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Smart biomaterials for precision drug delivery: emerging strategies for site-specific targeting and controlled therapeutic release

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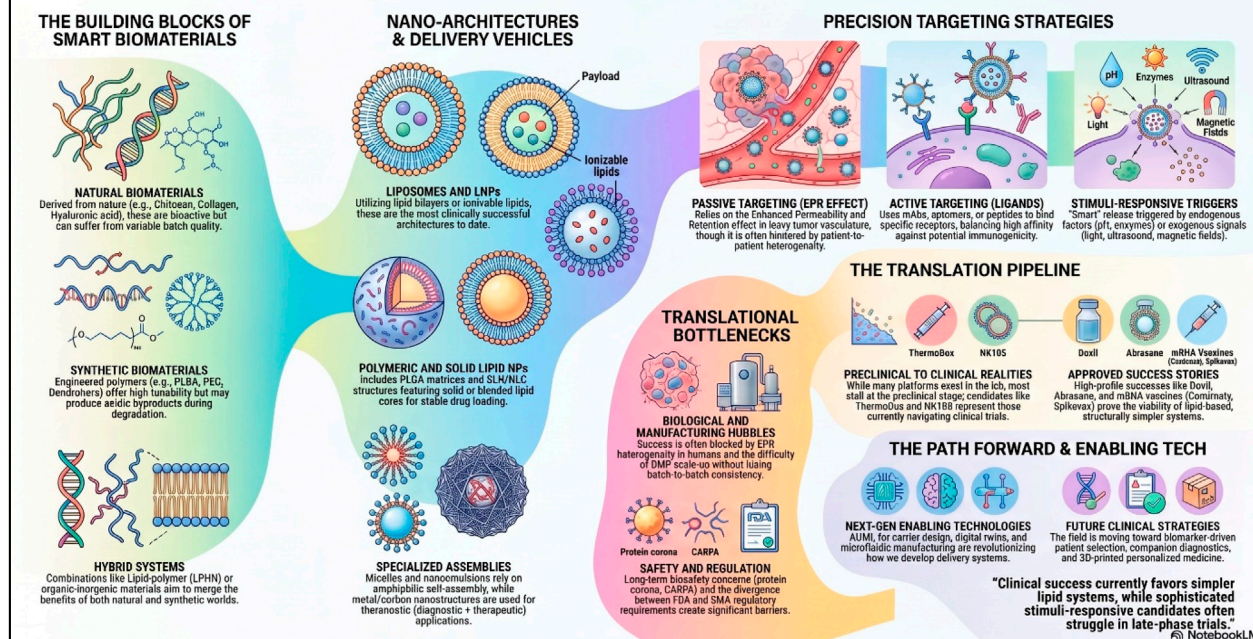
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Conventional drug delivery is constrained by several factors such as rapid distribution and elimination in the body, a narrow range of effective doses, and the inability of the system to adjust according to the situation of the disease. Smart biomaterials such as natural biomaterials (polysaccharides, proteins, and peptides), synthetic biomaterials (PLGA, PLA, dendrimers, and hydrogels), and hybrid lipid–polymer or organic–inorganic systems can provide a solution to these challenges by being the first active, responsive, stimuli, and controlled release carriers for targeted delivery. This review outlines the progress and development of smart biomaterials and their use in drug delivery. We will analyze the use of passive (enhanced permeability and retention (EPR)-driven) and active (ligand receptor) targeting, address the barriers to drug delivery in the body, and examine the impact of physical properties such as size, shape, and surface chemistry on delivery systems. For this review, we will also examine the available major classes of drug delivery nanocarriers and responsive systems that are triggered by pH, redox, enzymes, temperature, light, ultrasound, and magnetism. We will also consider new technologies such as intelligent systems, digital twins, organ-on-a-chip, microfluid robotics, and nanorobots, which are revolutionizing the drug delivery design process from non-systematic to systematic and aligned. With a focus on drug delivery designs that are aimed for use in practice, we will examine available drug delivery systems and discuss the toxicity of nanosystems, variability with respect to biology, the framework of design standards, and other relevant systems. We will deliver our opinion that the available drug delivery systems, when integrated with the use of biomarkers, will provide the most benefit.

KEYWORDS

controlled therapeutic release, drug delivery, pharmaceutical products, site-specific targeting, smart biomaterials

Smart Biomaterials for Precision Drug Delivery: From Lab Innovation to Patient Care



GRAPHICAL ABSTRACT

1 Introduction

The evolution of drug delivery represents a new level of managing the site, time, and method of therapeutic action in the human body. The early development of pharmaceutical products relied primarily on the pharmacokinetics of the drug, and little, if any, engineering, manipulation, or modification of the carrier was applied. This began to change with the introduction of the first sustained-release formulation in 1952. This led to the innovation of the first generation of drug delivery systems (1950–1980) with a focus on the sustained-release and controlled release of transdermal and oral formulations (Vargason et al., 2021). Drug delivery systems of this era introduced the following new technologies: drug–polymer systems; the first controlled-release device made of polymers, liposomes, and albumin nanoparticles; liposomal drug delivery systems; micelle drug delivery systems; controlled-release formulation approved by the Food and Drug Administration (FDA), the first PEGylated drug, and so on (Park, 2014; Afzal et al., 2022). The second generation of drug delivery systems, spanning 1980–2010, saw a surge in the use of nanoparticle carriers and a strong interest in sustained-release systems and self-regulated and responsive drug delivery systems. Nanotechnology was at the forefront in formulation development during this era. It began in the 1970s owing to an interest in using nanoparticles to improve the solubility of poorly soluble drugs and also improve their bioavailability following oral and parenteral routes of administration. The interest carried on into the next century along with the ever-growing arsenal of nanoparticle-based drug delivery systems. Today, there are an extensive number of platforms based on the use of nanoparticles as drug

delivery systems, including, but not limited to, liposomes, solid lipid nanoparticles (SLNs), polymeric micelles (PMs), nano-vaccines, and nano-antibodies (Park et al., 2022). The field of nanoparticle technology is also expanding to include delivery systems that use smart materials. Recently, the ingenuity of nanoparticle systems for the delivery of lipids and advanced RNA technology has begun to stimulate interest in the role of nanoparticles as delivery systems for nucleic acid therapeutics. This is the new era of medicine. While many improvements to traditional drug delivery systems have been made, these systems (e.g., oral tablets and intravenous injections) continue to be limited by enduring pharmacokinetic and biodistribution challenges (Park, 2014). Most drug delivery systems are designed to disperse a drug globally, rather than localizing it at the site of interest, resulting in most of the administered dose missing the intended target. This relatively nonselective distribution of drug formulations especially creates challenges for complex and difficult-to-treat diseases, such as cancer, viral diseases, and genetic diseases, for which conventional drug administration methods are unable to provide the requisite site specificity. Because of these constraints, high systemic doses are often required to provide the drug at the tissue target concentration, which increases the odds of adverse and off-target effects due to the dispersion of the drug to nontarget tissues (John, 2026). This is especially problematic for the treatment of cancer. Traditional cancer therapies suffer from treatment resistance and severe side effects, which highlights the importance of developing drug delivery systems that enable precise target localization of therapeutic agents. Beyond the problems of nonselective drug dispersion, traditional formulations have other constraints such as poor solubility, rapid

clearance, a narrow therapeutic index, an inability to adapt to dynamic changes in the pathological environment, and lack of pH- or redox-responsive drug release. These systems are also poorly optimized for chronic use due to frequent dosing requirements that reduce patient compliance. These limitations have brought about the prospect of designing, at the molecular and nanoscale, carrier systems that are more sophisticated and flexible than existing rigid and non-adaptive pharmaceutical formulations (Kowalski et al., 2018).

Precision drug delivery moves beyond the conventional “one-size-fits-all” model. Precision drug delivery systems aim to deliver the exact drug to the exact location, at the correct time and in the ideal dose. Achieving this spatiotemporal control, which entails the ability to release a drug at the optimal location and time, is one of the foundations of precision medicine. The objective of this control is to optimize the therapeutic efficacy of a drug while decreasing the potential for systemic adverse effects. In this framework, drug carriers must be more than the inert transport mechanisms of the drug; they must be “smart.” These systems must be able to sense and react to specific biological and/or external stimuli. Smart biomaterials represent a new frontier in controlled drug delivery systems for precision treatment of diseases (Hou and Yu, 2025). These materials must have the ability to respond to specific physiological conditions. Compared to previous generations of biomaterials, smart biomaterials must contain advanced systems that shift the paradigm of controlled drug delivery. These biomaterials are engineered to respond to a combination of internal and external stimuli. Smart biomaterials represent a versatile approach to respond to a multitude of different diseased states. These are especially useful for addressing the unique and complex microenvironments present in tumor tissues (Dutta et al., 2025). Smart biomaterials must be engineered with a combination of synthetic and biological materials. The addition of biological components to smart biomaterials has further advanced the field of smart biomaterials (Kowalski et al., 2018). In the past, fully synthetic polymers comprised the majority of smart biomaterials. Currently, smart biomaterials tend to focus integration with biological components, such as polysaccharides, proteins, peptides, and nucleic acids. These added biomolecules have superior biological compatibility and provide a biodegradation pathway. Furthermore, they contain high potential for intelligent design and biomimicry. Nanocarriers, such as polymers, are recognized for their nanoscale design. The provision of a variety of drug-loading packages that possess the ability to release on demand makes these carriers ideal tools for the highly targeted transport of small and large molecules (Hou and Yu, 2025). Progress in nanocarriers, in combination with hydrogels and bioresponsive polymers, revolutionizes delivery systems and provides superior opportunities for controlled release, targeting, and bioavailability. Ultimately, advanced drug (and biotech) delivery systems integrate the synergistic use of nanotechnology, materials science, and molecular biology in highly site-specific, on-demand, and variable kinetics drug delivery systems (Liu et al., 2026).

This review aims to comprehensively unify information regarding the integrated and systematic development of smart biomaterial systems for precision drug delivery systems. We focus primarily on the approaches to achieve (Vargason et al., 2021) targeted drug delivery to specific sites and (Park, 2014) the

controlled release of therapeutic agents. Some of the key mechanistic principles considered are the precision of drug delivery approaches to endosomal escape, modulation of the immune response, and controlled release mechanisms, among others. The purpose of this review is to (i) identify the principal classes of smart biomaterials and systems that include, but are not limited to, stimulus-modified polymers, lipid and polymer-based nanocarriers, hydrogels, and systems derived from biomolecules designed for precision drug delivery; (ii) outline the principal mechanisms of passive and active targeting that are designed to increase the accumulation of drug(s) at defined sites; (iii) describe the nature and extent of research on various stimuli (i.e., pH, oxidation/reduction, enzymatic, thermal, light, and magnetic) and their role in controlled, timely, and responsive release of drug(s); and (iv) provide a candid summary of the current barriers and challenges that limit the application of these technologies and describe the innovative approaches to facilitate their use in clinical practice. This review aims to draw attention toward the evolving use of computer-based and simulation technologies used to refine the design, prototyping, and manufacturing practice of smart biomaterials for drug delivery systems.

This narrative, integrative review relied on peer-reviewed literature available on PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Boolean operator combinations with the search terms “smart biomaterials,” “stimuli-responsive,” “precision/targeted drug delivery,” “controlled release,” “nanocarrier,” “nanoparticle,” “liposome,” “polymeric micelle,” “hydrogel,” “ligand-mediated targeting,” “EPR effect,” “artificial intelligence/machine learning drug delivery,” “digital twin,” “organ-on-chip,” and “nanotoxicity” were used to perform literature searches. Articles published from 2015 to 2026 were prioritized to identify contemporary literature; however, older literature were included to provide a historical context (e.g., original works on the EPR effect and the first controlled-release systems). Original and review articles published in English and focusing on smart biomaterials and/or the use of biomaterials for their precision delivery in clinical and preclinical studies were included. Articles published in nonreviewed journals, conference abstracts without complete datasets, and studies that were not in the scope of this review were excluded. Due to the nature of the field, an integrative approach was taken (as opposed to systematic, based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines), where study selection was based on mechanistic insight and clinical and representational relevance of various drug delivery platform classes.

For this review, we have arranged the different classes of materials, targeting strategies, computing tools, stimulus-responsive mechanisms, and advanced platforms around one principle: that they are all components toward the same goal of developing patient-adaptive therapeutic release systems that operate on a spatiotemporal basis. We take each of the technologies considered and place them along the precision-delivery continuum. They are to be understood not as technological advancements in isolation but as instrumental steps in the continuum of design relating to material choice, targeting, stimulus-triggered release, and the translation of these systems to a clinical setting.

2 Fundamentals of targeted drug delivery

2.1 Passive targeting mechanisms

Passive targeting happens when drug carriers accumulate in diseased areas based on the drug carrier's properties and the properties of the diseased tissues. In this case, drug carriers preferentially accumulate in diseased areas due to the absence of an active targeting element. The main phenomenon that occurs during passive targeting is the EPR effect (Ulbrich and Lamprecht, 2009). This effect is derived from the disorganized nature of tumor's blood and lymph vessels, and drug carriers in the form of nanoparticles extravasate into the tumor, thus increasing the desired concentration of the therapeutic agent at the tumor and, in turn, the efficacy of the therapeutic. Specific ligand–receptor interactions can be omitted thanks to the EPR effect. A considerable EPR effect is observed in larger nanocarriers such as liposomes and polymeric nanoparticles compared to smaller molecular structures (Hasan et al., 2024).

However, there are limitations to relying only on passive targeting. The EPR effect does not have consistent strength across different patients and tumor types. In cases where tumors have a high density of stromal tissue or poor blood vessels, the EPR effect may be severely compromised, leading to very low accumulation of nanoparticles. Though the EPR effect justified the emergence of the first generation of nanomedicines, many patients are heterogeneous, and subsequent clinical studies have given evidence of the limited efficacy of nanomedicines (Nakamura et al., 2016). Also, when nanocarriers rely on the EPR effect to accumulate in tumors, passive targeting is still unreliable because of many factors. These include the random distribution of nanocarriers in the tumor and poor drug permeability to tumor cells. It is because of these challenges that combined passive and active targeting strategies, including the active targeting strategies, are being developed. This is discussed below (Shi et al., 2023).

Passive accumulation is just the first stage of delivery, with its challenges outlining the next steps (Figure 1). Since EPR-centric delivery relies on abnormalities in the pathology of the vasculature, rather than the properties of the targeted cells, it places carriers near the diseased tissue regardless of whether the cells are malignant or healthy, and its intensity can greatly differ both between patients and among tumor types (Upponi and Torchilin, 2014). The main issue left unaddressed by accumulation is the selectivity of binding. Therefore, in order to overcome the issue of selective binding, active targeting entails the addition of molecular recognition motifs on the surface of the carriers. The following section will discuss this in greater detail, but for now, the two mechanisms should be viewed as complementary to one another as they are both necessary to achieve the end goal of targeted delivery systems (Muro, 2012).

