

Graphical Abstract

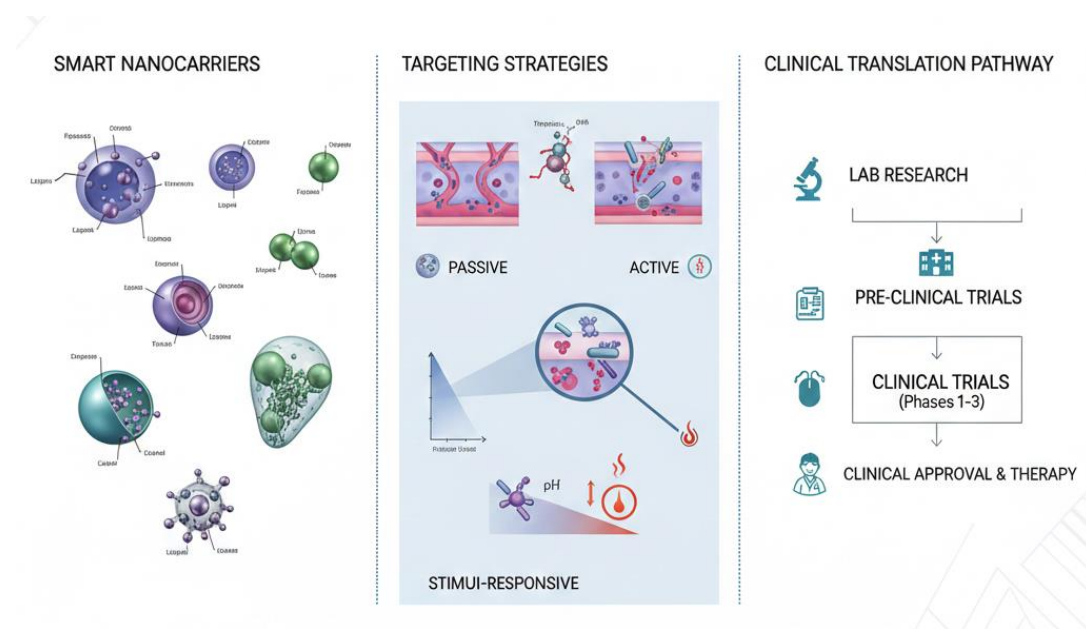


Figure 1. Schematic overview of smart nanocarriers, targeting strategies (passive/active/stimuli-responsive) and clinical translation pathway.

INTRODUCTION

Background

Although significant progress has been made in drug discovery and identification of thousands of active pharmaceutical compounds (APIs), clinical success of numerous therapeutic agents is still low. One of the key causes of this gap is the very low efficiency of the traditional forms of drug delivery, which may not be sufficient to guarantee sufficient levels of bioavailability, accurate targeting and sustained pharmacologic levels of drug at the site of activity. In fact, it is approximated that approximately 90 percent of the drug candidates that go through clinical trials never get to the market, often because of unfavorable pharmacokinetic behavior, as opposed to the absence of inherent biological activity (Sun et al., 2022). The creation of novel API is also a very time-consuming and expensive process that, on average, takes 10-17 years to reach the clinical stage (Murteira et al., 2013). Therefore, the obstacle to the translational potential of new and existing drugs is rather substantial due to the challenges of delivery. Drug delivery refers to the methodologies and mechanisms through which pharmaceutical agents are delivered in order to have a therapeutic effect (Adepu, 2021; Sultana et al., 2022; Tiwari et al., 2012). Traditional drug delivery is based mostly on enteral and parenteral routes (Chamundeeswari et al., 2019). Enteral routes involve oral, rectal, buccal, and sublingual routes, whereas parenteral ones involve intravenous, intramuscular, transdermal, and subcutaneous administrations (Adepu, 2021; Chamundeeswari et al., 2019; Jeong et al., 2021). After administration, drugs undergo absorption, distribution, metabolism, and excretion (ADME), which play a significant role in determining the systemic exposure and therapeutic effect (Ernstmeyer and Christman, 2023).

Limitations Linked to Traditional Delivery Routes

Oral Drug Delivery: Oral drug delivery is the most common and the most convenient administration route. Upon absorption, drugs move through the gastrointestinal tract and are mainly absorbed in the small intestine and then they enter the systemic circulation (Bhutani et al., 2021; Dinh & Yan, 2023). Nevertheless, drug stability and absorption are significantly reduced by the harsh acidic conditions of the stomach (1-2), the presence of the intestine and hepatic first-pass metabolism (Bhutani et al., 2021; Dinh and Yan, 2023; Hua, 2019). Consequently, therapy levels of drugs often necessitate high or repeated dosing, which exposes the patient to the risks of systemic toxicity and non-compliance. In addition, oral medications take relatively a long time to be absorbed, and this mode of administration cannot be used in the case of an emergency when the speed of pharmacological action is needed (Hua, 2019).

Buccal and Sublingual Drug Delivery: Buccal and sublingual routes represent the alternative administration to oral routes because they avoid gastrointestinal degradation and hepatic first-pass metabolism. The absorption route of drugs via the superior vena cava takes place when the formulation is placed under the tongue or between the cheeks and gums (Hua, 2019; Chinna Reddy et al., 2011; Khalid and El-Say, 2022). Such pathways are especially beneficial in the case of highly soluble drugs that have a short half-life on an oral route (Hua, 2019; Chinna Reddy et al., 2011). However, they have a rather narrow range of application because not every drug can have appropriate physicochemical characteristics to be absorbed in the buccal cavity or under the tongue (Hua, 2019; Chinna Reddy et al., 2011).

Transdermal Drug Delivery: Transdermal drug delivery allows drugs to enter the body through the skin, which results in a continuous and controlled exposure to the systemic level (Ernstmeyer and Christman, 2023). It bypasses the gastrointestinal tract and the first-pass hepatic metabolism, which means that it is beneficial in chronic therapy, including pain management and motion sickness (Adepu, 2021; Ernstmeyer and Christman, 2023; Alkilani et al., 2015). The limited variety of drugs that can be effectively administered transdermally is severely limited by the barrier action of the skin, though. Lipophilic molecules with low molecular weight (usually less than 1 kDa) are the only ones that can easily penetrate the skin, whereas larger or hydrophilic drugs may need penetration enhancers or special formulations (Adepu, 2021; Martin et al., 2017). These limitations greatly reduce the usefulness of transdermal delivery of a wide variety of therapeutic agents.

Parenteral Drug Delivery: Parenteral routes, including intravenous, intramuscular and subcutaneous administration, allow drugs to bypass the gastrointestinal tract and avoid first-pass metabolism, resulting in rapid and efficient systemic absorption (Javier et al., 2024; Heremans et al., 2022). Such pathways are usually used to deliver macromolecules like proteins and peptides (Alkilani et al., 2015; Labiris & Dolovich, 2003). The intravenous route offers the highest rate of drug delivery, but the subcutaneous route allows slower prolonged delivery of drugs, and longer plasma concentrations on the therapeutic threshold (Martin et al., 2017; Heremans et al., 2022). In spite of these benefits, parenteral delivery is invasive, can sometimes involve professional healthcare skills, and can also be accompanied by pain, risk of infections, and low patient compliance especially in the long run therapy.

Inefficient Bioavailability and Off-Target Toxicity

Poor bioavailability is widespread in the traditional routes of delivery and often requires large doses and repeated dosing to occur therapeutically (Adepu, 2021; Martin et al., 2017). This dosing regime causes intermittent plasma drug concentrations, decreased total effect and adverse effects. Non-specific distribution of drugs in the body causes off-target toxicity that exposes normal tissues to pharmacologically active substances and usually leads to dose-limiting side effects. A typical one is coumarin and its derivatives, which have a wide range of biological properties, such as antimicrobial, antioxidant, anti-

inflammatory, anticancer, anticoagulant and antiviral effects (Loncar et al., 2020). In spite of such versatility, coumarin experiences a very low bioavailability as the proportion of absorbed dose reaching the systemic circulation is only 2-6% as a result of a high first-pass metabolism (Leonart et al., 2017). It is quickly turned into 7-hydroxycoumarin and its glucuronic acid derivative which is then excreted through the urine (Leonart et al., 2017). Despite clinical use in the treatment of lymphedema, short half-life of coumarin of about 1 hour required high doses that caused hepatotoxicity and instances of drug-induced hepatitis have been reported. This has led to a massive withdrawal of coumarin in the market, with the exception of low-concentration preparations (Ramelet, 2011).

Physicochemical Constraints and Bioavailability

Physicochemical properties are highly affecting drug bioavailability, which is explained by the “rule of five” of Lipinski and colleagues (Sultana et al., 2022; Javier et al., 2024; Gupta et al., 2013). High molecular weight drugs that are poorly aqueous soluble have poor absorption and highly hydrophobic molecules have a likelihood of precipitation in the biological fluid (Loncar et al., 2020). On the other hand, too hydrophilic drugs can be quickly cleared and easily overcome lipid-boundary biological barriers like the blood-brain barrier, causing lowered bioavailability, and reduced systemic half-life (Loncar et al., 2020). The poor aqueous solubility of 40-70% of new drug project candidates is estimated and many promising peptides and proteins have half-lives of minutes to hours, and are abandoned during development (Gupta et al., 2013). In the absence of suitable delivery mechanisms, these restrictions may make otherwise effective therapeutics clinically useless (Gupta et al., 2013; Adepur, 2021). Despite the need to investigate formulation systems like colloidal dispersions and prodrug strategies to enhance absorption and bioavailability (Gupta et al., 2013), the discussed strategies usually yield only slight improvements. All these deficiencies highlight the imperative of developing the sophisticated drugs delivery that would be able to achieve high bioavailability, low toxicity, and low off-target effects.

Urgency of Nanotechnology in Medicine

Carrier prodrugs were initially designed as formulation and molecular modification strategies, are made of active drug molecules that have been covalently attached to a temporary moiety through cleavable chemical bonds such as esters, carbonates, carbamates and amides, which are transformed into the parent drug in vivo (Rautio et al., 2008). Prodrug approaches have been successfully utilized to increase bioavailability, as well as to allow clinical use of compounds which would otherwise have poor absorption/distribution characteristics (Markovic et al., 2020). Although the prodrug approaches have a high rate of adoption (around 10% of all marketed drugs worldwide) due to modern active feature (Markovic et al., 2020), but they are still constrained by the fact that they depend on random activation pathways of the enzymes. In addition, multi-step prodrugs can cause complicated pharmacokinetic dynamics and co-existence of many drug species, which makes it difficult to adjust the dose and measure safety (Subbaiah et al., 2024). The inadequacies of the traditional methods of drug delivery and those of prodrug delivery led to the realization of the necessity of radically new approaches that could achieve a higher level of spatial, temporal and biological control of drug delivery. This requirement triggered the development of nanotechnology in medicine leading to the interdisciplinary science called nanomedicine. Entry of nanotechnology in pharmaceutical sciences has changed the idea of drug delivery where a drug is delivered passively to where it is delivered in a controlled, targeted and responsive system of delivery. It is important to note that many nanomedicine-based formulations are already approved by the regulators and this number is expected to grow as the development of novel nanoscale delivery platforms continues to approach clinical use (Thapa & Kim, 2023).

Scope and Objectives of the Review

This review critically discussed of smart nanocarriers as advanced systems to deliver drugs to the target site with special focus on their design, stimulus-responsive, therapeutic use in the key disease fronts and translation issues that must be overcome to enable their clinical usage. This article also attempted to offer comprehensive overview of the rational development and clinical translation of next-generation nanocarrier systems by combining more recent innovations of nanomaterial engineering with biology and bioregulation.

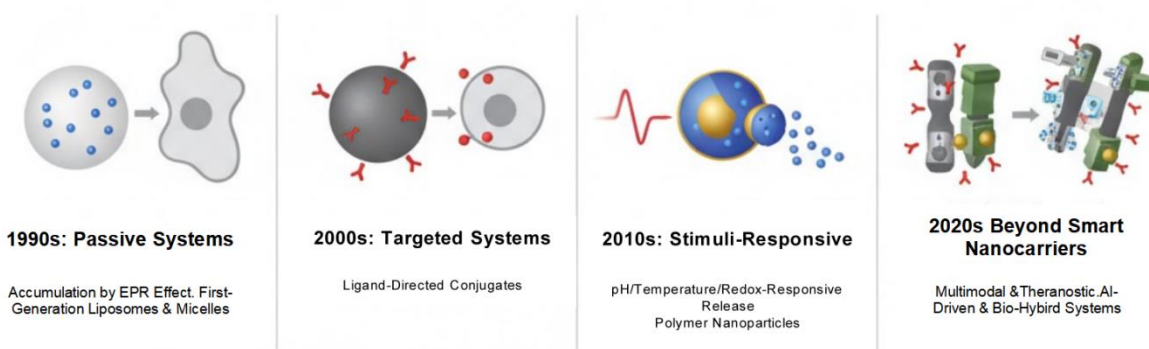


Figure 2. Timeline illustrating the development of nanocarriers as passive system to smart nanocarrier.

Classification of Nanocarriers for Drug Delivery

Organic Nanocarriers

Organic nanocarriers are considered to be one of the most widely studied types of nanoscale drug delivery systems because of their ability to be biocompatible, structurally versatile and can be surface functionalized. These systems are usually formed using organic materials, or lipids or polymers and may be engineered to entrap, conjugate or adsorb therapeutic agents. Liposomes, polymeric nanoparticles, dendrimers and micelles are among the most popular organic nanocarriers that have the potential to increase the solubility of drugs, enhance pharmacokinetic performance, and decrease the toxicity of the system (Din et al., 2017).

Liposomes

One of the earliest and most widely studied nanocarriers are liposomes, which are self-assembled vesicles are mainly made of phospholipid bi-layer that surround an aqueous core. The origin of the word liposome can be traced with the aid of lipos (fat) and soma (body) in Greek language as the lipid-based vesicles in their structure. The amphiphilic property in them allows the enclosed of both hydrophilic drug in the aqueous core and hydrophobic drug in the lipid bilayer (Dua et al., 2012). The resulting supramolecular assemblies are extremely dynamic and occur due to lipid-lipid interactions and they are capable of rearranging their structure under any perturbation of the membrane, to form smaller multilamellar vesicles or micellar structures (Lee et al., 2013). The release of the drugs through liposomes can be through membrane fusion with the cellular membranes, uptake by the macrophages or ligand-mediated endocytosis whereby the liposomes are surface-modified with targeting moieties. Gene delivery using liposomes has also been greatly utilized and this is also known as lipofection (Balazs & Godbey, 2011). The progress in lipid engineering has touched off the clinical translation of several liposomal preparations successfully. In 1995, the first liposomal drug to be approved by the FDA was Doxil®, which was used to treat ovarian cancer and Kaposi sarcoma in AIDS patients (Barenholz, 2012). Thereafter, a number of preparations have

been developed that include oncological indications and include DaunoXome®, Depocyt®, Myocet®, and Mepact® (Immordino et al., 2006; Leonard et al., 2009) as well.

Dendrimers

Dendrimers are macromolecules that are highly branched, three dimensional structures comprising of a central core, repeated branching units and a number of terminal functional groups at the periphery that enable huge surface modification. These special characteristics make dendrimers very desirable as drugs delivery vectors. Dendrimers are normally produced through either convergent or divergent methods. In the divergent strategy, different branches extend radially around the core, the first example of which was reported by Tomalia et al. (1985) in the synthesis of poly(amidoamine) (PAMAM) dendrimers. Surface-modified PAMAM dendrimers, especially those coupled with folic acid and PEG chains, have been shown to have a high drug loading capacity, controlled release and lower haemolytic potential. As an example, the third-generation PAMAM dendrimers loaded with indomethacin had a high drug release duration in comparison with cellulose membrane controls (Zinselmeyer et al., 2002). One of the studies described the inclusion of glucosamine-conjugated polyether-copolymer dendrimers conjugated with methotrexate, with increased penetration of the bloodbrain barrier and higher uptake in glioma cell lines, using endocytosis (Parajapati et al., 2016). Another type of lipid-dendrimer hybrid nanoparticles have also been shown to be effective in the delivery of antibiotics like vancomycin against the infection of the methicillin-resistant *Staphylococcus aureus* (Sonawane et al., 2016). In spite of these developments, there are a significant number of dendrimer-based systems that are in preclinical phase and thus there is the requirement of further in vivo validation and toxicity studies.