A concern in the latest literature is that the EPR effect, primarily identified in rapidly developing rodent xenografts, is weaker and more variable in human tumors, which tend to grow slower and have more heterogeneous stroma and vasculature (Fenaroli et al., 2018). A widely referenced meta-analysis reported a median of around 0.7% of the injected dose of nanoparticles that reaches the solid tumor, showing the disparity of the EPR effect in preclinical scenarios when compared to the clinic. A major

concern is that the extent of EPR-mediated accumulation in tumors poorly correlates with the therapeutic effect. Accumulation near the tumor vasculature does not mean penetration and uptake by the tumor cells. The high interstitial fluid pressure and a dense extracellular matrix impede deep and uniform distribution of the therapeutic agent. Therefore, it has been suggested that the EPR effect should be considered a patient- and tumor-specific variable; for example, patient stratification by using companion imaging agents or nanoparticle diagnostics may be warranted for the rational use of EPR-dependent therapies (Chen Q. et al., 2023). In the latest literature, the EPR effect is described in even greater depth to determine whether the EPR effect is even the main transport mechanism. Much of the nanoparticle transport to tumors may be due to the active transendothelial pathways (Belyaev et al., 2025).

2.2 Active targeting approaches

Active targeting strategies begin with dealing with the major nonspecificity challenge of passive accumulation. This requires incorporating molecular recognition elements on the surface of drug carriers. These elements provide passive drug carriers with the ability to selectively bind to cell-surface employed markers. In active drug targeting, ligands such as small molecules, peptides, antibodies, antibody fragments, and aptamers are conjugated to the surfaces of nanocarriers (Muro, 2012). These nanocarriers can be liposomes and PMs, among others. This conjugation enables the targeted drug carrier to selectively bind to cell-surface receptors. This design aims to improve the limitations of passive drug targeting strategies that solely depend on the abnormal structuring of the diseased vasculature to where the nanocarrier can accumulate (Upponi and Torchilin, 2014).

Numerous active targeting strategies have been investigated in various disease areas. Traditional chemotherapeutics have high systemic toxicity, in part because they use poor targeting mechanisms. Ligand-modified neocarriers are a promising strategy for causing improved targeting and decreased toxicity in the design of novel nanodrug delivery systems. Many schemes for different targeting strategies have been developed. It should be noted that active targeting and passive targeting are not independent of each other and that most successful systems incorporate both strategies. For instance, the combination of active targeting through receptors with passive targeting through the EPR effect significantly enhances the accumulation of drug delivery systems at the diseased site compared to the use of each targeting strategy separately (Din et al., 2017). In dual-targeting systems, the nanoparticles are first allowed to accumulate within the tumor site through the EPR effect and then are directed to the specific tumor cells via surface ligands. These systems have demonstrated significant therapeutic improvements in multiple preclinical studies by maximizing drug delivery and reducing unwanted side effects in complex and heterogeneous tumor environments. Despite the significant advances in the field, the customization of ligand density and the stabilization of nanoparticles are ongoing and are crucial for the integration of passive and active targeting systems to be fully realized (Cheng et al., 2025). In Section 6, we provide an in-depth examination of the individual ligand classes discussed in this work, specifically focusing on antibodies, aptamers, peptides, receptor-specific systems, and cell-penetrating systems.

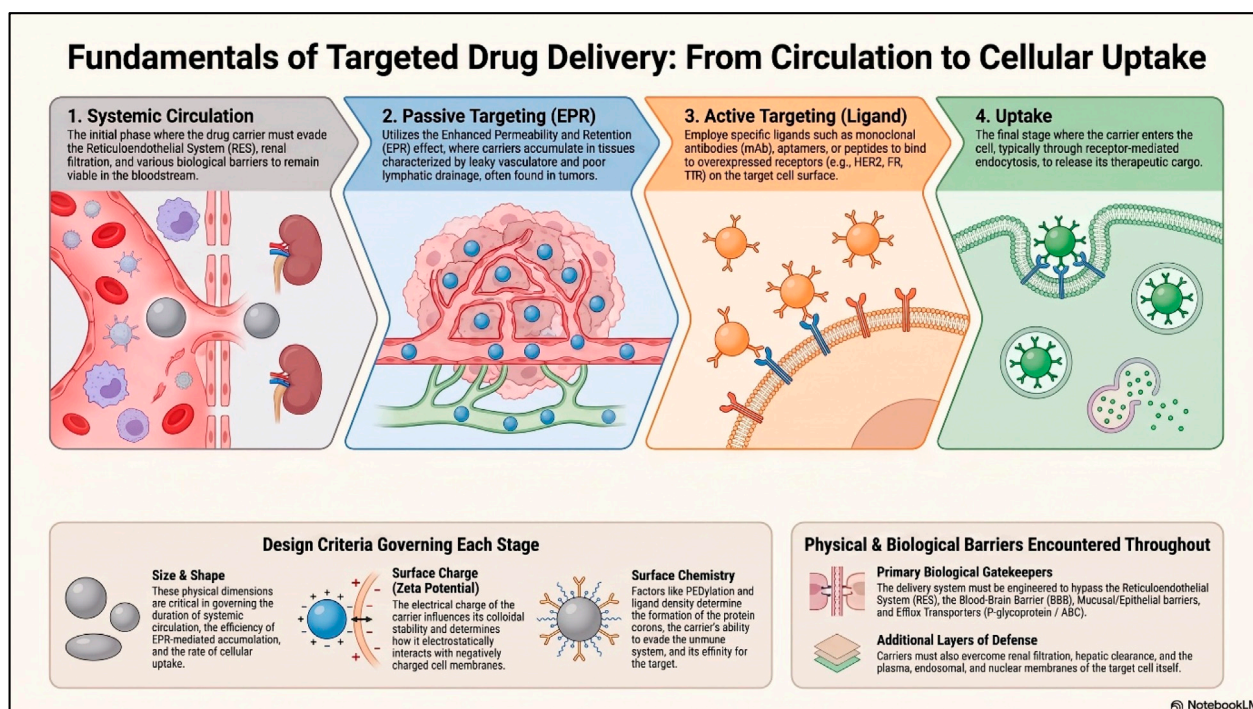


FIGURE 1

Fundamentals of targeted drug delivery, illustrating the sequential stages from systemic circulation through passive (EPR-mediated) and active (ligand-mediated) targeting to receptor-mediated cellular uptake, alongside the key design criteria and biological barriers governing each stage.

2.3 Physical and biological barriers

Even a well-targeted carrier must navigate a series of formidable physiological barriers between the site of administration and the intended target tissue, cell, or subcellular compartment. Following systemic administration, a drug or drug carrier must overcome barriers including cells of the reticuloendothelial system (RES) in organs such as the spleen and liver, renal filtration in the kidney, and biological membrane barriers such as the plasma membrane, the endosomal membrane, and the nuclear membrane of the target cell, with submicron-scale carriers helping evade physical barriers and RES uptake (Muzykantov and Muro, 2011). Indeed, the RES can recognize nanoparticles as a foreign material and engulf them during circulation, a major factor limiting the circulation time and biodistribution of many nanocarrier systems (Öztürk et al., 2024).

The blood–brain barrier (BBB) is highly obstructive for drug delivery to the central nervous system (CNS) because it is a natural defense that maintains CNS integrity. The BBB further complicates the development of therapeutic agents to treat CNS disorders. The majority of available drugs, both small molecules and biopharmaceuticals, fail to penetrate the brain. In addition to causing low drug effectiveness, the accumulation of drugs in other organs increases the adverse side effects of those drugs (Luo et al., 2025). Drug development for treatment of CNS-related disorders continues to be delayed and largely unsuccessful because of the significant restriction that the BBB poses. It is estimated that less than 5% of all tested small-molecule drugs gain access to the brain (Wu et al., 2023).

Mucosal and epithelial barriers form additional, route-specific challenges, especially for oral and intranasal delivery systems. Mucus and the extracellular matrix form a cross-linked mesh that retards the diffusion of drugs and carriers at the target site of the mesh, which worsens the problem of nonspecific drug delivery (McCright and Maisel, 2020). Nonspecific drug delivery exposes healthy organs to excessive concentrations of drugs and causes unwanted side effects. On the cellular and molecular level, efflux transporters represent an additional obstacle, especially for oral bioavailability and the penetration of drugs to the CNS. P-glycoprotein is an ATP-dependent efflux transport system that is located at the apical membrane of the intestinal epithelium and other epithelial and endothelial sites, and its function is to clear lipophilic drugs from within the cell back to the intestinal lumen (Prasher et al., 2022). Related ATP-binding cassette (ABC) efflux transporters are present along the gastrointestinal tract, the hepatobiliary tract, the renal tubules, and the BBB, and their overexpression is implicated in the phenomenon of multidrug resistance in cancer chemotherapy. Together, the RES, the BBB, mucosal barriers, and efflux transporters form a multilayered defense system that any precision delivery system must be designed to circumvent (Hunter and Hirst, 1997).

2.4 Biological determinants of carrier fate

A precision delivery carrier must navigate several biological challenges the instant that it enters circulation. These challenges all affect whether the carrier will reach the target in an active state. Within seconds of being injected, serum proteins form a dynamic

“protein corona” around the carrier (Wilhelm et al., 2016). The composition of this corona, rather than the engineered carrier surface, will define the carrier’s biological identity. The corona may also completely conceal targeting ligands, essentially tagging the carrier for recognition and clearance, and, as a result, may also shorten circulation time. For this reason, a surface that is rationally designed for a carrier may behave in a manner that is completely contrary to the behavior that it was designed to exhibit (Price et al., 2020). The resultant corona will be opsonized, and the carrier will be rapidly cleared by the mononuclear phagocyte system, specifically in the liver and spleen. This is a key reason that the efficiency of carrier delivery to tumors is disappointingly low. Stealth strategies, such as PEGylation, can reduce the clearance, but cannot prevent it completely, and have been complicated by anti-PEG immunity following repeated injections (Yunna et al., 2021).

Carriers that manage to survive circulation face more obstacles at the actual tissue target. The ECM forms a tough network that may trap carriers before they reach the target cells. In solid tumors, a desmoplastic stroma increases interstitial fluid pressure. This creates hostile transport and leads to an uneven and, at times, superficial distribution of carriers. Because of these transport and mechanical barriers, it is easy to see that passive carrier accumulation near tumor blood vessels will not lead to successful therapeutic agent uptake. These barriers are also responsible for the low efficiency of passive accumulation carriers in clinical applications. Along these lines, interpatient biological variability is another significant problem. Differences in immune systems, protein corona composition, matrix density, tumor vascular density, and receptor expression make it so that a carrier that is optimized for one patient population may behave unpredictably in another. This encourages the use of stratified biomarker systems, as detailed in the following sections, and emphasizes the challenge of patient-specific biology when designing delivery systems (Shin et al., 2026). Targeting mechanisms, biological barriers, and design criteria in targeted drug deliveries are summarized in Table 1.

2.5 Design criteria for precision delivery systems

Taking into account the targeting mechanisms and biological barriers outlined above, the rational design of precision drug delivery carriers demands that multiple physicochemical parameters be optimized, often simultaneously and precisely. In particular, properties such as their material composition, size and shape, surface charge, and core characteristics and surface modifications (e.g., PEGylation) can affect the behavior of drug delivery systems. These properties affect the systems’ drug release, interaction with phagocytic cells, circulation time, organ-specific accumulation, drug delivery, toxicity, and ultimately biological release (Kurul et al., 2025).

Particle size is a highly significant design parameter. Size has a strong influence on cellular uptake, drug loading capacity, and drug release as these characteristics are controlled by the surface-to-volume ratio of the nanocarrier. Size is also associated with biodistribution, blood circulation time, and tumor penetration. Therefore, design parameters that consider nanocarrier size and shape must also be considered in design strategies that involve cellular uptake, drug loading capacity, and drug release (Liu et al., 2012). Shape, like size, must also be considered if a design strategy is

targeted at increasing cellular uptake, drug loading, and release. For example, low-curvature spherical shapes undergo faster phagocytic internalization than other shapes. In the case of nanocarriers, it provides the basis for selecting ellipsoidal, cylindrical, discoidal, and worm-like shapes with smaller diameters and larger aspect ratios. Tumor accumulation may be improved, and premature clearance from the systemic circulation may be reduced by using these designs. A third important design parameter is surface charge (zeta potential). Positive charge may facilitate uptake by a negatively charged cell; in contrast, a negatively charged carrier may interact with a positively charged cellular surface with greater effectiveness (Blanco et al., 2015).

Therapeutic nanoparticle design requires tuning multiple factors, including the stability of the particle, drug-loading capacity, surface binding, and drug-targeting ligands. To facilitate cellular uptake and influence the colloidal properties of the nanoparticle, size and surface charge need to be balanced with surface chemistry. Although factors influencing cellular uptake can be designed and optimized, the lack of standard methodologies for and scale-up of these designs is a barrier to clinical use of therapeutic nanoparticles. Ligand orientation, surface charge density, PEGylation, and hydrophobicity can be systematically adjusted to optimize the protein corona and influence the kinetics of membrane penetration and adhesion for biomimetic nanoparticles (Kamaly et al., 2012). Molecular dynamics (MD) simulations and other computational design methodologies for bio-nanoparticle interfaces have become popular for creating nanoparticles with predictable therapeutic behavior. For an optimal therapeutic nanoparticle system that integrates functional properties, size, surface charge, and surface chemistry, the intended therapeutic target, and the barriers at the target site, the design principles of smart biomaterials can be customized and used. These design principles are a focus of research into therapeutic nanoparticles and biomaterials (Rodriguez-Cruz et al., 2025).

3 Biomaterials in modern drug delivery

The precision in delivery first depends on the carrier material. The platforms below are, therefore, analyzed based on how they enable or limit the realization of controlled release (Figure 2).

3.1 Natural biomaterials

Polysaccharides and proteins are widely used as carriers in modern drug delivery systems because drug delivery systems need to be biocompatible, and these biomaterials exhibit a high degree of biocompatibility and low immunogenicity and are biodegradable. These biomaterials have many different functional groups in their backbones and are natural in origin which makes them nontoxic and nonirritant. Because of the low cost and abundant availability of these biomaterials, they have the added beneficial effects of protecting drugs from the reticuloendothelial system; thus, biomacromolecules become stable, and their bioavailability is enhanced with the use of these natural biomaterials. Many of these biopolymers respond to different stimuli, making them smart and ideal candidates for carrier materials of a drug delivery system (Ngwuluka, 2018).

TABLE 1 Summary of targeting mechanisms, biological barriers, and design criteria in targeted drug delivery.