Polymeric Micelles

One of the recent categories of organic nanocarriers has been polymeric micelles (PMs), which have become a leading mode of delivery of poorly water-soluble drugs, anticancer agents, imaging probes, and peptides (Zhang et al., 2014). They are usually made up of amphiphilic block copolymers which can then self-assemble into core-shell nanostructures at a critical micellar concentration (CMC) in water. The lipophobic drug is contained in the hydrophobic core of polymeric micelles, with steric stability, reduced opsonization and decreased reticuloendothelial system (RES) clearance being provided by the hydrophilic corona. Regardless of these benefits, polymeric micelles have a drawback of inherent instability owing to their dynamic balance with unimeric polymer chains. Interaction with plasma proteins including albumin may cause a decrease in micellar integrity, resulting in premature drug release and a quick clearance through the mononuclear phagocytic system, especially the liver and the spleen (Wakaskar, 2017). The triblock copolymer Poloxamer 407 (F127), which is an FDA-approved GRAS compound, is characterized by high biocompatibility and thermoreversible gelation (Nagarajan, 1999). Nevertheless, similar to most of the micellar systems Pluronic micelles also tend to disassemble in physiological conditions. To address stability limitations, cross-linking strategies have been developed to reinforce micellar architectures, either within the core, shell, or at the core-shell interface (Wakaskar, 2017). Such stabilization enhances in vivo robustness, prolongs circulation time, and improves bioavailability, albeit sometimes at the expense of drug-loading efficiency or release kinetics.

Inorganic Nanocarriers

The inorganic nanoparticles are very stable and hydrophilic compared to organic nanoparticles and do possess inherent exceptional physicochemical performance (magnetic, thermal, optical and catalytic), thus, these nanosized materials can be utilized as a robust scaffold on which two or more dopants can be loaded to achieve multifunctional capabilities (Paul and Sharma, 2020; Zhou et al., 2020). The inorganic nanoparticles can broadly be divided into metals based nanoparticles and metal oxide based nanoparticles.

Nanoparticles of metals are produced using metals like Fe, Cu, Zn, Cd and Ag and metal oxide nanoparticles are produced using zinc oxide, iron oxides and aluminium oxide among others.

Gold Nanoparticles (AuNPs)

Gold nanoparticles (AuNPs) have been demonstrated to have size-specific optical and electronic characteristics, drew considerable attention toward their application in photovoltaics, drugs delivery and biosensing of biomolecules due to the size-dependent optical characteristics, high X-ray absorption coefficient and the ability to functionalize them (Desai et al., 2023; Kumari et al., 2023). The AuNPs are also highly biocompatible, photostable and light-to-heat converting. AuNPs can be utilized in bioimaging, biosensors, targeted drug delivery and localized hyperthermia, hollow and multifunctional systems of encapsulating therapeutic agents (Zhu et al., 2023; Kurapov & Bakhtenko, 2019). Despite the fact that AuNPs can be regarded as biocompatible, its toxicity depends on size, shape, surface charge and functionalizing agents. Cytotoxicity has also been observed to be shape- and size-dependent and biosafety concerns need to be taken into account when designing drug delivery by AuNP (Senut et al., 2016).

Silver Nanoparticles (AgNPs)

Silver nanoparticles (AgNPs) have outstanding physical, chemical and biological characteristics, Ag ions are antimicrobial, antifungal, anti-inflammatory and antiviral with comparatively a low level of toxicity in humans (Rizwana et al., 2023). AgNPs have a high surface area and controlled release of Ag ions and the antimicrobial activity of the particles is determined by their size, shape, surface coating and agglomeration status (Burdusel et al., 2018). Nevertheless, toxicity issues have been reported and these depend on dosage, size, shape and surface functionalization (Gao et al., 2023). Thus, close optimization will be necessary in order to manage efficacy and safety. The SPR effects are also high in AgNPs leading to high absorption and scattering efficiencies.

Graphene Derivatives

Graphene planar π -conjugated structure gives it the capability of efficient immobilization of drugs and biomolecules and hence useful in drug delivery. Graphene derivatives are graphene oxide (GO) and reduced graphene oxide (rGO). Graphene has a high surface area and an increase in the drug loading capacity because of its monolayer structure (Novoselov et al., 2012). GO is a hydrophilic material that can be used in aqueous dispersions, but pristine graphene is a hydrophobic material and requires surface modification to be used in biomedical applications (Joy et al., 2023). The associated toxicity issues of the graphene derivatives would be impurity-related effects, sharp edges and dose-dependent cytotoxicity (Pelin et al., 2023). Hence, self-regulation of therapeutic efficiency and biosafety is essential in graphene-based drug delivery.

Metal Oxide Nanoparticles

Iron oxide nanoparticles (IONPs): Iron oxide nanoparticles (IONPs), which consist of Fe_3O_4 , $\alpha\text{-Fe}_2\text{O}_3$ and $\gamma\text{-Fe}_2\text{O}_3$ are much investigated in the field of biomedicine, their nanoscale size makes them more permeable to biological barriers and more effective in drug delivery. Between 10 and 20 nm in size, these IONPs are said to have superparamagnetic behaviour, which is why they are the best candidates to deliver drugs to target areas (Raghunath & Perumal, 2017; Arias et al., 2018). Nevertheless, agglomeration and possible toxicity are still an issue.

Zinc Oxide Nanoparticles: Zinc oxide nanoparticles (ZnO NPs) are cheap, have low toxicity and have antibacterial, antimicrobial and anti-inflammatory effects. ZnNPs have anti-bacterial effect ascribed to

release of Zn^{2+} and the formation of ROS (Unnikrishnan et al., 2023; Siddiqi et al., 2018). The ZnO NPs have large surface area and enhanced drug solubility and anticancer potency. Nonetheless, a high level of exposure can cause organ toxicity as a result of oxidative stress

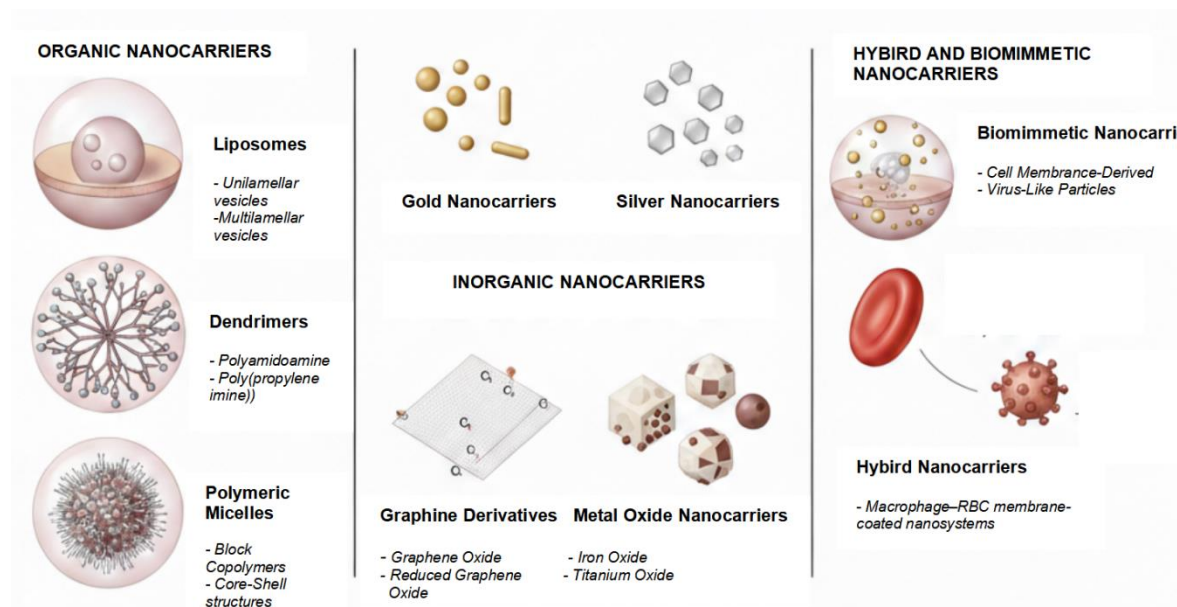


Figure 3: Classification and Structural Diversity of Organic, Inorganic and Hybrid and Biomimetic Nanocarriers

Biomimetic and Hybrid Nanocarriers

Lipid-Polymer Hybrid Nanoparticles

Lipid-polymer hybrid nanoparticles (LPHNs) have been broadly defined as the hybrid systems that are created by interacting lipid-based carriers with polymeric materials through noncovalent forces including hydrogen bond, electrostatic forces, van der Waals forces or hydrophobic forces and are useful when using a combinatorial approach to drug delivery, especially in cancer chemotherapy (Zhao et al., 2012; Gajbhiye et al., 2023). LPHNs have a high stability to enzyme degradation, in vitro and in vivo structural integrity compared to traditional lipid or polymeric nanoparticles, which is mostly explained by the polymeric content (Guo et al., 2020). Polymeric coating improves transmucosal delivery stabilizing the carrier at the biological interface and increasing residence (Seedat et al., 2016). The lipid constituent, in its turn, increases biocompatibility and pharmacological availability and serves as a hydrophobic barrier slowing down drug leakage, decreasing water diffusion and enhance the sustained release, as it slows down the degradation of polymers (Seedat et al., 2016). The application of LPHNs in therapeutic and diagnostic applications has been explored over a broad spectrum of applications, the most studied has been in anticancer drug delivery where multidrug resistance remains a major obstacle, though the most detailed studies have focused on other therapeutic applications, including antiepileptic, cardiovascular, anti-inflammatory, antimicrobial, antidiabetic agents, vaccines, peptides, proteins, genes and imaging agents, all of which are delivered via encapsulation, adsorption or surface conjugation.

Cell membrane-coated nanoparticles

Cell membrane-coated nanoparticles (CMCNPs) exhibit source-dependent properties of the membrane of the cell membrane. CMCNPs have a number of advantages over conventional NPs, such as transport specificity, biodegradability, low immunogenicity, access to hard-to-reach locations, like the blood-brain barrier, biologically regulated drug delivery through inactive transport, exocytosis or efflux pumps and sensitivity to the microenvironment (Zhao and Yan, 2022; Sabu et al., 2018).

RBCs-derived nanostructures: Red blood cells (RBCs) are one of the most common cells in circulation, transporting oxygen and carbon dioxide and possessing an amazing deformatory capacity, having immunomodulatory proteins on the membrane that extend circulation time and provide immune evasion (Xu et al., 2020; Xuan et al., 2019). The absence of nucleus and mitochondria, high structural rigidity and stability, ensures the ability to extract and purify membranes, and is exhibited by RBC membrane-coated NPs (Xu et al., 2020; Xuan et al., 2019; Yaman et al., 2020). The presence of IL-12 and TNF- α levels had been significantly lowered and fibroblast proliferation had been stimulated by the presence of RBC membrane-coated PLGA nanoparticles incorporated as macroporous alginate scaffolds in comparison to the uncoated NPs. Likewise, RBC membrane-derived mimetic liposomes that delivered curcumin had been confirmed to be biocompatible and stimulate fibroblast growth, indicating their potential in wound-healing (Fan et al., 2018; Safarpour et al., 2022).

Platelet-derived nanostructures: Platelet membranes carry CD47 and CD55 / 59,56,73,84 and other ligands that allow them to escape immunity and prevent the action of complement (Guido et al., 2020). PLGA NPs that are membrane-coated with curcumin and resveratrol exhibited increased biocompatibility, minimised haemolysis, pulmonary-specific accumulation, and reduced inflammatory mediators in models of acute lung injury (Jin et al., 2022). Identical regimens loaded with tacrolimus selectively amassed in inflamed joints, decreased inflammation, increased circulation time and decreased bone erosion in models of rheumatoid arthritis (He et al., 2018).

Leukocyte-derived nanostructures: The most common leukocytes, Neutrophils, Neutrophil membrane-coated NPs accumulate selectively, release drugs selectively and reduce inflammatory cytokines in models of pulmonary inflammation, pancreatitis and atherosclerosis. Adaptive immunity is mediated by lymphocytes (B cells, NK cells, T cells). NPs that are coated with membranes of T-cells or NK-cells can be used to regulate immune responses and induce specific tissues, including periodontitis, which can be suppressed with the help of membrane-coated NPs (Wang et al., 2020; Li et al., 2021). Glucocorticoid-coated NPs that are covered by monocytes or macrophages show a longer circulation time, immune evasion, the concentration in a disease focus (e.g., atherosclerotic plaque, tumors) and a reduction in inflammatory mediators, which enhance therapeutic efficacy (Wang et al., 2021). Mesenchymal stem cell (MSCs)-coated NPs have demonstrated increased targetability and reduced cytotoxicity and regenerative or anti-inflammatory qualities in cartilage repair, wound healing and acne treatment (Chen et al., 2024).

Hybrid membranes

Biomimetic hybrid membrane-based nanoparticles (BHMNPs) are membranes of various cell types that are integrated together to combine complementary biological activity. Generally, one membrane is known to possess targeting capabilities and the other is responsible of improving immune evasion or circulation (Zhu et al., 2022; Rampado et al., 2022). The BHMNPs can be made by isolating the membranes individually and fusing them or by fusing the cells before membrane isolation (Rampado et al., 2022). RBC-macrophage, neutrophil-RBC and macrophage-RBC membrane-coated nanosystems have shown to persist in circulation, avoid immune action, target, controlled drug release and that they significantly decrease inflammatory mediators in models of rheumatoid arthritis, osteoarthritis and atherosclerosis (Lin et al., 2022; You et al.,

2022). Nanoparticles based on BSA, bionic neutrophil-inspired, apoptotic cell-mimicking liposomes and proteoglycan-inspired nanocarriers were shown to have immune modulation, ROS scavenging, tissue regeneration and anti-inflammatory activity in spinal cord injury, diabetic wound healing and osteoarthritis (Zhang et al., 2021).

Table 1. Structural classification of smart nanocarriers with functional characteristics and translational considerations

Nanocarrier Type	Core Composition	Structural Features	Functional Strengths	Key Translational Challenges
Lipid-based nanocarriers (Liposomes, LNPs, SLNs)	Phospholipids, cholesterol, ionizable lipids	Bilayer or solid lipid matrix, amphiphilic architecture	High biocompatibility, good drug encapsulation (hydrophilic & hydrophobic), clinically validated platforms	Stability issues, leakage, fast clearance by the RES (if non-PEGylated), reproducible scale-up
Polymeric nanoparticles (PLGA, PEG, chitosan, dendrimers)	Synthetic or natural polymers	Matrix or core-shell systems; tunable degradation kinetics	Controlled/sustained release, surface functionalization flexibility, stimuli-responsive design	Polymer toxicity (in some systems), batch variability, complex regulatory evaluation
Inorganic nanoparticles (Gold, silica, iron oxide)	Metals or metal oxides	Solid core, vast surface area fixed/rigid structure	Imaging capability (MRI/CT), photothermal/photodynamic therapy, theranostics	Prolong accumulation, biodegradability issued, safety profiling
Hybrid nanocarriers	Combination of lipid-polymer, polymer-metal, or carbon-based materials	Several-layered or composite structures	Multipurpose (targeting + imaging + therapy), structural stability	Manufacturing difficulties, regulatory issues
Biomimetic nanocarriers	Cell membrane-coated or peptide-assembled	Biological membrane interface	Immune evasion, longterm circulation, homotypic targeting	Variability in sources, huge-scale membrane extraction,

	systems			quality control
Stimuli-responsive nanocarriers	Polymer, lipid, or hybrid systems with responsive linkers	pH-, enzyme-, redox-, thermal-, light-sensitive bonds	On-need drug release, efficient tumor specificity	Trigger Variability in triggers in vivo, premature activation challenge

Design Principles of Smart Nanocarriers

Physicochemical Properties

Size, Shape, and Surface Charge: The size of a particle is an important factor in physicochemical properties of nanocarrier that determines the circulation and tissue distribution. Nanocarriers that are below about 10 nm are eliminated via renal filtration at a high rate and bigger particles get retaken by the reticuloendothelial system (Cong et al., 2024). Nano carriers of intermediate sizes show greater accumulation at pathological sites, but very small sizes can also reduce the loading capacity of drugs and impair the control of their release (Lee & Yeo, 2015). In addition to size, the shape of the particle also brings more complexity to the performance of biology. Nanocarriers that are not spherical have a changed hydrodynamic character, vascular marginalization and interaction with cell membranes (Kowalczyk et al., 2011). The long or discoidal ones have been demonstrated to enhance the endothelial adhesion and tissue penetration but the added complexity and scalability of their fabrication opens up barriers to clinical translation (Kowalczyk et al., 2011). Surface charge is also a very potent factor in contact with biological membrane and circulating proteins. Nanocarriers with a positive charge aid in cellular internalization through electrostatic interactions, whereas they are linked to high protein adsorption, cytotoxicity, and clearance (Zeinali et al., 2025). On the other hand, neutral or slightly negative surfaces cause a decreased nonspecific interaction and extend systemic circulation, usually at the cost of decreased cellular uptake efficiency.