Category	Mechanism/component	Key features	Representative example(s)
Passive targeting	EPR	Exploits leaky tumor vasculature and poor lymphatic drainage; no ligand required; highly heterogeneous across tumor types/patients	PEGylated liposomal/polymeric nanocarriers accumulating in solid tumors
Active targeting	Ligand-functionalized nanocarriers	Surface-conjugated antibodies, aptamers, peptides, or small molecules bind overexpressed receptors; high cell-level specificity	Antibody-, folate-, and transferrin-conjugated nanoparticles
Biological barrier	Reticuloendothelial system (RES)	Recognizes and engulfs nanoparticles as a foreign material; limits circulation time and biodistribution	Hepatic and splenic macrophage uptake of unmodified nanocarriers
Biological barrier	Blood–brain barrier (BBB)	Restricts >95% of small-molecule drugs and nearly all biologics from CNS entry	Limits delivery for neurodegenerative disease therapeutics
Biological barrier	Mucosal/epithelial barriers	Cross-linked mucus mesh restricts diffusion; relevant for oral and intranasal delivery	Gastrointestinal mucus layer impeding oral nanocarrier absorption
Biological barrier	Efflux transporters (P-glycoprotein/ABC family)	ATP-dependent pumps clear lipophilic drugs from cells; contributes to multidrug resistance	P-gp at the intestinal epithelium and BBB
Design parameter	Particle size	Governs cellular uptake, circulation time, biodistribution, and tumor penetration via the surface-to-volume ratio	10–200 nm range typical for EPR-mediated accumulation
Design parameter	Particle shape	Spherical (low curvature) particles undergo faster phagocytic clearance than nonspherical ones	Ellipsoidal, cylindrical, discoidal, and worm-like carriers for reduced clearance
Design parameter	Surface charge (zeta potential)	Positively charged particles favor uptake by negatively charged cells and <i>vice versa</i>	Cationic vs. anionic nanoparticle formulations
Design parameter	Surface chemistry/PEGylation	Tunable ligand orientation, charge density, and hydrophobicity optimize protein corona and membrane interaction; supports computational (MD simulation) design	PEGylated “stealth” nanoparticles; MD-optimized bio-nano interfaces

3.1.1 Polysaccharides

Polysaccharides are advantageous drug delivery systems and vehicle constructions due to their availability, affordability, and innate biological correspondence. We look primarily to natural, polysaccharide-based systems because they offer protection to sensitive active agents with the added potential for site-specific controlled release and can be designed with the consideration of biocompatibility, nontoxicity, and the willingness to be biodegraded and integrated into natural systems (Miao et al., 2018). The repeating units of glycosidically bound, monosaccharides make up chains that can be digested by numerous enzymes and recyclable to many biopolymers. Because of their inherent low toxicity and immunogenicity, many polysaccharides and biopolymers can be digestibly designed for drug delivery systems and are highly beneficial applications in the field of biomedicine (Dhapte and Pokharkar, 2019).

Polysaccharides do not just provide structural support. Several have exciting intrinsic biological activities that enable their use in active targeting. For example, hyaluronic acid is appreciated for its binding to CD44, which is overexpressed in many cancer cells. This allows for the use of CD44-targeted anticancer drug delivery systems based on hyaluronic acid in the design of nanocarriers. Chitosan is an abundant cationic polysaccharide and excellent drug delivery scaffold due to its biodegradability and biocompatibility, in addition to its nontoxicity, nonimmunogenicity, and sterility (Llanes et al., 2020). Alginate is an anionic biopolymer derived from brown

seaweed that has made its way to countless pharmaceutical formulations due to its excellent biocompatibility and low toxicity and cost (Mbese et al., 2026). Chitosan and alginate, when combined as polyelectrolyte complexes, upon electrostatic interaction, address the shortcomings of alginate hydrogels, such as a lack of sufficient drug release and structural integrity. These hydrogels have found new applications in drug delivery due to their excellent release profile for targeting the specific site for drug delivery. Chitosan, hyaluronic acid, alginate, and gelatin hydrogels, due to their stimuli-responsiveness, have been used for localized drug delivery to the oral mucosa. They have a superior release profile compared to oral dosage forms (Hunter and Hirst, 1997).

3.1.2 Protein and peptides

Protein- and peptide-based carriers comprise another significant group of natural biomaterials. They are characterized by their modularity and precision, their biodegradability, and their potential for genetic engineering. Proteins, as biomolecules, also represent a safe, biocompatible, and fully degradable class of materials. This allows for a safer alternative to synthetic polymers. Among the proteins, gelatin, albumin, collagen, gliadin, and silk proteins can be employed to derive biomaterials that are stable in physiological conditions and allow controlled and sustained release of drugs (Varanko et al., 2020).

The performance of carriers and their cargo is dependent on the choice of the protein building block. Collagen-based peptides form

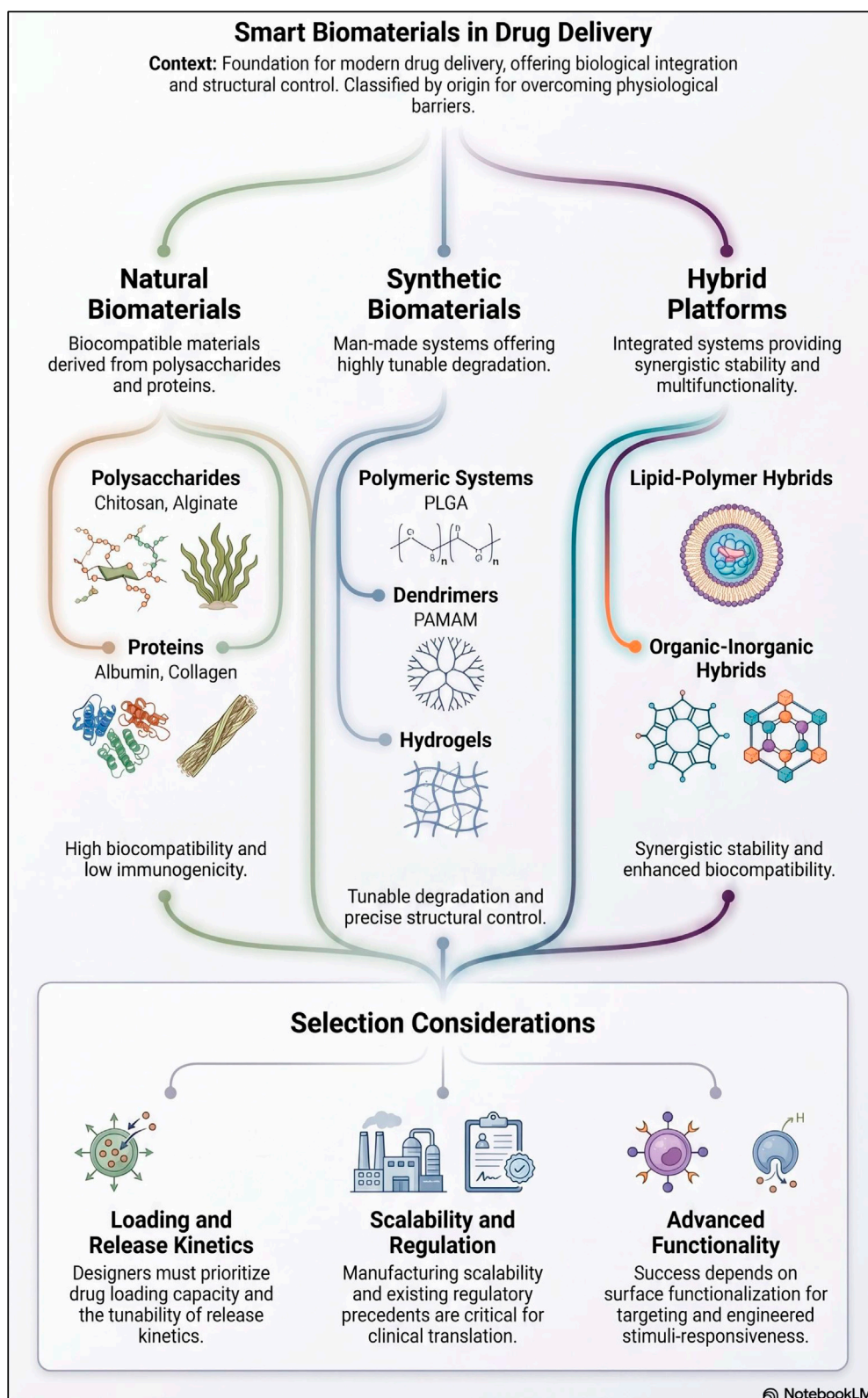


FIGURE 2

Classification of biomaterials used in modern drug delivery, spanning natural (polysaccharide- and protein/peptide-based), synthetic (polymeric, dendrimer, and hydrogel-based), and hybrid (lipid-polymer and organic-inorganic) platforms.

stable, slowly degrading gels. For faster degrading options, gelatin is employed. As a soluble drug carrier, albumin is widely used, while gliadin helps drug carriers breach the gastric mucosa for stomach-targeted delivery. For positively charged cargo, silk and keratin are advantageous (Ferraro et al., 2024). However, for nucleic acid therapeutics that are negatively charged, the use of those proteins is discouraged. For temperature-responsive delivery vehicles, elastin and collagen are favored. For pH sensitivity, silk is used. In addition, the choice of building blocks in the assembling of the hydrophobic or peptide can alter the structure of the nanoparticles, where the self-assembly can form a worm-like structure that is elongated and increases the binding affinity for receptors, while the spherical structure can remain (Rani et al., 2024).

This particular class has also been expanded by protein polymers that are genetically altered. Elastin-like polypeptides (ELPs) are biopolymers derived from natural elastin, are thermally responsive, and have a tunable lower critical solution temperature phase transition. This particular property has been utilized in drug delivery and tissue repair. As ELP nanoparticles self-assemble above a transition temperature that is determined by the amino acid sequence, the desired properties of the nanoparticles can be determined by designing the amino acid sequence (MacEwan and Chilkoti, 2014). This is illustrated in the case of the creation of amphiphilic ELP di-block copolymers, which form uniform micelles in which hydrophobic cores can contain cytotoxic payloads and where hydrophilic targeting ligands can be placed in the micelles' coronal shells. Hybrid protein systems that combine multiple natural motifs are very promising as well. Silk elastin-like protein polymers, for example, integrate both the compositional properties of silk and elastin, and hydrophobic drugs like doxorubicin, that exert anticancer effects, have been shown to elicit the self-assembly of these polymers into uniform micelles that are capable of pH-dependent release and, thus, lysosomal accumulation (Li et al., 2024).

3.2 Synthetic biomaterials

Since the 1970s, synthetic, biodegradable polyesters became the preferred option as drug delivery systems, and their acceptance by the biomedical community as adequate alternatives to natural materials has significantly increased. They can form a wide variety of nanostructures (e.g., nanofibers, nanoparticles, nanocapsules, nanogels, micelles, and dendrimers) that can be designed with very specific, required mechanical and physiochemical characteristics such as size, shape, surface charge, and surface chemistry. These design characteristics can be manipulated, permitting the use of the materials in a broad spectrum of biomedical applications and creating a highly flexible and robust platform (Cao et al., 2024). Biodegradable systems (e.g., polyesters), by virtue of their degradation mechanisms and byproducts, offer an improved therapeutic index and a lower side-effect profile. Systems based on such polymers facilitate prolonged delivery of a therapeutic agent to the target site, and the sustained release of drugs is achieved by a combination of methods that include diffusion and degradation of the polymer, as well as other mechanisms that are responsive to external stimuli. In addition, augmentation of other characteristics, such as increased cellular uptake and

improved design for target localization, can be achieved by nanoscale structural alterations to the polymers (Geszke-Moritz and Moritz, 2024).

3.2.1 Polymeric systems

The clinical versatility of poly(lactic-co-glycolic acid) (PLGA) is due in part to four-factor combinations. First, the lactide:glycolide ratio can be used to fine-tune PLGA's degradation rate, which can take place over weeks to months. Second, PLGA has a fully developed and documented Drug Master File and a well-established GMP supply chain, which can ease the development of new PLGA-containing products. Third, PLGA is capable of carrying both hydrophilic and hydrophobic therapeutic agents. Fourth, the hydrolytic degradation of PLGA yields lactic and glycolic acids which are used and cleared by the body (Jumadi et al., 2026). The strong combination of versatile properties allows PLGA to dominate systems of slow and controlled drug release, for example, leuprolide and goserelin implants. Many of these benefits PLGA offers also have known drawbacks. Arburg Plastic Freeforming (APF) in PLGA is especially known for its tri-phasic release, which includes an uncontrollable initial burst release, which is often greater than the therapeutic window. Additionally, the bulk-eroding PLGA matrices create a localized microclimate that is acidified and can lead to tissue acidosis and inflammation and can denature acid-labile peptide and protein therapeutics (Omidian and Wilson, 2025). Newer PLGA replacements have recently been developed but do not incorporate all of the benefits of PLGA, for example, surface-eroding polyanhydrides and poly(ortho esters), which confine degradation to a receding surface layer and achieve near-zero order release, but do not have PLGA's regulatory and research development track, and broad payload compatibility. Other systems such as PEGylation and PLA-PEG-PLA triblock systems ease PLGA's burst release effects and extend circulation, but at the price of ease of production (Sun et al., 2024). PLGA remains in use not because it is the best option, but because other polymers struggle to compete with the benefits provided by PLGA owing to experiences with production and regulation as well as clinical use. PLGA will likely not be displaced in the near future. It will instead be modified in the form of coatings to suppress the burst release of drugs, the addition of excipients to neutralize the microclimate buffer, and polymer blends to separate the degradation rate from the mechanical strength of the polymer (Sheffey et al., 2022). Synthetic biodegradable aliphatic polyesters like poly(lactic acid) (PLA) and PLGA are still modes of choice for controlled release owing to their customizable characteristics of biodegradability and an established track record for regulatory safety and compliance. As they are compatible with biological systems, they are of great significance in the development of drug delivery systems (Makadia and Siegel, 2011). The primary aim of sophisticated systems employing these polymers is the control of release to coincide with the repair of the body. In particular, PLGA-based hydrogels serve as a robust and flexible platform for the controlled release of macromolecules of varying size and types, from small molecules to proteins and nucleic acids, while their biocompatibility and adaptable degradation rates and broad drug loading capacity make them appropriate for use in many different therapeutic areas (Xia et al., 2014).

Copolymerization with poly (ethylene glycol) (PEG) is a crucial method to modify the *in vivo* characteristics of drug delivery systems. Temperature-sensitive copolymer hydrogels PLA-PEG-PLA and PLGA-PEG-PLGA maintain a liquid state at room temperature but form a soft gel at body temperature. These systems offer sustained and controlled release to maintain a steady concentration of the drug, unlike conventional systems, which offer rapid release with consequent rapid decline. In such ABA or BAB block copolymer systems, the hydrophobic segments of the polyester chains form crosslinks, while the hydrophilic PEG segments disperse the copolymer at low temperature (Strus and Sztark, 2025). As the temperature increases, the weakening of the hydrogen bonds and strengthening of the hydrophobic interactions result in sol–gel transition. After this transition, the drug is released from the polymer matrix by diffusion. This is followed by matrix hydrogel degradation. In addition, the incorporation of PLGA in PEG-based hydrogels improves overall system biocompatibility and stability. In this case, the number of the repeat units in the polyester segment is critical in controlling the rate of drug release and degradation of the system (Jabeen and Atif, 2024).