Surface Functionalization and PEGylation: Surface modification of nanocarriers is used to decrease nonspecific adsorption and increase compatibility with physiological environments. PEGylation is one of the most commonly used methods to increase circulation time and decrease immune recognition. Opsonization and reticuloendothelial clearance are inhibited by the presence of polyethylene glycol chains, which increases bioavailability (Santhanakrishnan et al., 2024). Nevertheless, repeated dosages can cause the anti-PEG immune response, which could reduce the long-term effectiveness and emphasize the necessity to seek alternative stealth tactics.

Targeting Strategies

Passive Targeting (EPR Effect): Passive targeting is based on the increased permeability and retention effect of the pathological tissues including solid tumors. Nanocarrier accumulation is facilitated by leaky vasculature and impaired lymphatic drainage but heterogeneity in tumor vascularization and extracellular matrix density usually causes uneven distribution (Bertrand et al., 2014; Jain, 2001). These shortcomings have contributed to the problem of trusting EPR-based targeting, especially in clinical practice, which highlights the necessity of complementary approaches to targeting.

Active Targeting (Ligands, Antibodies, Aptamers): Active targeting refers to ligand-based functionalization of nanocarrier surfaces, i.e. targeting that is selective because of the over-expression of receptors on target cells (Allen & Cullis, 2013). The ligand-mediated recognition stimulates receptor-mediated endocytosis and increases the intracellular delivery of drugs. Active targeting is not able to completely overcome the accumulation of nonspecific components, despite a more tailored approach: active targeting still relies on the physicochemical characteristics of the underlying biodistribution (Bazak et al., 2015).

Stimuli-Responsive Nanocarriers

Internal Stimuli (pH, Enzymes, Redox Conditions)

Pathological microenvironmental cues, including acidic pH, enzyme activity and redox potential, are exploited by internal stimulus-responsive nanocarriers, whereas enzyme-cleavable linkers are based on disease-associated enzymatic signatures (Mi, 2020). Redox-reactive scaffolds are intracellular glutathione gradients used to release them after cellular internalization to improve intracellular specificity (Abed et al., 2022).

External Stimuli (Temperature, Light, Magnetic Field, Ultrasound)

Some nanocarriers are externally triggered react to physical stimuli such as temperature, light, magnetic field and ultrasound. These systems allow the specific time control of drug release and local activation. Nevertheless, low tissue penetration, the necessity of special equipment, and safety concerns are the obstacles to the universal clinical use (Abouelmagd et al., 2014).

Drug Loading and Release Mechanisms

Encapsulation vs Conjugation

Encapsulation involves the technique of physical entrapment of drug molecules into a nanocarrier or core-shell system. The process of entrapment of a drug core between a mechanism shell of nanomaterials is known as nanoencapsulation (Cano-Sarabia and MasPOCH, 2014). Drug molecules in polymeric nanospheres are carried within polymeric carriers and create a physical barrier of drug and external environment. Polymers commonly used in the encapsulation based drug delivery system are polyethylene glycol (PEG), poloxamers, polyvinyl alcohol (PVA), polyesters and polysaccharides. The polysaccharides like alginate, chitosan, carrageenan play their major role as protective barriers to the external conditions. The properties of polymers have a strong effect on the mechanical behavior of nanoparticles, bio-distribution, release kinetics (Aboudzadeh & Hamzehlou, 2022). Conversely, conjugation is based on the covalent attachment of the therapeutic molecules on the surface or backbone of nanoparticles. The bioconjugation is more stable than reversible protein adsorptions because these methods are sensitive to the environmental conditions, including pH, ionic strength, and temperature (Martin et al., 2025). The type of conjugation strategy to be used is determined by the physicochemical characteristics of the nanoparticle and the biomolecule. Proteins have reactive functional groups which include amino (-NH₂), carboxyl (-COOH), hydroxyl (-OH) and thiol (-SH) functional groups where covalent coupling is possible. Nanoparticle surface charge, porosity, hydrophobicity and polydispersivity however have a strong influence on conjugation efficiency and stability of the product. Although conjugation enables a high degree of control of drug delivery and targeting, the release of drugs occurs as a result of bond cleavage mechanisms and not passive diffusion (Pinals et al., 2020).

Controlled and Triggered Release

Controlled-release systems are designed to give sustained or zero-order release curves to reduce the variability of drug doses. The mechanism of drug release depends on the carrier composition, drug-carrier interactions and preparation methods. Depending on the prevailing pathway of release, the drug may release using diffusion-controlled, solvent-controlled or degradation-controlled or stimuli-controlled (Siegel and Rathbone, 2012; Langer and Peppas, 1983).

In diffusion-controlled systems, the migration of the drugs in the carrier is directed by the concentration gradients. A reservoir-type system comprises a drug-loaded core located in the centre and is encircled by a polymeric membrane, whereas a matrix-type system disperses the drug all through the polymer matrix and is mostly characterised by a sharp burst release followed by a decreasing release rate (Cauchetier et al., 2003). Solvents release has osmosis-controlled and swelling-controlled releases. Osmotic systems utilize the influx of water through semi-permeable membranes to obtain the near-zero-order release. Hydrogels, which are swelling-controlled systems, liberate drugs into release when polymer networks are distended following the intake of water, and relaxations of the polymer and mesh size determines drug release kinetics (Kaity, Isaac, and Ghosh, 2013).

Lastly, due to the presence of acidic tumor microenvironment, pH-sensitive systems have been widely investigated as site-specific drug delivery systems; thermosensitive carriers use temperature-dependent changes in polymer phase to achieve site-specific delivery (Yuba et al., 2013).

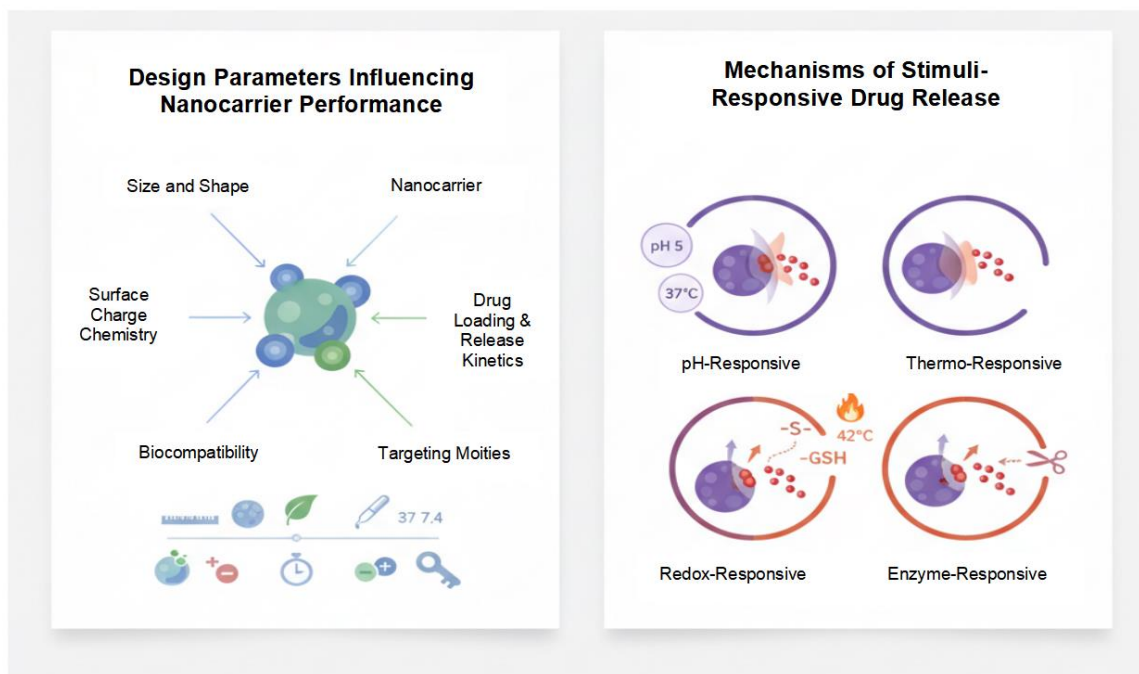


Figure 3. Design factors that affect the performance and stimuli-responsive drug delivery of nanocarriers.