3.2.2 Dendrimers

Dendrimers have well-defined branched structures, leading to a precise control over size, surface groups, and functionalities. In particular, polyamidoamine (PAMAM) dendrimers raise concerns for chronic toxicity due to being retained in the liver and kidneys since they are nonbiodegradable. Dendrimers of poly-L-lysine (PLL) also are retained in the same organs but are degraded into monomers. However, surface modification can help address these issues. PAMAM and PLL dendrimers can be modified with PEG to neutralize their surface-positive charges to reduce cell lysis and acute toxicity (Alamos-Musre et al., 2025). The PEGylation of dendrimers also increases the hydrophilicity and promotes an EPR effect, leading to an accumulation in tumor tissues; hence, PEGylated dendrimers are excellent carriers of antitumor drugs. Bioavailability of PEGylated PLL dendrimers when injected is also very high (>90%). This high bioavailability is an important factor in improving patient compliance since it enables an easier method of administration (Samiraninezhad et al., 2023).

Dendrimers have been utilized in composite delivery systems to take advantage of disparate classes of materials. A hybrid PAMAM dendrimer hydrogel/PLGA nanoparticle system which uses partially cross-linked PAMAM dendritic polymer to chemically create mucosal adhesion and increase bonding interactions with the ocular surface was used to co-deliver a pair of anti-glaucoma drugs and was reported to sustain therapeutic concentrations *in vitro* for 28–35 days and exert a significant sustained intraocular-pressure-lowering effect for 4 days after a single drug application in a rabbit model (Guastaferrero et al., 2021a).

3.2.3 Hydrogels

Hydrogels, or three-dimensional polymer cross-link networks swollen with water, possess tunable mechanical properties and facilitate engineering biomaterials with adjustable elasticity, high water retention, and built-in stimuli responsiveness (Dhibar et al., 2023). These attributes make hydrogels a promising medium for

temporal and spatial delivery of therapeutics (Maier et al., 2024). Injectable hydrogels, owing to their excellent physical and chemical properties, have great potential in targeted therapies and regenerative medicine (Dhibar et al., 2025a). In particular, polymer systems with chitosan and hyaluronic acid having heat-responsive phase transition behavior are promising, especially in the realm of cancer and diabetes (Nájera-Maldonado et al., 2025; Guastaferrero et al., 2021b). This makes such technologies safe and appropriate for controlled drug delivery. Also, self-assembled nanogels naturally derived from chitosan, alginate, and hyaluronan can be used to design nanocarriers (Dhibar et al., 2025b). With minimal changes to their structure, these natural polysaccharides retain their physicochemical and biological properties (Bhattacharjee et al., 2026). Nanogels also feature amazing drug delivery capabilities thanks to the multiple ionic cross-linking, drug coordination, and drug loading sites that are provided by various functional groups (García-González et al., 2011).

3.3 Hybrid biomaterial platforms

Hybrid biomaterials consist of organic and inorganic components or lipids and polymers combined as nanosized structures. These have become prominent for combining the advantages and working around the challenges of different materials. Hybrid drug delivery systems aim to enhance the bioavailability and biocompatibility of the prescribed medications, customize the release kinetics of drugs, and assist in overcoming biological barriers and controlling the targeting, cellular uptake, and intracellular trafficking of the drugs. In addition to hybrid polysaccharides, hybrid systems have been proven to provide the beneficial properties of the different classes of organic/inorganic, lipid/inorganic, polymer/inorganic, and lipid/polymeric systems (Chambre et al., 2020).

Lipid-polymer hybrid nanoparticles (LPHNs) are a prime example of this method. Polymeric lipid hybrid nanoparticles display a core-shell structure wherein the polymeric core is encompassed by shells of lipids or lipid-PEG. This structure capitalizes on the physical stability and biocompatibility of both polymeric nanoparticles and liposomes and establishes these nanoparticles as promising advanced nanocarriers. These nanoparticles have shown great potential for multiple applications such as bioimaging and various therapeutic nanocarriers for anticancer therapies, vaccines, and genes (Gajbhiye et al., 2023). The incorporation of both polymer and lipid ingredients enables robust stability and flexibility for tunable release. Polymeric lipid hybrid nanoparticles are capable of forming a wide variety of therapeutic agents. These agents consist of both hydrophilic and hydrophobic species as well as proteins and nucleic acids. LPHNs are among the greater variety of nanotechnology-based products that have been commercialized and entered clinical studies. Also, liposomes, polymeric nanoparticles, albumin nanoparticles, and inorganic nanoparticles are included. Out of these various products, liposomes and polymeric nanoparticles are the most extensively studied (Varanko et al., 2020).

Organic–inorganic hybrids represent another major area of focus. An example is the development of hybrid nanoparticles

with a HA/PEG polymer shell and a core of nano-hydroxyapatite loaded with zoledronic acid. These nanoparticles are used for osteosarcoma therapy, and investigations of their properties show high drug loading, sustained release, and good biocompatibility and low cytotoxicity with good acceptance of the immune response both *in vitro* and *in vivo* (Xu et al., 2021). More generally, the hybrid nanoplateforms of cerasomes and silica-based mesoporous hybrids are becoming more important because of their improved porous characteristics, documented drug delivery, and flexibility to develop hybrid materials of advanced organizations of polymer and inorganic silicates, among others. These hybrid systems show how the careful selection and integration of natural and synthetic biomaterials can create carriers that are stable and biocompatible and can deliver many types of cargo, from small drug molecules to large proteins and nucleic acids, for tailored drug delivery systems (Chambre et al., 2020).

When studying these platforms together rather than in isolation, we see similar outcomes for various applications. Natural polymers have some intrinsic bioactivity and contain cell-instructive cues, but these polymers suffer from problems such as variability, poor mechanical strength, and immunogenicity. Synthetic polyesters provide better mechanical reliability and tunability but, in turn, sacrifice some of their inherent bioactivity. As a result, PLGA dominates FDA-approved controlled-release polymer systems, such as leuprolide and goserelin implants, despite the irritation of localized tissue acidosis associated with lactic/glycolic degradation. Hydrogels are mechanically soft and mimic the moisture content of biological systems but still allow rapid release of their contents. PLGA is a primary example of a polymer that addresses these problems, and of the three polymer systems, it well represents each of the primary problems that researchers are working to address. Natural and synthetic biomaterials are compared in Table 2.

4 Nanotechnology-driven drug delivery systems

While the previous section laid out the material substrate, how that substrate may be transformed in architecture at the nanoscale into a circulating carrier that can reach, and selectively unload at, the target site will be discussed here.

4.1 Liposomes

Liposomes are the most widely studied class of nanocarriers and the most advanced in the clinic. Due to their bilayer construction, liposomes possess several advantages over traditional drug delivery systems, including enhanced biocompatibility, biodegradability, and reduced toxicity (Figure 3). Compared to other systems, liposomes have improved sustained drug release and an elevated therapeutic index. With an aqueous core and a lipid-based bilayer, liposomes are also very advantageous in drug emerging technologies such as AI block-delivery systems because they can load both hydrophilic and hydrophobic drugs simultaneously. This makes them a highly favorable delivery system for targeted and controlled release of anticancer drugs, as well as other research areas (Nsairat et al., 2022).

Surface engineering has been central to optimizing the *in vivo* performance of liposomes. PEGylation, in which polyethylene glycol chains are grafted onto the liposome surface, is one of the most impactful modifications. So-called “stealth” liposomes, produced by PEG surface coating, can evade mononuclear phagocyte system (MPS) uptake and achieve half-lives more than three-fold greater than conventional liposomes; a study investigating PEGylation of cisplatin-loaded liposomes in bladder cancer mouse models demonstrated a 4.8-fold increase in drug efficacy and a 3.3-fold decrease in drug toxicity over non-PEGylated counterparts (Mohamed et al., 2019). As of 2023, 15 liposomal drug products have been approved by the FDA for indications spanning cancer treatment, vaccines, infections, and pain management, underscoring the translatability of this platform (Abughalia et al., 2025).

Going past passive and stealth methods, modern liposomal formulations show much more molecular variety. This includes liposomes that are long-circulating and PEGylated, liposomes that are functionalized by ligands, stimuli-responsive liposomes, and other advanced types, such as cell membrane-coated biomimetic nanocarriers. Each provides distinct physiological functions for liposomal drug delivery that target cancer (Azimizonuzi et al., 2025). There have been advances in the design of liposomal nanomedicines that aid in the targeted delivery of drugs to cancer cells in order to maximize the impact and minimize the collateral damage caused to healthy cells and tissues. This area of nanomedicine is rapidly evolving and offers many new opportunities for the treatment of cancer. Number of clinical approvals, possibilities for surface functionalization, and ability to stimulate responsive release all indicate that liposomes are a core nanocarrier system (Michael et al., 2026).

4.2 Polymeric nanoparticles

Due to their structural flexibility, design tunability, adaptability, and biocompatibility, polymeric nanoparticles (PNPs) are among the most widely researched classes of nanotechnology-based drug delivery systems. PNPs typically consist of PLGA, PEG, and PLA derivatives. PNPs have the advantage of tunable physicochemical properties; thus, through alteration of polymer composition and modularity, molecular mass, and the structure of the polymers, researchers can customize the size, surface charge, and the rate of drug release from the nanoparticles, among other properties. This allows for the design of nanoparticles in accordance to therapeutic needs (Robinson and Tiriveedhi, 2020).

PLGA is becoming a gold-standard polymeric carrier. It has particularly favorable degradation kinetics since it is a biodegradable and biocompatible copolymer. PLGA also offers anticancer agents many therapeutic benefits such as enhanced solubility, prolonged retention within the body, and the ability to be delivered in a targeted manner. PLGA has many key physicochemical characteristics that influence the degradation process and release kinetics. PLGA has been utilized to develop delivery carriers for small-molecule drugs, antibiotics, and antiviral drugs, as well as macromolecular drugs such as peptides and proteins to treat a variety of diseases including cancer and inflammation and other disorders associated with pain and the nervous system (Alsaab et al., 2022). The ability to deliver multiple agents has made PLGA

TABLE 2 Natural and synthetic biomaterials.

Biomaterial	Class	Structural basis	Degradation	Advantages	Limitations	Clinical status
Collagen	Natural	Fibrous structural protein	Enzymatic (collagenase)	Bioactive, cell-adhesive, and low immunogenicity	Batch variability and weak mechanics	Approved (tissue/wound)
Chitosan	Natural	Cationic polysaccharide	Enzymatic (lysozyme)	Mucoadhesive and antibacterial	pH-dependent solubility and variability	Approved excipient/preclinical
Alginate	Natural	Anionic polysaccharide	Ionic/slow dissolution	Mild gelation and cell encapsulation	Weak mechanics and uncontrolled degradation	Approved (dressings)
Hyaluronic acid	Natural	Glycosaminoglycan	Enzymatic (hyaluronidase)	CD44 targeting and biocompatible	Rapid degradation and cost	Approved (dermal/ophthalmic)
PLGA	Synthetic	Polyester copolymer	Hydrolytic (tunable, wks–mos)	FDA-approved and tunable release	Acidic byproducts and burst release	Approved (depots)
PLA/PCL	Synthetic	Polyesters	Hydrolytic (slow)	Sustained release and mechanical strength	Slow/hydrophobic and low hydrophilic loading	Approved (implants/sutures)
PEG	Synthetic	Hydrophilic polyether	Non-degradable (low-MW renal)	Stealth and prolonged circulation	Anti-PEG immunity and nondegradable	Approved (coatings/conjugates)
PEI	Synthetic	Cationic polymer	Nondegradable	Efficient nucleic-acid condensation	Charge-related cytotoxicity	Preclinical
Lipid–polymer hybrid (LPHN)	Hybrid	Polymer core/lipid shell	Hydrolytic (core)	Combines polymer stability with lipid biocompatibility; high loading	Complex multi-step manufacture; scale-up difficulty	Preclinical/early clinical
Organic–inorganic hybrid (e.g., HA-PEG/nano-HAP)	Hybrid	Polymer shell/inorganic core	Polymer shell/inorganic core	Tunable release; imaging/theranostic capacity	Reproducibility and characterization complexity	Preclinical

popular for combination therapy. Folate-conjugated PLGA nanoparticles that are taken up by cancer cells with an overabundance of the folate receptor also help in overcoming the systemic toxicity of anticancer drugs and improve the delivery of these drugs to the cancer cells. PLGA nanoparticles with a PEG coating are not taken up by the reticuloendothelial or the phagocyte systems, so they are also used in cancer therapy (Darusman et al., 2025).

4.3 Solid lipid nanoparticles

In the 1990s, innovative drug delivery methods sought to remedy the shortcomings associated with emulsion and polymer systems. They aimed to integrate the benefits of both systems into one method. SLNs are revolutionary in the drug delivery field. SLNs aid novel drug design because *in vitro* and *in vivo* biocompatibility and biodegradability are guaranteed with the constituents of the formulation. SLNs afford more benefits contingent on the route of administration and the physicochemical nature of the drug (Parveen et al., 2023). They are more flexible than PNP systems because of ease of manufacturability, lipophilic drug load capacity, pharmaceutical stability, and

controlled and sustained release of both hydrophilic and hydrophobic drugs. Production takes place in aqueous media and eliminates harmful, volatile organic solvents, making SLNs biofriendly and less hazardous than their polymeric counterparts. The use of SLNs affords an easier route to gain the approval of regulatory bodies than other delivery systems (Samiraninezhad et al., 2023).

SLNs, which are lipid-based formulations, use different methods to maximize drug absorption such as enhancing the solubility capacity and membrane permeability and defeating the P-glycoprotein efflux transport system and Cyp450 enzymatic activity. They also help increase the lymphatic transport rate and chylomicron biosynthesis. Even though SLNs have many benefits, they have a poorer drug loading capacity compared to others (Pandey et al., 2021). This is because of the highly organized lipid crystalline matrix of SLNs. Drugs that are added are highly ordered between the fatty acid chains, between the lipid layers of the SLN, and in the chinks of the crystals. Because of this highly organized crystal lattice, an increase in the lipid mixture is required. This poor capacity has fueled research into the next generation of lipid nanocarriers, nanostructured lipid carriers (NLCs) (Guastaferrero et al., 2021a).