Applications of Smart Nanocarriers in therapy

Cancer Therapy

Passive and active targeting of nanoparticles carrying anticancer agents enhance the pharmacokinetic stability of anticancer agents and their selective delivery via passive and active targeting. Nevertheless, resistance to drugs has become a significant drawback in cancer treatment, which is usually mediated by hypoxia, efflux transporters, genetic mutations and the altered intracellular trafficking. Engineered nanoparticles take advantage of the EPR effect to enhance drug concentration in neoplastic tissues and this enhances therapeutic efficacy (Dechbumroong et al., 2024). The multidrug resistance protein-2 (MRP2) which is regulated by hypoxia-inducible factor-1 (HIF-1) is important in diminishing the effectiveness of platinum-based chemotherapeutics. The development of a microporous silica-based co-delivery system (PMONA) that allowed the simultaneous administration of the HIF-1-inhibitor cisplatin and platinum-binding peptide significantly decreased the tumor growth by suppressing proteins that were induced by HIF-1 (Zhang et al., 2020). Nanoparticle systems with conjugated polymers that are triggered by near-infrared light create focalized hyperthermia and tumors are sensitized to chemotherapy (Yu et al., 2019). The pH-responsive lysosomal escape and mitochondrion-targeted shell-core nanosystem (DOX-PLGA/CPT/PD) is a system that effectively overcomes the doxorubicin resistance in MCF-7/ADR breast cancer cells and achieves 84.9% of tumor inhibition rate. By regulating simultaneous drug delivery and lysosomal evasion, dual inhibition techniques based on pH-sensitive nanoparticles to EGFR1 and autophagy enhanced the outcomes of treatment in non-small cell lung cancer that is resistant to AZD9291 (Gu et al., 2020). Anticancer agents and resistance inhibitors can be co-encapsulated to improve solubility, stability, and pharmacokinetic behavior and silence resistance-associated proteins like Bcl-2, Akt and P-glycoprotein (P-gp) (Yoo et al., 2024).

Infectious Diseases

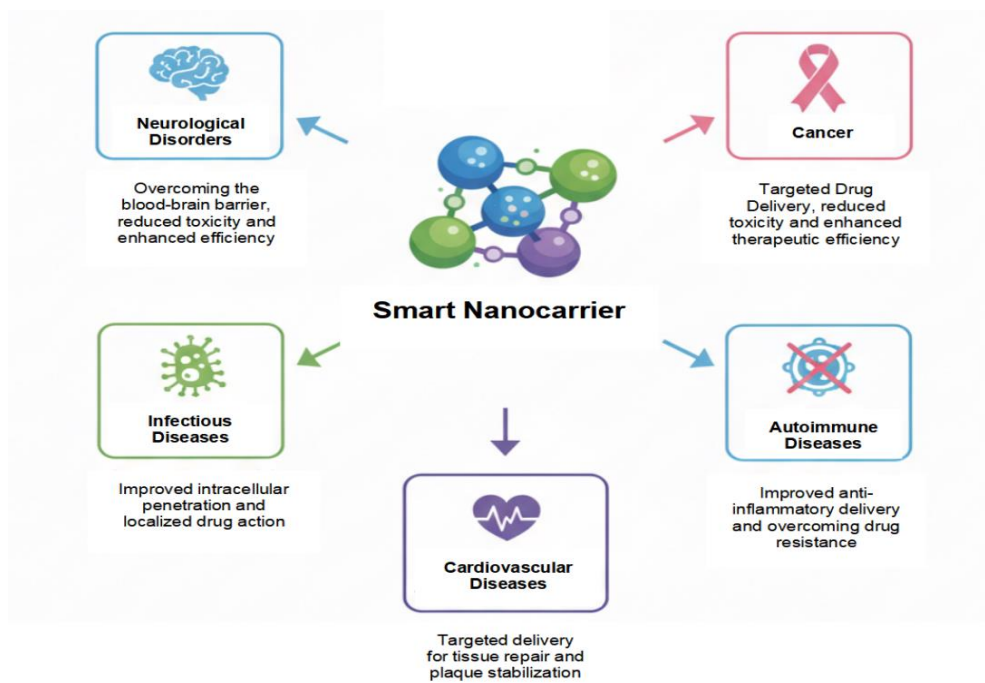


Figure 4. Smart nanocarrier-based disease-specific targeting

Nanomaterials have been widely investigated to assist preventive procedures, diagnostics and symptom-based treatment. Metallic nanoparticles, including TiO₂ and AgNPs, have inherent antiviral properties and have been added to disinfectants, self-cleaning surfaces, and personal protective equipment to reduce the transmission of viruses. Carbon nanoparticles have been extensively used in air and membrane filtration systems to eliminate pathogens, and disinfectants in the form of nanostructures, like CAC-717, have proven to be effective in the removal of enveloped and non-enveloped viruses (Nakashima et al., 2017; Sakudo et al., 2020).

In case of antimicrobial therapy, lipid- and polymer-based nanocarrier facilitate targeted therapy and more effective bacterial eradication. The adsorption, fusion and endocytosis between the liposomes and bacterial cells boost intracellular drug delivery (Ghosh & De, 2023). Cationic lipid nanoparticles utilize negative surface charge present in the bacterial membranes and enhance the binding and localized drug delivery. Lipid nanoparticles modified with DOTAP and loaded with rifampicin had a potent inhibitory effect on minimum inhibitory concentration in relation to *Staphylococcus aureus* through membrane disruption (Tran et al., 2018). Fusion of the mechanisms is based on the DOPE- or DPPC/DMPG-liposomes to achieve bacteria cytoplasmic antibiotic delivery and overcome extracellular biofilm defense (Sachetelli et al., 2000). The liposomes containing cholesterol also boost toxin-mediated interactions, which augment biofilm penetration and the release of drugs (Natsaridis et al., 2025). Specificity and biofilm penetration get improved with active targeting through surface functionalization with peptides or antibodies, causing bacterial cell death. Antibiotics such as vancomycin are specifically released by environmentally responsive polymeric nanocarriers, such as pH-sensitive PLGA-PLH-PEG systems, in acidic sites of infection, reducing off-target targeting (Radovic-Moreno et al., 2012).

Neurological Disorders

In spite of this increasing burden, the development of Central nervous system (CNS) drugs is still inefficient, in part, because of the low bioavailability of the brain and the restraint effect of the blood-brain barrier (BBB) (Vilella et al., 2015). Nanocarriers are able to outperform BBB and avoid prompt elimination by the reticuloendothelial system, extend the length of time in the circulation and greatly enhance the concentration of the drug in brain tissue, which is important in both experimental and clinical translation (Fornaguera et al., 2015). There are various plans that have been worked out to improve NP transport in the BBB. They are the momentary BBB breakage through ultrasound-driven microbubbles or osmotic agents to loosen endothelial tight junctions (Mearns, 2014). The use of advanced liposomal preparations has shown a higher therapeutic effect in the treatment of glioma, e.g., CB5005-PEGylated liposomes, in which the addition of cell-penetrating peptide and NF- κ B inhibitor led to a significant improvement in glioma cell uptake, brain retention, and survival in glioblastoma-bearing mice (Wang et al., 2023). Moreover, ligand-conjugated liposomes, i.e., transferrin-, folate-, EGF-, or integrin-targeted vehicles, enhance receptor-mediated BBB delivery and active vascular targeting, enhancing drug bioavailability and therapeutic specificity (Hu et al., 2024). The NPs made of PLGA that entrap antituberculosis drugs allowed bacteria to be cleared out of the meninges with significantly lower doses, which can also illustrate how nanocarrier-based therapies could enhance the compliance and effectiveness of CNS tuberculosis treatment. Recent examples of nanotechnology in molecular biology include quantum dot (QD)-delivery systems complexed with MMP-9 siRNA which have been demonstrated to suppress MMP-9 expression in brain microvascular endothelial cells resulting in increased extracellular matrix protein levels and increased transendothelial electrical resistance and decreased BBB permeability. The fact that the MMP-9/TIMP-1 axis is modulated in this way highlights the ability of nanocarrier-based gene silencing approaches to retain BBB integrity, reduce neuroinflammation, and facilitate CNS homeostasis.

Cardiovascular Diseases

The atherosclerosis is marked by the gradual thickening of the artery walls, the shrinkage of the lumen, the formation of a plaque with the possible rupture and the occurrence of thrombosis, which results in myocardial infarction and ischemic stroke (El-Sherbiny et al., 2014). Nanoparticles (NPs) consisting of polymer showed some of the best results as delivery systems of anti-atherosclerotic agents, and lipid-based nanocarriers, such as liposomes and HDL-mimetic NPs, have also been of interest due to their high biocompatibility and biomimetic attributes (Leuschner et al., 2011). Multimodal diagnostic and therapeutic (theranostic) uses are also possible due to the integration of these nanosystems with imaging agents. Nanoparticles that formed were platelet-like (PLNs), which showed discoidal morphology and mechanical flexibility and displayed greater vascular adhesion and injury-specific aggregation than did spherical and rigid particles (Anselmo et al., 2014). Nanocarriers have also been extended in terms of targeting abilities due to biomimetic strategies. Nanocarriers consisting of leukosomes loaded with rapamycin resulted in a great decrease in proinflammatory levels of cytokines, and decreased macrophage proliferation, which was followed by desirable remodeling of the plaque. Equally, NPs that were coated with macrophage membrane and released rapamycin successfully inhibited the development of the plaque and phagocytosis of the macrophage in vivo (Wang et al., 2021). In vivo experimental studies in arterial restenosis models have shown a high level of inhibition of neointimal hyperplasia after intravenous injection of rapamycin-loaded nanocarriers. This was further enhanced with bilayered nanoparticles that can release pentraxin-3 and VEGF sequentially to induce rapid endothelial regeneration and inhibition of restenosis when applied locally during angioplasty (Hu et al., 2022).

Inflammatory and Autoimmune Diseases

Autoimmune rheumatoid arthritis is a chronic inflammatory disorder that is an autoimmune disease involving immune-mediated synovial joint destruction, which leads to pain, swelling and joint deformity (Liao et al., 2024). pH-responsive nanoparticles of polymers like polyacrylic acid have been applied to entrap anti-inflammatory drugs, including methotrexate and corticosteroids, to be released selectively in acidic synovial fluid thus enhancing therapeutic outcome (Liao et al., 2024). Nanocarriers such as ligand-functionalized liposomes and polymeric nanoparticles increase the drug concentration in inflamed joints and reduce systemic immunosuppression and gastrointestinal toxicity of conventional therapies. PLGA-based nanoparticles intra-articularly have shown sustained local drug release and enhanced efficacy of glucocorticoids and biologics, decreasing the dosage frequency and increasing treatment effect (Guo et al., 2023).

Multiple sclerosis is a chronic autoimmune disease which is neuroinflammatory, demyelinated and progressively impairs the nervous system, and has limited therapeutic efficacy due to the restrictive nature of the blood-brain barrier (Zha et al., 2024). Nanoparticle-based immunomodulation approaches to inhibit T cell responses pathways through the delivery of glucocorticoids or pro-inflammatory cytokines siRNAs have permitted a local immune modulation keeping systemic immune responses intact (Chountoulesi and Demetzos, 2020). Inflammatory colonic areas were found to release more 5-aminosalicylic acid to the nanoparticles and the nano-particles yielded significantly less inflammation and induced mucosal healing in the animal models with few undesired side effects (Tang et al., 2024).

Approved Nanomedicine

Nanomedicine has evolved over time, beginning with the discovery of liposomes in the 1960s and the current clinical acceptance of nanomedicines. Nanoscaled drug delivery systems (NDDSs) have proved to be more clinically effective and less toxic than conventional drugs in the past decades. The following table gives a summary of the primary types of approved nanomedicines as well as their clinical indications.

Table no. 2 Clinically Approved Nanocarrier-Based Therapeutics Categorized by Platform and Indication

Nanocarrier Platform	Representative Approved Products	Major Therapeutic Areas
Liposomes	Doxil®, AmBisome®, Vyxeos®, Onivyde™, Exparel®	Oncology (breast, ovarian, AML, pancreatic); antifungal therapy; infectious diseases; pain management
Lipid Nanoparticles (LNPs)	Onpattro™, Spikevax®, Comirnaty®	Genetic disorders (hATTR); mRNA vaccines (COVID-19)
Drug Nanocrystals (NCs)	Tricor®, Cabenuva®, Apretude®, Rapamune®	Cardiovascular diseases; HIV treatment/prevention; transplant medicine; CNS disorders
Polymeric Nanoparticles / Micelles	Abraxane®, Genexol® PM, Paclical®	Solid tumors (pancreatic, breast, ovarian, NSCLC)
Dendrimer-Based Nanoparticles	VivaGel®	Antiviral prophylaxis (HIV, HSV)
Other Nanomedicines	Ontak®, Restasis®	Oncology; autoimmune disorders; ophthalmology

Translational Challenges and Limitations

Although significant advances have been made in nanocarrier design and there are a growing number of clinical trials, the clinical translation

Biological Barriers and Biodistribution

Protein corona formation: After entering the bloodstream, biomolecules adsorb nanocarriers and consequently redefine their surface potential, hydrodynamic behavior, and biological identity (Chen et al., 2016). This corona regulates the circulation time, biodistribution and cellular interactions usually dominating the original design of the nanoparticle. Antifouling coating is able to minimize nonspecific adsorption, but it fails to abate corona formation and can redirect the pathways of association with apolipoproteins (Liu et al., 2023). Since corona composition is very dynamic and patient-specific, the challenge is still an outstanding issue to be resolved on the path to achieving homogenous results with the use of nanocarrier-based therapeutics.

Clearance by the reticuloendothelial system: Nanocarriers, in parallel with corona formation, are removed fast by the reticuloendothelial system. After intravenous exposure, nanoparticles engage with macrophages located in the liver, spleen, and lymph nodes, and Kupffer cells tend to take a large proportion in a few minutes, thus limiting extrahepatic exposure (Hosseini-Kharat, Bremmell, and Prestidge, 2025). Repeated administration also increases the complexity of biodistribution through the generation of anti-

PEG immune responses, which hasten the clearance of blood and changes trafficking behavior. Consequently, poly(2-oxazoline), poly(glycerol), polysarcosine, and zwitterionic polymers have been the subject of the focus of those who believe that they can preserve the benefits of circulation at a low immunogenicity cost (Dal Magro et al., 2017).

Toxicity, Safety and Immunogenicity

Some of the barriers to clinical translation of nanocarriers are safety, toxicity and immunogenicity, as most of them are composed of complex substances and have extended interactions with biologic systems. As one example, the transcript-level analyses revealed that nucleic acid-functionalized gold nanoparticles were advantageous in terms of biocompatibility (Zhang et al., 2022). But when nanoparticles are introduced systemically they are quickly complexed with serum proteins to create a biomolecular corona that changes the surface charge, hydrodynamic size and biological identity. Although PEGylation and other inaccessible hydrophilic surface alterations have been achieved, 100% suppression of the protein adsorption in vivo has not been achieved. Biodegradable polymer membranes, PEGylation, and amino-based peptide-like membranes can further enhance safety and circulation time, but the overlaying of cells can adversely affect cellular uptake (Ahmad et al., 2021). Hemocompatibility tests, such as hemolysis, and stable body mass and no organ damage in vivo are all critical safety validation parameters (Chen et al., 2021). The toxicity of nanoparticles is generally dose and time-dependent, and the oxidative stress, inflammation, and dysregulation of cytokines were found to be the preponderant cell death pathways. Long-term risks, such as carcinogenicity have not been fully defined especially of high surface area small particles with high tissue retention. Particles smaller than 300 nm often do not have a significant effect on toxicity, but dose, surface charge, shape, and ion release determine adverse effects stronger than the size does (Fan et al., 2021). On this basis, optimization of nanoparticle architecture and biocompatible surface coating should be carefully considered in order to reduce toxicity and facilitate clinical translation success.

Scalability, Manufacturing and Reproducibility

The production of a nanomedicine product is a multistage process that involves constant regulation of key qualities of nanomaterials, such as size, shape, surface charge, structure, composition, physicochemical behavior, pharmacokinetics and biopharmaceutical properties (Paliwal et al., 2014). Therefore, the emerging challenge in the development of clinically viable nanomedicines is closely linked to improved manufacturing technologies that are capable of facilitating scalable and reproducible processes that adhere to Good Manufacturing Practice (GMP) quality standards. Implementing GMP controls the quality of processes and products with the help of written procedures that regulate every step of the manufacturing process which can influence the end-product (Jarvis, 2014). Moreover, GMP systems reduce risks at every phase of production, including raw materials and equipment but also workers training, and offer documented proof about the adherence of procedures at the manufacturing chain.