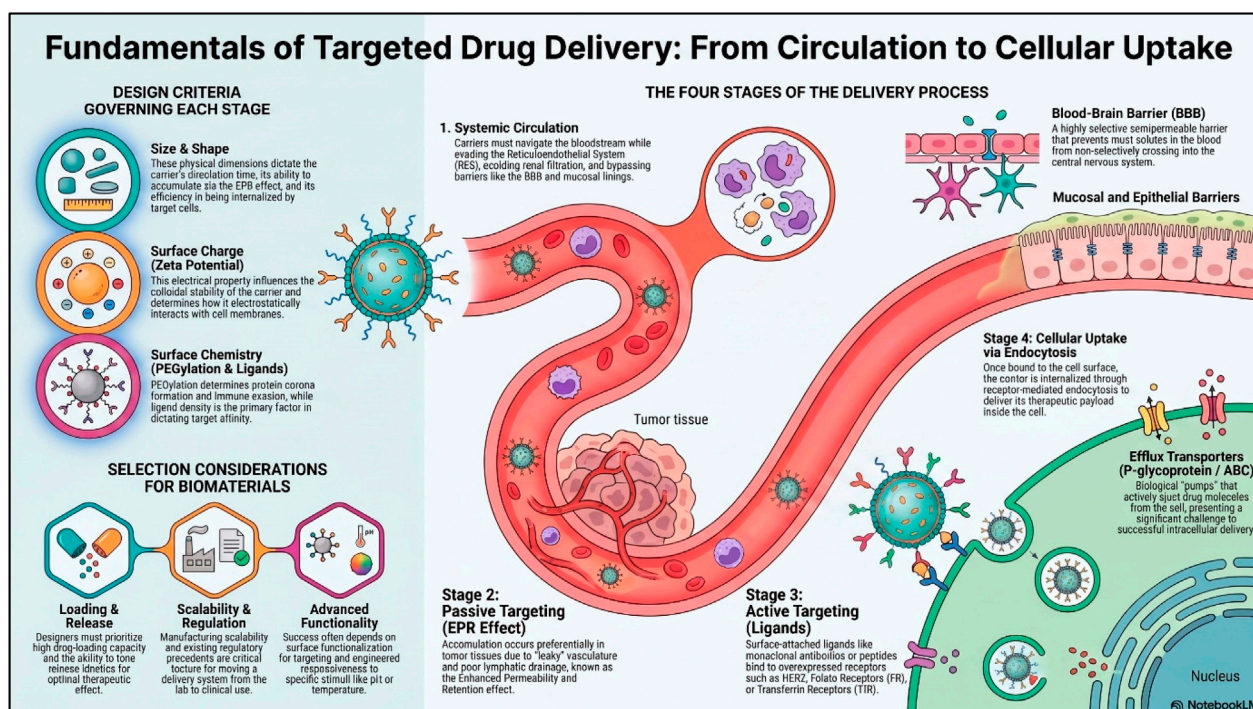


FIGURE 3

Structural overview of major nanotechnology-driven drug delivery carrier architectures, including liposomes, PNPs, solid lipid nanoparticles/nanostructured lipid carriers, micelles, metal-based nanocarriers, nanoemulsions, carbon-based nanocarriers, and dendrimer/hybrid lipid-polymer systems.

4.4 Nanostructured lipid carriers

NLCs are a type of second-generation lipid nanoparticles (LNPs). They were developed to enhance drug loading and alleviate drug expulsion issues of traditional SLNs. The differences in NLCs and SLNs is the liquid lipid and solid lipid inclusion, respectively. This combination creates a more disordered and less crystalline matrix and allows for a higher drug loading and release, while also improving storage stability (Elmowafy and Al-Sanea, 2021). This prevents unwanted drug expulsion during shelf life. Even with SLNs being better at drug stability, liposomal delivery, and also being more biocompatible than some PNPs, NLCs have even more advantages because of their imperfect lipid matrix structure (Patra et al., 2024; Farasati Far et al., 2022).

Both SLNs and NLCs boost drug solubility and permeability, thus increasing bioavailability and extending drug residence time in the body, while combining low toxicity and the ability for selective delivery. These systems allow for the delivery of drugs at defined dosages to specific tissues while decreasing leakage and binding to nontarget tissues. SLNs and NLCs are associated with high drug bioavailability and ease of incorporation of both hydrophobic and hydrophilic drugs, with the potential for industrial-scale production. NLCs have higher drug accommodation capacity than SLNs owing to the controlled structural disorder in the lipid matrix of NLCs. These features make NLCs a very attractive lipid nanocarrier platform for production of formulations of highly lipophilic and poorly aqueous soluble drugs that are also labile in storage (Xia et al., 2014; Khatibi et al., 2024).

4.5 Nanoemulsions

Nanoemulsions (NEs) have significant potential in the realm of biopharmaceuticals. An NE is a biphasic liquid system that is heterogeneous on the nano-scale (with dimensions on the order of 20–500 nm). High-quality NEs are remarkable owing to their ability to remain physically transparent and kinetically stable. Because of their large surface area and small droplet size, they are ready to digest, physically stable, and have an increased bioavailability (Preeti et al., 2023). This allows them to be suitable vehicles for a large number of active substances. Because of their small droplet size, they provide a large area of interface for a drug to be dissolved in a liquid, therefore improving the solubility of a drug as well as its bioavailability. Additionally, NEs provide a lot of versatility and can be used to encapsulate a wide range of both hydrophilic and hydrophobic drugs and support a number of different drug forms. NEs can be formulated in the form of gels, creams, foams, aerosols, and sprays and can be used for oral as well as other routes of drug delivery (Al-Sahlawi et al., 2024; Wang et al., 2023).

NEs enhance drug delivery systems in several ways. Research suggests that NEs help poorly water-soluble drugs/bioactive compounds that are incorporated in a polymeric system show improved bioavailability, stability, and absorption, especially when they are in the form of hydrogel-NE, polymeric-coated systems and improved emulsifier systems. Nanoemulgels, used in drug delivery systems, are formulations of NEs incorporated in a gel base that enhance the delivery and availability through the skin of lipophilic anti-inflammatory agents. They use gel bases to provide

the necessary firmness and spreadability of the topical application, while the surfactant/cosurfactant systems and the NE provide the permeability of the skin. This increased efficiency of NEs is coupled with the challenge of thermodynamic instability and large-scale production. These challenges continue to create a motivation for new formulations in the use of NEs (Chen et al., 2024; Gatto et al., 2024).

4.6 Micelles

PMs consist of self-assembled nanostructures and are made from amphiphilic block copolymers. Such structures house an inner core around which drug loading is facilitated and which is assembled from hydrophobic segments that are encircled by a hydrophilic corona. The polymeric micelle is sterically stabilized via hydrophilic corona about an aqueous environment (Hwang et al., 2020). Compared to the other types of nanocarriers, PMs are very useful because of a number of advantages that include improved solubility of challenging drug candidates, better engagement, and accumulation at the cancer site with a higher level of chemotherapy drug passive sensitization and an extended circulation time. Considering the advantages in targeted delivery to specific tissues and extended blood circulation, various types of PMs are under evaluation in their capacity as nanomedicines to treat cancer in the clinics and in preclinical studies (Varanko et al., 2020; Nitta and Numata, 2013).

An example of biological exploitation of stimuli is found in micellar systems. Cancer therapy delivery using PMs that respond to factors in the tumor microenvironment (TME) is an attractive proposition during the development of cancer-delivering therapeutics. The design, synthesis, or modification of environmentally responsive polymeric materials, being of significant importance to the controlled delivery of therapeutics, incorporates strategically the pH, the concentration of reactive oxygen species, and the activity of enzymes in the TME (Negut and Bita, 2023). An example of the former systems is found in micellar systems responsive to pH, and these systems have been shown to be highly effective in bringing together two classes of chemotherapy: doxorubicin and docetaxel. It has been shown that micelles delivering doxorubicin and docetaxel work in an acidic environment of pH 5.5, and, in that environment, the docetaxel- and doxorubicin-loaded micelles show the largest synergistic cytotoxic effect, resulting in the targeting of multiple pathways in breast cancer cells susceptible to the development of resistance. In addition to the standard delivery of cytotoxic agents, PMs have found use in cancer immunotherapy. Here, the focus of responsive and targeted systems is the modification of the TME. In this case, the targets are the limitations of highly responsive immunotherapeutics (Milligan et al., 2022; Guo et al., 2023).

4.7 Metal-based nanocarriers

Metal-based nanocarriers utilize the exceptional properties of metals to integrate therapeutic and diagnostic (theranostic) applications thanks to their modular physicochemical, optical, and magnetic properties. There are increasing safety concerns regarding the use of metal nanoparticles in drug delivery systems. However, the physicochemical properties of metals, including their

high surface-to-volume ratios, tunable surfaces, and their ability to cross biological barriers, facilitate the use of metal nanoparticles in targeted drug delivery systems and theranostics (Manuja et al., 2021). Gold, silver, iron oxide, zinc oxide, and platinum nanoparticles can be used in targeted drug delivery systems. There are additional size-dependent properties of most metal nanoparticles that can be used in the sustained and controlled release of drugs. These properties have allowed researchers to consider metal nanoparticles as alternatives to traditional drug delivery systems, especially because they can be easily synthesized with a low dispersal index, are biocompatible, and nontoxic. Metal nanoparticles also offer easy and versatile surface functionalization (Makadia and Siegel, 2011; Visan and Negut, 2024).

Noble metals, especially gold, have aroused some interest among researchers due to their potential cancer theranostics. AuNPs have proven to be an excellent cancer theranostic platform due to their tunable size and excellent optical properties that can be exploited for *in vivo* imaging while their high surface area-to-volume ratio can provide conjugation of therapeutics and targeting moieties. Their shape and surface properties invoke an important role in impacting their behavior and interactions within biological systems; uptake by cells, distribution in the body, and toxicity. Superparamagnetic iron oxide nanoparticles (SPIONs) provide an empty space (Fernandes, 2024). In cancer, SPIONs have provided significant clinical utility in providing an intratumoral magnetic hyperthermia to achieve temperatures of 42°–48.5 °C for hyperthermia treatment and provide a median overall survival of 13.4 months in patients with relapsed glioblastoma. Iron oxide nanoparticles have provided a significant contrast in MRI for diagnosis, a significant role in the delivery of therapeutics and a treatment agent for hyperthermia with a promising result and an opportunity for further improvement from nanocomposite theranostics. It is the unique and disparate properties of some metallic nanomaterials, e.g., gold and iron oxide, that allow the development of advanced platforms for targeted delivery, controlled release and theranostics of its kind (Gusmão and Tedesco, 2022; Bikiaris et al., 2025).

4.8 Carbon-based nanocarriers

An emerging class of drug delivery systems includes diverse carbon nanomaterials like carbon nanotubes (CNTs), graphene and graphene oxide, carbon dots (CDs), graphene quantum dots (GQDs), nanodiamonds, and fullerenes. Carbon-based nanomaterials have considerable versatility, and the unique characteristics of carbon nanomaterials can be seen in carbon nanodots, graphene, CNTs, mesoporous carbon, and nanodiamonds. They have a high drug-loading capacity, and when considered for drug delivery applications in cancer therapy, they exhibit strong promise owing to their enhanced biocompatibility and lower levels of immunogenicity when compared to other polymeric or lipid-based nanomaterials (Mohanty et al., 2022).

CNTs are maybe the most renowned carbon-based nanocarriers, and their beneficial properties make them promising drug delivery vehicles. CNTs show great promise as nanocarriers compared to other nanocarrier transport systems because they have a high payload capacity, a large surface area, continuous and controlled release, and the ability to target release. CNTs can either be

categorized as single-walled (SWNT) or multiwalled (MWCNT) based on how many graphene layers are present (Debnath and Srivastava, 2021). As a result of their extraordinary mechanical, electronic, and physiochemical characteristics, CNTs have triggered remarkable interest in the areas of imaging, drug delivery, and combination therapies for cancer. In addition to those properties, CNTs are also able to penetrate biological membranes, allowing them to circumvent cellular barriers and obtain access to cytoplasmic and nuclear domains. Because of these properties and characteristics, CNTs can be useful for the delivery of anticancer drugs in a targeted system in order to increase the ability of the drugs to act and also to decrease the negative side effects that the drugs have on the other non-cancerous (and, therefore, healthy) cells (Mukherjee et al., 2019; Okafor et al., 2025).

Carbon-based nanostructures exhibit excellent mechanical, electrical, and thermal properties to enable drug delivery, targeting, and imaging and offer multifunctional theranostic applications. Carbon quantum dots and graphene quantum dots improve photoluminescent carbon-based drug delivery. Natural carbon-based graphene quantum dots, as nanocarriers for drug and gene delivery in cancer treatment, have great potential, but further study to reduce cytotoxicity and improve scaling in addition to precise bandgap engineering and uniform size and shape will help better enable their use in clinical settings (Qureshi et al., 2024). Inorganic, carbon-based nanoparticles are stable and versatile with a great range of physicochemical and mechanical properties that can be enhanced by optical properties that are also tunable through modification with ligands for enhanced targeting, thus being favored for use in bio-imaging and drug delivery in pulmonary, ocular, wound healing, and antibacterial therapies. Though non-graphene carbon-based nanocarriers remain less advanced in terms of clinical usage than lipid-based and polymer-based delivery systems, the impressive properties of carbon-based nanocarriers and their delivery systems remain limited to non-usage, for which long-term studies on biodegradability, controlled functionalization, and potential toxicity of nonfunctionalized products are warranted (Sivadasan et al., 2021; Kashapov et al., 2021).

When compared with one another, these carrier classes show a clear translational hierarchy. Clinical translation has favored lipid-based systems. For example, from Doxil and Onpattro to the LNPs used in mRNA vaccines, GRAS lipid systems have had successful chemistry, large scale manufacturing, and clinical acceptability. Lipid based systems have continued to dominate, despite the storage and clearance challenges they present. Doxil, Onpattro, and LNPs for mRNA vaccines are prime examples. In contrast, SLNs were largely displaced in favor of NLCs, due to the storage issues that caused drug expulsion from SLNs. Lipid systems, despite the challenges they present to the system, have had significant clinical success. PMs have high solubility and dispersion for hydrophobic compounds but are also subject to leakage of the drug and dissociation below the Critical Micelle Concentration (CMC). Expanding the carrier landscape, metallic and carbon-based systems also face similar challenges of undegradability and unsolved long-term toxicity that also ultimately limit their applications to the preclinical space, though these systems are also known for their high therapeutic

and diagnostic multifunctionality. Nanotechnology-enabled drug delivery systems are summarized in Table 3.

The comparative summary of major biomaterial/nanocarrier platforms is summarized in Table 4.

5 Stimuli-responsive and intelligent drug delivery systems

A smart drug delivery system should remain passive while circulating the body. These systems only release their drug payload when triggered by a specific stimulus. The TME is a system in itself and consists of several entities (such as blood vessels and immune cells) with complex interactions. These entities of the TME also contribute to the progression of cancer. The elements of the TME include a combination of hypoxia and its acidity. The TME also has a range of reactive oxygen species (ROS) and varying concentrations of different enzymes (Younas et al., 2025). These characteristics of TMEs can be used in the design of specialized nanodrug delivery systems. The next sections discuss some pH, redox, and some enzyme factors, which represent endogenous or systemic stimuli, and heat, light, sound, and magnetism, which represent exogenous or external stimuli. Stimuli responsibility of the delivery system also determines the payload and its carrier. The carrier and payload are delivered to the same location, an example of the precision dimension of delivery systems. Spatial targeting is also a dimension of delivery systems, but it cannot be compared to precision targeting (Babos et al., 2018). Stimuli-responsive systems (trigger → mechanism → representative system) are summarized in Table 5.