In 2005, the European Commission in partnership with the pharmaceutical industry was able to create the European Technology Platform on Nanomedicine (ETPN), a project aimed at enhancing the use of nanotechnology in medical practice (European Technology Platform on Nanomedicine, n.d.). The ETPN aims to speed up the process of translation by facilitating focused public investment and by building a specific technical infrastructure with the help of the Nanomedicine Translation Hub. This service offers custom mentoring through Translation Advisory Boards, standard product characterization through the Nanotechnology Characterization Laboratory (NCL), and access to GMP production through pilot production lines (Martins et al., 2020). Through these services, which are provided at no cost to academic laboratories, small and medium-sized enterprises, and industry partners, the main challenges to growth are removed, and the clinical development of promising nanomedicine candidates is speeded up.

Emerging Trends and Future Prepectives

The inherited nature of nanocarriers (NCs) makes them flexible by nature, both in terms of material composition and encapsulation, and allows the application of nanocarriers in a broad spectrum of therapeutic applications. NCs may also be combined with imaging agents or biosensors, allowing biodistribution, drug release, and therapeutic response to be monitored in real time (Gawne et al., 2023). These characteristics are especially consistent with the objectives of personalized medicine whereby the treatment needs to be adapted to patient-specific disease features and treatment outcomes. Nevertheless, this adaptability, which NC utility can rely on, is also a source of translational complexity, as loading cargo, maintaining formulation stability, and ensuring reproducibility are some of the challenges (Hua et al., 2018). The dynamics between NCs and biological systems and the mechanisms of diseases are extremely complicated, and the traditional animal models cannot predict them (Hua et al., 2018). Clinical outcomes of nanomedicines are not as predictable compared to conventional drugs due to the use of animal models (Dugger et al., 2018). To achieve this potential in the field of personalized nanomedicine, the necessity to have sophisticated model systems that can recap nanoscale transport and biological mechanisms is increasing, since the application of NCs in human bodies is exposed to laminar flow, cell collision, biodistribution and drug release that are quite different in animal systems (Metselaar & Lammers, 2020). To realize the promise of personalized nanomedicine, there is a growing need for advanced model systems capable of capturing nanoscale transport and biological complexity. New platforms like microfluidic devices, that seek to mimic physiological characteristics unique to human tissues, vascular structure, tissue structure, cellular uptake routes and toxicity kinetics and allow the use of patient-derived materials. Microfluidic organ-on-a-chip, such as vessel-on-a-chip (VoC) models, allow to control the study of NC behavior in physiologically realistic flow and shear regimes and give useful information about vascular transport barriers (Zhang et al., 2018). Through the application of AI techniques like machine learning, deep learning and computational modeling it is possible to explore this multidimensional space systematically, discover non-obvious correlations and narrow down on the most promising nanocarrier prospects with ideal therapeutic characteristics. Such strategies lower the burden, and cost of experiments, and enhance translational predictability, contributing to the continued gap between preclinical discovery and clinical application. The development of AI-assisted nanocarriers cuts across a variety of related fields, such as design and screening, mechanistic insights, optimization and discovery, and clinical translation and regulation. The machine learning (ML) algorithms including support vectors machine, random forests, gradient boosting models (e.g., XGBoost) and ensemble frameworks have been effectively used to forecast major physicochemical and biological parameters, which include the particle size distribution, zeta potential, colloidal stability, drugs encapsulation efficiency, and in vitro cytotoxicity (Chou et al., 2025).

These models can reduce the number of trial-and-error cycles needed to determine complex, nonlinear relationships between the synthesis conditions and nanocarrier properties and offer mechanistic understanding of the effects of the formulation variables on downstream biological performance (Almansour and Alqahtani, 2025). Convolutional and recurrent neural networks are capable of working with high-dimensional data, such as that obtained by microscopy morphology and time-resolved pharmacodynamics, enhancing the prediction of biodistribution, cellular uptake, and therapeutic efficacy depending on design parameters such as polymer composition, ligand density, and surface charge (Mishra et al., 2025). Notably, deep learning models allow integration of multimodal data, that is, integrating chemical descriptors, omics readouts, bioassay data, and imaging features, giving a comprehensive view that surpasses conventional regression or QSAR-based models. They may be DNN-augmented PBPK-based models that learn nonlinear structure-biodistribution relations of tumor delivery and CNNs that are able to automatically learn morphology descriptors associated with biological performance (Chandrasekar et al., 2025; Leong et al., 2022).

Molecular dynamics simulations can provide atomistic understanding of the interaction of nanoparticles with lipid bi-layers, proteins and nucleic acids to guide predictions in the membrane penetration, endocytosis, and drug release pathways (Trezza et al., 2025). Electronic structure, binding energy, and surface reactivity are also solved using quantum mechanical calculations, producing datasets of high resolution, which de-risk early phase development (Robertson et al., 2021). By combining these simulations with ML, biodistribution and clearance can be predicted in a scalable fashion. An example is where ML-enhanced versions of PBPK models have been capable of accurately projecting organ-level nanoparticle distributions amongst different materials and species, and making meaningful predictions on humans and eliminating the need to use the expensive in vivo screening. Competing papers demonstrate the potential to integrate such data-driven models with QSAR and multi-omics data to facilitate patient-centered nanomedicine design and simplify regulatory assessment (Alqarni & Huwaimel, 2025). In the future, patient-specific genomic, epigenomic, and metabolomic data integration into AI-driven design pipelines will be one of the major steps towards precision nanomedicine. This personalization has been particularly pertinent in oncology and neurological diseases, in which biological heterogeneity and barriers to delivery restrict the application of a single size. Artificial intelligence (AI)- and data-driven strategies can provide a potent structure to enhance rapid nanocarrier innovation and augment translational reliability and clinical impact.

CONCLUSION AND FUTURE OUTLOOK OF SMART NANOCARRIERS

Smart nanocarriers have developed beyond the mere delivery vehicle of a drug into a multi-purpose, highly sophisticated platform that can deal with some of the most intractable problems in contemporary medicine. In this review, we have discussed the impact of nanocarrier therapeutic potential in oncology, infectious diseases, inflammatory and regenerative medicine due to advances in material design, surface functionalization, stimuli-responsiveness, biomimicry, hybrid architectures and data-driven design strategies. Highly flexible nanocarrier characteristics allow specific control of biodistribution, drug release dynamics and targeting, which makes them one of the enablers of precision medicine in the next generation. Nanocarrier-based therapies have been shown by clinically approved nanomedicines and those in advanced clinical trials have the potential to significantly increase the solubility of drugs, decrease systemic toxicity and increase therapeutic indices relative to conventional formulations.

The review however also highlights the consistent bottlenecks of translation, such as the small tumor accumulation, interpatient fluctuations, scale-up issues and the discrepancies between preclinical and clinical phenomena. Such shortcomings highlight biological complexity, not the design of nanomaterials as such, as the predominant determiner of therapeutic efficacy. In the future, the smart nanocarrier holds its future in integrating, as opposed to isolating. More predictive platforms are provided by personalized and precision nanomedicine strategies, which are reinforced by in vitro models, organ-on-chip model, and patient-derived tissues to assess the behavior of nanocarriers in human-relevant environments. Simultaneously, AI- and data-based design models are radically reshaping nanocarrier development as they can be rationalized, discovered through generative discovery and modeled by predicting biodistribution, efficacy and safety.

Combination-based hybrid methods between mechanistic modeling and machine learning are especially feasible to close the gap between in silico projections and in vivo performance. To achieve a successful clinical translation, it is necessary that the future focus should be on reproducibility, regulatory openness and scalable production and innovation. Unified characterization guidelines, clarity in AI-based applications and early interaction with regulatory bodies will play a vital role in speeding up the approval processes. Finally, smart nanocarriers are destined to cease being a one-size-fits-all therapeutic approach and become a patient-specific, adaptable, therapeutic, diagnostics and real-time-monitoring system. As future interdisciplinary projects ensure the sustained interdisciplinary collaboration between materials

scientists, biologists, clinicians and data scientists, smart nanocarriers will likely be at the heart of the future of precision and translational medicine.

Conflicts of Interest

All authors have no conflict.

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