5.1 pH-responsive systems

pH gradients are at the forefront of most of the stimuli used by smart drug delivery systems. This can be attributed to the knowledge regarding the differences in the pH levels between tumor and healthy tissues and tumor and healthy tissues and blood. It is known that the Warburg effect causes tumor cells to produce both lactate and hydrogen ions. As a consequence, the pH of the TME becomes more acidic (pH 6.5) (Liu Y. et al., 2025). In light of this, pH-sensitive nanocarriers respond to the needs of precise tumor therapies by passively accumulating at sites of higher acidity and actively releasing encapsulated therapeutics. The pH of tumor cells is below 6.0, whereas that of regular tissue is approximately 7.4. These differences form the backbone of the conception of numerous diseased cell targeting systems. pH-sensitive drug delivery systems are designed to remain stable at physiological pH but release drugs specifically at the tumor environment, thus enhancing the efficacy of the treatment while reducing the adverse impact on healthy tissues (Ghazi et al., 2025; Wang L. et al., 2025).

The pH gradient that exists in the extracellular TME also extends into the intracellular environments, further increasing the flexibility of pH selectivity. The pH levels in the extracellular TME drop as you move into the cytoplasm and then into the intracellular organelles, such as endosomes (pH 5.5) and lysosomes (pH < 5.5). Together with the abnormal

TABLE 3 Comparative overview of major nanotechnology-driven drug delivery carriers.

Nanocarrier type	Structural basis	Key advantages	Key limitations	Representative application
Liposomes	Phospholipid bilayer vesicle with an aqueous core	Loads both hydrophilic and hydrophobic drugs; PEGylation enables long circulation (“stealth”); 15+ FDA-approved products	Physical/chemical instability on storage; potential complement activation	Doxil (PEGylated liposomal doxorubicin)
Polymeric nanoparticles	PLGA/PLA/PEG polymer matrix	Tunable degradation kinetics; co-delivery of multiple agents; ligand conjugation (e.g., folate)	Burst release in some formulations; scale-up reproducibility	PLGA nanoparticles for sustained anticancer drug release
Solid lipid nanoparticles (SLNs)	Solid crystalline lipid core	Water-based production avoiding organic solvents; biocompatible; easy scale-up	Limited drug loading due to a highly ordered crystal lattice	Lipophilic drug delivery via oral/parenteral routes
Nanostructured lipid carriers (NLCs)	Mixed solid + liquid lipid (disordered matrix)	Higher drug loading than SLNs; reduced drug expulsion on storage	More complex formulation than SLNs	Improved storage-stable lipophilic drug carriers
Nanoemulsions	Oil-in-water or water-in-oil biphasic system (20–500 nm)	Enhances solubility/bioavailability of poorly soluble drugs; versatile dosage forms (gel, cream, and spray)	Thermodynamic instability; scale-up challenges	Oral and topical delivery of lipophilic actives
Micelles	Amphiphilic block copolymer self-assembly (core-corona)	Solubilizes hydrophobic drugs; tumor accumulation; stimuli-responsive variants	Drug leakage prior to the target site; relatively low drug loading	Genexol-PM (paclitaxel polymeric micelle)
Metal-based nanocarriers	Gold, iron oxide (SPION), silver, and platinum cores	Theranostic capability (imaging + therapy); magnetic hyperthermia; tunable optical properties	Long-term clearance/toxicity concerns; cost	SPIONs for MRI contrast and hyperthermia
Carbon-based nanocarriers	Carbon nanotubes, graphene, and carbon/graphene quantum dots	High drug-loading capacity; membrane penetration; imaging/theranostic potential	Limited clinical translation; biodegradability and toxicity concerns	CNT-mediated anticancer drug delivery

pH gradients, the design of nanocarriers has the potential for pH-responsive controlled release of therapeutic agents for cancer treatment (Pérez-Herrero and Fernández-Medarde, 2021). This can be realized by pH-responsive controlled release mechanisms and various gatekeeping strategies, which incorporate polyelectrolyte coatings, supramolecular nanovalves, pH-sensitive linkers, and acid-decomposable inorganic materials. The breadth of pH-responsive chemistry and the reactive bonds that have been employed in these systems include boronic acid/ester dynamic linkages. Boronic esters, for example, create amphiphilic networks that self-assemble into stable nanoparticles that exhibit excellent drug encapsulation and delivery in a triggered manner. These nanoparticles show a strong pH response and high anticancer activity with low systemic toxicity, both *in vitro* and *in vivo*. The separation of healthy and tumor cells based on pH also offers a highly versatile design for pH response in drug delivery systems for precision oncology. This includes systems based on PNPs, micelles, liposomes, NLCs, dendrimers, SLNs, and NEs (Osorio et al., 2024; Singh et al., 2025).

5.2 Temperature-responsive systems

Temperature-responsive drug delivery systems utilize the phase-transition of thermoresponsive polymers for controlled drug release, triggered by either mild hyperthermia naturally present in cancerous cells or heat that is applied from an external source. A more advanced version of polymer-based thermosensitive systems is based on the controlled, reversible solubility transition of the thermosensitive polymer in the presence of water, which can be controlled by the polymer's LCST and UCST (Amin et al., 2022). The most studied temperature-responsive polymer for drug delivery systems is Poly (N-isopropylacrylamide) (PNIPAM), which has an LCST of approximately 32 °C. This temperature is of special interest in drug delivery system research as it is very close to the temperature of the human body and room temperature. When the temperature is lower than the LCST of PNIPAM, the polymer is soluble and easily swells in water; however, if the temperature is higher than the LCST, then the polymer drastically collapses by becoming hydrophobic and expelling water. The fact that PNIPAM is very thermosensitive, as well as biocompatible, makes it an excellent candidate polymer for

TABLE 4 Comparative summary of major biomaterial/nanocarrier platforms.

Platform	Composition/structural basis	Targeting strategy	Stimuli responsiveness	Advantages	Limitations	Clinical status
Liposomes	Phospholipid bilayer vesicles ($\pm$ cholesterol, $\pm$ PEG)	Passive (EPR); active via surface ligands/antibodies	Engineerable (thermo- and pH-sensitive)	Biocompatible; carry hydrophilic and hydrophobic drugs; clinically proven	Storage stability; RES clearance; CARPA with PEG	Approved (Doxil and AmBisome)
Lipid nanoparticles (LNP)	Ionizable lipid + helper lipid + cholesterol + PEG-lipid	Passive; hepatocyte tropism (ApoE); tunable	pH-responsive ionizable lipids (endosomal escape)	Highly effective nucleic-acid delivery; scalable	Cold-chain; immunogenicity; mostly liver-restricted	Approved (Onpattro; COVID mRNA vaccines)
Solid lipid NPs/NLC	Solid lipid core (SLN); solid + liquid lipid blend (NLC)	Passive; surface-modifiable	Limited intrinsic	Physical stability; controlled release; scalable	SLN drug expulsion on storage; low loading	Preclinical/topical products
Polymeric NPs (PLGA)	Biodegradable polyester matrix	Passive; ligand-conjugated for active	Engineerable (pH and enzyme)	Tunable degradation; sustained release; regulatory precedent	Acidic degradation byproducts; burst release	Approved depots (e.g., leuprolide)
Polymeric micelles	Self-assembled amphiphilic block copolymers	Passive; active via ligands	pH-/redox-responsive designs	Solubilize hydrophobic drugs; small size	Premature leakage; dissociation below CMC	Approved (Genexol-PM, S. Korea); trials (NK105)
Dendrimers	Hyperbranched, monodisperse polymers	Surface groups for ligand conjugation	pH-responsive designs	Precise architecture; multivalency; high loading	Cationic-surface toxicity; cost	Preclinical/early clinical
Metal and inorganic (Au, silica, and iron oxide)	Metallic/metal-oxide/silica cores	Surface-functionalizable	Light (plasmonic); magnetic (iron oxide)	Theranostic/imaging multifunctionality; tunable	Non-biodegradable; long-term accumulation/toxicity	Mostly preclinical; some imaging agents approved
Carbon-based (CNT and graphene)	sp ² carbon nanostructures	Surface-functionalizable	NIR photothermal	High surface area/loading; photothermal capacity	Biodegradability and long-term toxicity unresolved	Preclinical
Hydrogels	Crosslinked hydrophilic polymer networks	Local/implantable; passive	Highly responsive (pH, temperature, and enzyme)	Tissue-mimetic; high water content; local sustained release	Burst release; mechanical fragility	Approved (local depot products)

encapsulated drug delivery systems (Vikal et al., 2025; Chatzidaki and Mitsou, 2025).

Combinations of additional monomers allow for modifying the LCST in PNIPAM-based systems that meet the demands of specific applications which are above the physiological temperatures of 37 °C. pNIPAm-based polymer nanoparticles undergo LCST phase transitions of shrink and swell. This, in turn, changes their hydrophilicity/hydrophobicity and the nanoparticles' affinity for their cargo. Paclitaxel, for example, an anticancer drug of low molecular weight, can be embedded in the hydrophilically swollen polymer matrix of the nanoparticles and be completely released when the temperature of the system is increased above the LCST (Amin et al., 2022). The system can be designed such that the LCST of the polymer matrix is at the desired temperature by optimizing the other incorporated monomers that have functional groups. In addition to the thermoresponsive systems, other inorganic nanomaterials have been incorporated to make dual

theranostic systems. Among all the hard metallic nanoparticles, AuNPs are the most incorporated with thermoresponsive polymer shells. This is due to the polymer shells collapsing and therefore triggering drug release when gold plasmonic nanoparticles are heated through light and are made to undergo localized surface plasmon resonance. Similarly, the combination of the magnetocaloric effect and the thermosensitivity of PNIPAM provides the possibility of drug release from polymer systems that is completely controlled by a magnetic field (Chatzidaki and Mitsou, 2025).

5.3 Redox-responsive systems

Use of redox-responsive drug delivery systems results in considerable differences in redox potential between TMEs and healthy tissue and particularly a significant increase in intracellular glutathione (GSH) of cancer cells. This method

TABLE 5 Stimuli-responsive systems.

Stimulus	Type	Trigger mechanism	Representative system	Clinical status
pH	Endogenous	Protonation of ionizable groups; acid-labile bond cleavage	pH-sensitive liposomes and ionizable LNPs	LNPs approved; others preclinical
Redox (GSH)	Endogenous	Disulfide cleavage by high intracellular glutathione	Disulfide-crosslinked micelles/NPs	Preclinical
Enzyme	Endogenous	Cleavage by overexpressed enzymes (MMPs and esterases)	MMP-cleavable peptide carriers	Preclinical
Temperature	Endo/ exogenous	Phase transition of thermosensitive lipids/ polymers	Thermosensitive liposomes (ThermoDox)	Phase III (endpoint not met)
Light/NIR	Exogenous	Photothermal/photochemical activation	Gold nanoparticles and photosensitizers	Preclinical/early clinical
Magnetic	Exogenous	Field-guided localization and heating	Iron oxide nanoparticles	Imaging agents approved; therapy preclinical
Ultrasound	Exogenous	Cavitation/acoustic release	Microbubbles and acoustically triggered carriers	Early clinical

provides a more selective and triggered release. A benefit of nanocarriers in antitumor therapy is their ability to control the release of the drug in space and time. GSH and disulfide bonds in the TME provide the basis, and a high concentration of GSH in the TME provides the basis and serves as an example of an exchange reaction in which the release of the drug is facilitated by its binding to disulfide carriers (Liu Y. et al., 2025).

Aside from acting as a release trigger, GSH depletion can be applied therapeutically. Continued GSH depletion can be utilized through redox-manipulating nanocarriers in the tumor microenvironment (TME) to increase oxidative stress, heightening the impact of reactive oxygen species (ROS)-mediated cancer therapies. While GSH depletion can be coupled with the inhibition of glutathione peroxidase 4 (GPX4) and the oligomerization of DLAT, it can also promote tumor cell sensitivity via the initiation of ferroptosis and cuproptosis. Numerous redox-sensitive frameworks have been utilized in the design of nanocarriers (Zhan et al., 2026). Examples of redox-responsive nanocarriers that can be classified according to the functional groups that they feature are GSH-responsive disulfides, ditellurides, and multivalent metal ions; ROS-responsive thioketals, arylboronic esters, aminoacrylates, and bilirubin; as well as GSH/ROS dual-responsive dicarbonyl thioethers and diselenides. As an example, the use of redox-disulfide hyaluronic acid-based nanoparticles was able to achieve CD44 receptor-mediated active targeting and facilitated intracellular drug release in a GSH-responsive manner. This shows an example of how both active targeting and stimulus-response release could be combined into one system (Jacob et al., 2024; Tapponi et al., 2025).

5.4 Enzyme-responsive systems

Drug delivery systems that respond to enzymes take advantage of certain enzymes that are overexpressed in specific tissues. These include the most notable examples of matrix metalloproteinases (MMPs), phospholipases, cathepsins, and glycosidases. These are found in the TME. These systems are able to selectively target the unmasking, activation, or release of therapeutic payloads with very

high and precise spatiotemporal targeting. Enzyme-responsive smart nanoparticles are able to interact under mild conditions with the internal enzymes of the nanoparticle, and with high efficiency, they destruct any of the nanoparticle's components. These include the hydrophobic core, the cleavable linker, the hydrophilic corona, and even the targeting ligand. Destruction of these components can result in either targeted drug delivery or the release of the drug in a controlled manner (Ribeiro et al., 2026).

Enzyme-responsive design and MMPs have gone hand in hand over the years. Enzyme-responsive nanoparticles are an ingenious use of the TME. This includes MMPs and phospholipase A2. These nanoparticles are designed with enzyme-cleavable linkers or coatings, that in the presence of these enzymes are able to release their cargo, which increases the specificity to the tumor and decreases the off-target effect. MMP-responsive mesoporous silica nanoparticles, for example, are systemically built, in that capping mesoporous silica with a collagen layer traps the cisplatin in normal physiological conditions, but MMP-2 in the TME will cleave the capping collagen and release the drug in a biocompatible manner in lung cancer cell lines (Srivastava, 2025). The MMP-responsive mechanism is also seen in the structure of cell-penetrating nanoparticles. Tri-block mPEG-peptide-PCL nanoparticles with the MMP-2-cleavable peptide sequence, GPLGIAGQ, are stable during circulation and are then cleaved in MMP-2-overexpressing cancer tissues to expose the cell-penetrating peptide, r9. This design also employs PEGylation to improve stability and extend the *in vivo* retention time. Enzyme-responsive nanocarriers designed to transport RNA have expanded this concept even further. Protease, nuclease, MMP, cathepsin, and glycosidase-sensitive natural nanocarriers utilize an enzyme-sensitive mechanism to achieve a biocompatible, site-targeting transport of siRNA, miRNA, and mRNA (Ryu et al., 2019).

5.5 Light-triggered drug release

One of the methods that offers the most precise controllability is a light-triggered drug delivery system. It presents a technique of

external stimulus via drug release focusing light on a particular tissue area, with exceptional spatiotemporal resolution on drug release. Recent designs of smart, photoactivated nanomaterials, as well as most of the systems developed in the field, take advantage of the ability of light to control the release of drugs in specific points/cells/tissues with ultra-high spatiotemporal resolution. Mechanisms such as photocleavage, photoisomerization, photopolymerization, photosensitization, photothermal phenomena, and photorearrangement are involved, which allow systems to be triggered by ultraviolet to visible to near-infrared (NIR) light (Throat and Bhattacharya, 2024).

Previously, researchers studied UV–visible light systems. However, the shallow tissue penetration of UV and visible wavelengths resulted in a shift to NIR systems. Drug delivery systems that respond to UV–visible light suffer from shallow tissue penetration and phototoxicity. As a solution to this problem, systems that are responsive to NIR light and employ mechanisms of photothermal, photodynamic, and photoconversion processes achieve remote trigger of drug release to animal tumors. Photodynamic therapy (PDT) is one of those mechanisms. In PDT, a light-activated photosensitizer generates ROS to induce cell death (Chen et al., 2020). Photodynamic nanodrugs consist of photosensitizers and nanocarriers, which provide the means to deliver photosensitizers and ROS to diseased cells upon light exposure. Because of this, the approach is highly selective with a high degree of safety. In contrast, photothermal therapy (PTT) provides a means to activate nanocarriers that convert NIR light to heat to assist in further cell death. There have been NIR light-activated strategies that employ a thermal-labile azo bond and that, upon NIR light irradiation, solve the “PEG dilemma” by removing the PEG corona and exposing cRGD, a targeting ligand, to increase intracellular and intratumoral delivery and help improve photothermal-chemotherapy. Synergistic use of PTT and PDT in the same nanoplatform is highly effective, especially when coupled with organic photothermal agents that yield a photothermal conversion efficiency exceeding 88%, enabling complete tumor destruction with a single, brief NIR laser exposure (El Sadda, 2026; Yang and Sun, 2022).

5.6 Ultrasound-mediated delivery

Ultrasound-mediated drug delivery utilizes the mechanical and thermal characteristics of sound waves to facilitate the release of therapeutic compounds in a noninvasive manner. This technique is versatile, cost-effective, and noninvasive, providing significant spatial and temporal control over the release of therapeutic compounds (Bouakaz and Escoffre, 2024). The interaction between ultrasound and nanocarriers employs mechanical and thermal characteristics of ultrasound, including tissue cavitation, sonoporation, and temporary disruption of cellular membranes, to facilitate the penetration of compounds across tissue barriers and can induce cell death. Research employing the interactions of nanocarriers and ultrasound in a variety of tissues *in vitro* and *in vivo*, including the skeletal muscle, cardiac tissue, kidney tissue, smooth muscle, and tumor tissue, has shown the immense potential versatility of this technique in multiple organ systems (Cao et al., 2023).

Ultrasound-mediated drug delivery systems distinguish between high-intensity and low-intensity approaches. High-intensity and low-intensity ultrasound systems have also played a critical role in the development of nanoparticle drug delivery systems that use temperature-sensitive nanocarriers. Pulsed high-intensity focused ultrasound (pHIFU), where ultrasound is emitted in short bursts in the microsecond-to-millisecond time scales and at high acoustic pressures, is primarily a mechanical method and is used to activate drug carriers in the focus of an ultrasound beam (Yang et al., 2023). Drug delivery systems have been developed using both microbubbles and nanodroplet carriers that are responsive to ultrasound. Nanocarriers based on perfluorocarbon nanodroplets have relatively low toxicity and high efficacy. In contrast, gold nanoparticles that are loaded with doxorubicin are formed into a nanocarrier system that uses low-intensity, pulsed ultrasound to heat the medium to near the hyperthermia range (41 °C–44 °C), and drug release may be prompted by both thermal and non-thermal processes. Multi-physics mathematical models are being developed to aid in drug release, transport, and delivery. These models will help optimize the systems designed for clinical use (Sabit et al., 2025; Vaghasiya et al., 2020).

5.7 Magnetic field-guided delivery

Magnetic field-directed drug delivery systems utilize the unique magnetic properties of iron oxide nanoparticles, particularly SPIONs, to perform targeted, remote, and noninvasive drug delivery to specific sites in tissues using external magnetic fields. Considering the variety of inorganic nanomaterials, magnetic nanoparticles (MNPs) have been predominantly used for targeting tumors. Due to their exceptional magnetic characteristics, biocompatibility, low toxicity, and easy degradation, SPIONs that consist of cores of magnetite (Fe₃O₄) or maghemite (Fe₂O₃) with polymer or silica shells on the surface have been of great interest. MNPs have various benefits, including magnetic field-directed site specificity, controlled and triggered drug release, and improved imaging contrast with magnetic resonance imaging, which make them inherently theranostic platforms (Meng et al., 2023; Li and Xu, 2025).

SPIONs produce localized heat when exposed to an alternating magnetic field (AMF), allowing SPIONs to be used for magnetic hyperthermia even outside the context of drug delivery. Hypothetically, exposing an AMF to magnetic nanoparticles would cause them to generate heat above the requisite hyperthermia treatment temperature of 42 °C via Néel and Brown relaxation. In the presence of an AMF, SPIONs would then be used as hyperthermic agents. To treat the deficiencies of bare MNPs such as their low chemical and physical stability, LNPs and liposomes, in particular, have been used to improve their stability and allow them to be used to transport cancer therapeutics (Souiade et al., 2023). SPIONs are fabricated as an MNP core with an iron oxide and an organic coating, which can be fatty acids, polysaccharides, or polymers, to increase their stability in the column and their magnetic properties; by using an external magnetic field, the accumulation of SPIONs can be controlled; both SPIONs and MNPs, in general, are biocompatible. Many systems have integrated a combination of magnetic targeting and additional stimuli-responsive features. The use of PAM-coated pH-responsive

drug delivery SPIONs allowed for size control to be maintained at 60 nm–100 nm, with an 8.5% drug release at pH 7.4 and a 14.3% release at pH 6.5, and aAMF was applied to increase the drug release to 17.5% along with a dual-targeting strategy that integrated magnetic targeting and antibody conjugation to achieve an 8-fold increase in cellular uptake over nontargeted systems. Usually, systems for magnetic field-guided delivery stand out for their theranostic versatility. These systems integrated precision oncology as MRI contrast agents, drug carriers, and hyperthermia mediators (Ma et al., 2025; Geng et al., 2023; Guo et al., 2018).

6 Ligand-mediated precision targeting

This section examines the spatial dimension of precision. It discusses the molecular recognition that transforms passive accumulation into selective delivery. Stimuli-responsive release mechanisms and EPR effect-based passive targeting are impressive strategies, but they have limitations, in that they do not respond to tumor heterogeneity or subpopulation heterogeneity. The limitation of passive targeting is circumvented when drug carriers are equipped with molecular recognition elements like antibodies, aptamers, peptides, or small molecules which are decorated to drug carriers. Active targeting involves selective recognition and binding to tumor markers with drug carriers decorated with ligands. Over the years, research has established that drug carriers decorated with ligands that bind tumor markers have been useful in targeting a variety of cancers due to the variety of tumor markers that are present in different cancer types. In this review, we describe the major targeting ligands and their use in ensuring precision drug delivery (Sivadasan et al., 2021).

6.1 Antibody-based targeting

Because of their high receptor specificity and affinity as well as their endocytosis pathways, monoclonal antibodies (mAbs) are the best-studied targeting ligands for cancer delivery among all clinically used targeting ligands. mAbs enable selective cancer drug delivery systems. Chemotherapy can be targeted more effectively through two main methods. Chemotherapeutics can be passively accumulated within tumors using the EPR effect. Chemotherapeutic nanoparticles can also be designed for active targeting through their surfaces being decorated with tumor-homing ligands. These can be peptides, aptamers, oligonucleotides, and mAbs. mAbs have been most studied for specific cancer biomarker recognition and have been shown to treat a variety of cancers with greater specificity. Antibody-conjugated nanoparticle (ACNP) systems that utilize mAbs and nanoparticles permit the delivery of high amounts of chemotherapeutic agents directly to tumors (Despanie, 2016).

Two primary antibody-based delivery systems are antibody-drug conjugates (ADCs) and ACPNs. Combining small, lethal payloads and mAbs linked by a stable bond, ADCs provide a targeted, lethal therapeutic for cancer; as of 2023, there are 13 FDA-approved ADCs for several solid and blood cancers, showing the development of ADCs. In comparison to ADCs, ACPNs provide greater payload volume, release control and/or

trigger and reduced systemic volume and increased tumor uptake (Dixit et al., 2025). In precision oncology, especially breast cancer, ACPNs and ADCs are focused on target cell-associated antigens to mitigate off-target toxicity and drug resistance and aid ADC and ACPN development; TROP-2, HER2, HER3, and LIV-1 are common examples. There is growing interest in the use of liposomes with antibodies; by mimicking cell membranes, liposomes improve encapsulated pharmaceuticals and provide greater physicochemical properties. Multitarget antibodies also expand the systems. A nanoparticle-based system with dual mAbs targeting CD47 and PD-L1 used to inhibit two non-small-cell lung cancer immune pathways also illustrates the research into drug resistance and immune escape targeting pathways and the ability of multi-antigen recognition combined systems (Varanko et al., 2020).

6.2 Aptamer-based targeting

Aptamers, which are short, single-stranded DNA or RNA selected by the *in vitro* process of Systematic Evolution of Ligands by Exponential enrichment (SELEX), have become an excellent alternative to antibodies for ligand targeting of nanoparticles in drug delivery systems. Aptamers are single-stranded oligonucleotides (20–80 nucleotides) with three-dimensional shapes that are specific for their targets. Aptamers are SELEX derivatives that are highly modified for their pharmacology, affinity, specificity, and therapeutic half-life. They can even be directly synthesized as anticancer agents to inhibit the growth of tumor cells or indirectly as delivery systems to deliver anticancer agents to the tumor cells in order to limit the cytotoxicity to the normal, healthy tissues (Jumadi et al., 2026).

There are notable practical differences between aptamers and mAbs. The desirable characteristics of aptamers, in addition to their small size, are high affinity and specificity for their targets, low immunogenicity, cost-effectiveness, and stability, making them suitable and ideal candidates as specific ligands for the active targeting of cancer therapy nanoparticles. Aptamer-nanoparticle systems provide a flexible targeting platform for the delivery of therapeutic agents, as well as diagnostic tools, due to the positive effects of the enhanced uptake at the cellular level and the EPR effect. Computational and experimental research on the interactions between aptamers and nanoparticles has also provided valuable insights to improve the efficacy of therapy and reduce undesirable side effects. This research has produced advanced systems that integrate aptamers with stimulus-responsive materials (Hassibian et al., 2025). These integrated systems form a synergistic combination of aptamers coupled with gold, silica and carbon nanomaterials, for the delivery of therapeutic agents in a controlled, precise, and spatiotemporally directed manner. Responding to the conditions of the TME, such systems also incorporate nanoparticles that utilize aptamer recognition to facilitate triggered release. In prostate cancer, multifunctional PLGA-PEG nanoparticles conjugated with the cell-SELEX-selected Wy5a aptamer and designed to target PC-3 CRPC cells exemplify the potential of aptamer-targeted nanotechnology for advanced therapeutic delivery and diagnostic applications (Visan and Negut, 2024; Yang et al., 2012).

6.3 Peptide-mediated targeting

Because of their small size and versatility, low immunogenicity, ease of synthesis, and ability to bind to numerous steps in the tumor targeting cascade, tumor-homing and tumor-penetrating peptides have become popular candidates. By using homing peptides or antibodies, affinity targeting approaches exploit molecular recognition to direct carriers to tumor-associated receptors or biomarkers, minimizing off-target reaction and achieving maximal therapeutic and delivery efficiency. This enhances the selectivity and efficacy of the therapeutic. However, despite ongoing research in early clinical exposure, the penetration of nanoparticles to the tumor remains a significant obstacle (Mohanty et al., 2022).

The most studied tumor-targeting peptide family is the RGD (Arg-Gly-Asp) motif family, which target the integrins that are overexpressed on the tumor neovascular tissues. Integrins $\alpha\beta3$, $\alpha\beta5$, and $\alpha5\beta1$ can be found in the endothelial cells of newly formed blood vessels that are involved in tumor angiogenesis. There are many RGD-based amino acid sequence designs that allow the selective targeting of these integrins. *In vitro* studies showed that osteosarcoma models treated with doxorubicin-loaded polymeric micelles conjugated with RGD peptides showed better specificity and greater cytotoxicity. A more sophisticated peptide, the internalizing RGD (iRGD), provides an additional function that is more than just targeting on the surface (Lorenzoni et al., 2025). The iRGD peptide consists of an RGD motif, which serves as the drug cargo delivery system to the integrins of $\alpha\beta3/\alpha\beta5$. Furthermore, after proteolytic cleavage of the CDGR sequence, iRGD exposes a C-end Rule (CendR) motif that binds to neuropilin-1 (NRP-1), triggering NRP-1-mediated endocytosis in both endothelial and tumor cells. The dual-receptor system of iRGD provides improved access to the tumor vasculature and drug delivery. The advantage of iRGD is that, instead of conjugating iRGD to the targeted nanoparticles, iRGD can be administered with the nontargeted nanoparticles. In this scenario, iRGD binds the tumor vasculature and activates the CendR pathway to improve the TME permeability. This, in turn, allows nontargeted nanoparticles to cross the tumor vascular endothelium and penetrate the tumor tissue via a mechanism of transcytosis vesicle formation stimulated by proteolytic cleavage for tumor specificity. Preliminary data from a phase 1 clinical trial (the CEND trial) of patients with stage 4 pancreatic ductal adenocarcinoma indicate that the tumor-penetrating peptide iRGD may be twice as effective as the standard treatment of gemcitabine and nab-paclitaxel and would not increase the adverse side effects of the combination therapy (Mohanty et al., 2022; Okafor et al., 2025).

6.4 Receptor-specific drug delivery

It is common for cancer cells to have more cell surface receptors as compared to normal cells. Receptor-specific targeting takes advantage of that feature. Using nanocarriers, drugs can be targeted to specific cancer cells as the nanocarriers can be modified to include different ligands. Following receptor-mediated endocytosis, the drug is then delivered to the cancer cell. It has been shown that the overabundance of cell surface receptors is associated with cellular uptake of ligands conjugated

to nanocarriers. Additionally, it has been shown that targeted, functionalized nanoparticles enable better delivery to cells and better drug action in comparison to untargeted drugs and nanoparticles (Kashapov et al., 2021).

In this context, folate receptor (FR) targeting is also well positioned. The folate receptor is a hallmark of many cancer cell types and has been used to develop targeted drug delivery systems. Targeted nanocarriers and small-molecule–drug conjugates that utilize the cellular folate receptor have been developed with different chemistries and different mechanical characteristics. These systems can have unique characteristics that give individual advantages for precise drug delivery. As a targeting ligand, folic acid has practical advantages of high availability, low cost, and low immunogenicity, with the added benefit of no immune response in clinical use (Rana and Bhatnagar, 2021). This allows for the potential of FR-targeted drug delivery systems to cancer cell types in order to increase the potency of a given drug, while decreasing the side effects. Another high-priority target is the transferrin receptor (TfR). Transferrin is a glycoprotein found in blood and binds the transferrin receptor to carry out cell-mediated endocytosis of iron. Malignant cells have a greater requirement for iron and consequently have a greater expression of the TfR, with expression levels being up to 100 times that of normal cells. Thus, hemostat TfR is a good target for drug delivery systems designed to access tumors. The epidermal growth factor receptor (EGFR) is a 170-kDa transmembrane glycoprotein that binds the epidermal growth factor (EGF) and is overexpressed in aggressive tumors. Transferrin-conjugated niosomes that deliver doxorubicin to EGFR-positive breast cancer cells achieve a significantly higher cell death than free doxorubicin at the same dose. In an effort to address inter- and intra-tumor heterogeneity, the use of dual receptors has been studied. For example, simultaneous use of transferrin and folic acid as dual targeting ligands on MNPs improves the targeting and the chemo-thermal therapeutic efficiency of cancer cells. This surpasses single-receptor targeting (Mukherjee et al., 2019; AlSawaftah et al., 2021).

6.5 Cell-penetrating peptides

Cell-penetrating peptides (CPPs) are short peptides which are often fewer than 30 amino acids and able to cross membranes and deliver cargo. This cargo can include small and large molecules like drugs and even nanoparticles. The research on CPPs can be traced back to 1988 due to the publication of two separate HIV research groups. In both studies, it was found that HIV-1's transcription trans-activator (the Tat protein) could cross biological membranes (Tripathi et al., 2018). In 1991, a similar finding was discovered for the *Drosophila* Antennapedia homeodomain. This homeodomain could also be found in neuronal cells. From these studies, the first protein transduction domain was discovered in 1994. It was a 16-mer penetratin peptide derived from the third helix of the Antennapedia homeodomain. Tat-derived CPPs are typically driven by the peptide GRKKRRQRRR, which has a net charge of +8e; penetratin has a net charge of +7e; and polyarginine Rⁿ, where n is generally 7–9, carries a charge of +n. Moreover, transport and a variety of hybrid peptides are also included in this toolkit for membrane transduction (Al-Sahlawi et al., 2024).

The ways in which CPPs move across cell membranes is still being studied, with some evidence of both endocytosis and translocation. A number of CPPs induce membrane ruffling and macropinosome formation. This method is not as specific toward the cargo but is favorable in delivering several cargoes simultaneously and is exploited by CPPs that need to deliver materials to a high number of cells. There are a large number of potential applications for CPPs. They have been of use in pharmacology, particularly in the case of oral delivery of insulin and other peptide antibiotics. For example, Tat insulin conjugates travel through the Caco-2 cell monolayer with a high degree of permeability (approximately 700% greater) in relation to unconjugated insulin. CPPs are used in systems of immunotherapy in clinical research (Ruseska and Zimmer, 2020). An example of this is PGN-EDO51, which is an oligonucleotide antisense CPP used to skip a dystrophy exon of Duchenne's muscular dystrophy, which has been shown to successfully produce dystrophin in a clinical phase 1 study of healthy individuals, and nomlabofusp, involved in a clinical phase 1 study of Friedreich's ataxia. The use of CPPs with nanoparticles further increases this delivery method. The combined modification of nanoparticles with CPPs leads to significant improvements in their use for the diagnosis and treatment of cancer. For example, cell membrane CPP-conjugated trimagnetic nanoparticles for targeted magnetic hyperthermia of prostate cancer. When combined, CPPs help bind extracellular targeting with intracellular drug action. They help overcome endosomal escape and cytoplasmic delivery issues that affect most antibody and receptor-mediated drug delivery systems (Reardon et al., 2017). Major ligand classes used in active ligand-mediated precision drug targeting details are summarized in Table 6.

From a direct comparison of classes, it is apparent that ligand targeting is associated with the cost of specificity. Antibodies produce the highest targeting and bonding capability. Unfortunately, the large size (~150 kDa) of antibodies limits their access to deep tissues, and their fully murine variants carry the highest immunological cost. Progression from murine to chimeric, humanized, and fully human antibodies reduces the immunological cost, but the burden remains in the complementarity-determining regions, so humanization is an imprecise solution to the problem (Harding et al., 2010). Aptamers are at the other end of the trade-off, being small, chemically synthesized, and highly non-immunogenic. Unfortunately, shearing of aptamers by nucleases and costs of synthetic scalability limit their use (Fu and Xiang, 2020). Peptides are smaller and cheaper than aptamers, but they are highly susceptible to proteolytic cleavage and have an even lower binding affinity. There are further limitations with ligand density. Although increasing surface ligands enhances recognition, it leads to an increase in opsonization and clearance, and the protein corona discussed in Section 11.1 can completely conceal conjugated ligands. This explains the disparity between the successful results of *in vitro* studies and the poor *in vivo* results. The remaining challenge is not the identification of comprehensive new ligands but the development of a single construct. This ligation would allow for enhanced affinity and ligand density while simultaneously decreasing immunogenicity and providing stability and corona resistance.

7 Advanced drug delivery platforms

These technologies encapsulate the material principles described above: nanoscale and responsive, integrated, and deployable device formats. Each technology is tailored to meet specific deployment requirements for route and site precision (Figure 4). While the previous sections discussed the molecular framework for nanocarrier and targeting ligand systems, implementation of these systems in therapeutics calls for complex macroscopic delivery systems that control the path, place, and time of the application. The following subsections present the delivery systems that enable smart biomaterial-based therapeutics to reach their sites of action. These systems include injectable depots, implantable systems, and microneedle (MN)-based, transdermal, pulmonary, oral, and colon-targeted systems (Xu et al., 2025a).

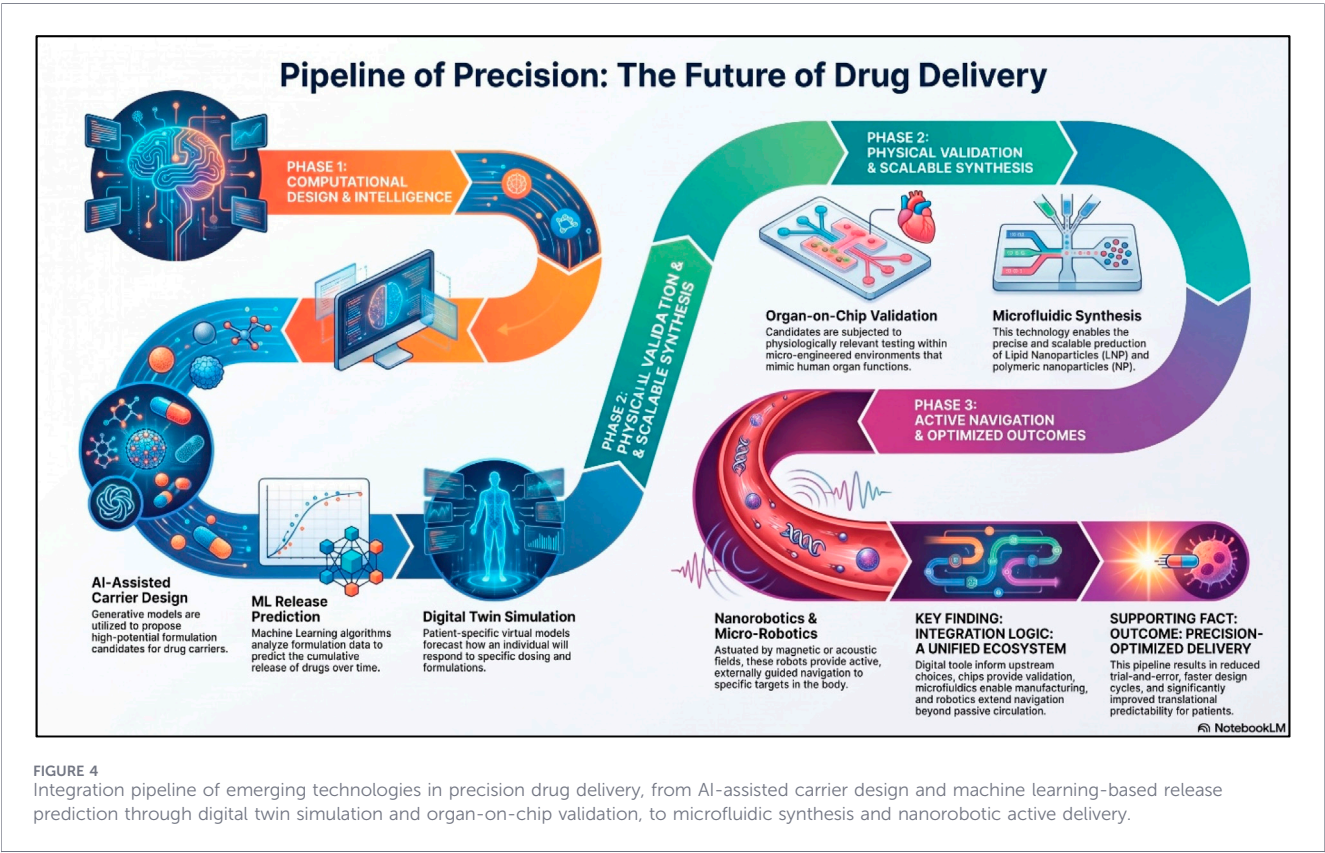
7.1 Injectable depot systems

Staying compliant with the prescribed drug regimen can be difficult for patients suffering from chronic illnesses as it requires regular trips to the pharmacy and multiple visits to the healthcare provider for injections or to replenish oral medications. Depot or sustained release formulations help alleviate this burden as they require a single administration of a drug to supply steady-state concentrations of the drug for days, weeks, or even months, depending on the formulation. Depot formulations assist patients in fulfilling their prescribed drug regimen by drastically reducing the frequency with which the patient must be administered the drug (Ingersoll and Cohen, 2008). Depot formulations can be much more complex and rigid compared to traditional drug formulations. However, they can be much more flexible than traditional formulations in the types of drugs that can be delivered. Liquid depot formulations rely on the formation of a solid drug depot at the site of administration. These formulations can be designed to allow for sustained release of the drug for long periods of time. When using these types of formulations to deliver drugs, it is common to use a polymer with the drug, which dictates the solidification at the administration site and also dictates the release rate of the drug (Viegas et al., 2023).

Two main types for producing injectable depot systems are as follows: implantable systems that form *in situ* based on PLGA dissolved in a biocompatible organic solvent and those based on *in situ*-forming gels comprising thermo-sensitive triblock copolymers. New systems for the 1-month delivery of risperidone are based on *in situ*-forming gels and *in situ*-forming systems that use PLGA. The systems are produced using risperidone in PLGA-PEG-PLGA triblock, which is a liquid at 25 °C and is injected in the body at 37 °C. Forming a thermosensitive gel at body temperature and H-bonding between the solvent NMP and the PEG segments of the PLGA-PEG-PLGA triblock also reduce the initial burst release of risperidone when compared to an ISFI system based on PLGA (Rezaeian Shideh et al., 2023). More sophisticated systems for the controlled release of drugs, such as the gel-based ISFI system for the controlled release of risperidone with PLGA-based microspheres, are able to sustain the release of risperidone without any initial burst. The pharmacokinetic data obtained for these systems show significant reductions in initial concentrations of risperidone in plasma when compared to other systems that are based on a single polymer. Depot systems based on PLGA when used as *in situ*-

TABLE 6 Major ligand classes used in active, ligand-mediated precision drug targeting.

Ligand class	Structural basis	Target/Mechanism	Advantages	Limitations
Monoclonal antibodies (mAbs)	Antibody–drug conjugates (ADCs) or antibody-conjugated nanoparticles (ACNPs)	Tumor-associated antigens (HER2, TROP-2, HER3, LIV-1, and CD47/PD-L1)	High specificity and affinity; 13+ FDA-approved ADCs (2023); ACNPs allow higher payload and controlled release	High production cost; potential immunogenicity
Aptamers	Short single-stranded DNA/RNA (20–80 nt) selected via SELEX	Disease-specific cell-surface markers (e.g., PSMA in prostate cancer)	Small size; low immunogenicity; cost-effective; stable; combinable with stimuli-responsive systems	Nuclease susceptibility; relatively new clinical experience
Tumor-homing/penetrating peptides	RGD and iRGD motifs (Arg-Gly-Asp)	Integrins $\alpha v\beta 3$, $\alpha v\beta 5$, and $\alpha 5\beta 1$ on the tumor neovasculature; iRGD additionally binds neuropilin-1 (NRP-1)	Small, versatile, and easy synthesis; iRGD enables co-administration with nontargeted nanoparticles; clinical signal in Phase 1 (CEND trial)	Proteolytic degradation; tumor penetration remains incomplete
Receptor-specific small molecules	Folate and transferrin conjugates	Folate receptor (FR) and transferrin receptor (TfR, up to 100× overexpressed in malignant cells)	Low cost, high availability, and low immunogenicity (folate); strong tumor selectivity (TfR)	Receptor expression heterogeneity across tumors
Cell-penetrating peptides (CPPs)	Cationic peptides (e.g., Tat, penetratin, and polyarginine)	Direct membrane translocation/ macropinocytosis-mediated entry	Enables intracellular and oral biomacromolecule delivery (e.g., Tat-insulin); active in clinical-stage antisense therapies	Limited target selectivity; potential cytotoxicity at high concentration



forming implants for the controlled delivery of paclitaxel have shown that the delivery of the drug through the implant system will sustain the release of the drug for 28 days. Substantial drug release was observed during the last stages of the delivery when the rate of dissolution of the polymer increases. These depot systems offer an alternative to daily oral administration of drugs in the treatment of cancer, psychiatric conditions, and chronic pain (Mukherjee et al., 2009; Akbari et al., 2022).

7.2 Implantable drug delivery devices

As drug delivery systems, implantable devices (IDDs) hold the capability to be placed at or near the target tissue. IDDs are frequently implanted directly at the tumor location and have a number of advantages over systemic delivery, which include the suppression of anticancer activity of drugs, stabilization of embedded drugs, and the ability to control and predict release. IDDs have a proven utility in the treatment of several cancers, including breast cancer, glioblastoma, and liver cancers. Poly (lactide-co-glycolides) have become the most popular drug delivery systems. Their drug delivery and regenerative medicine applications are used in cancer treatment, drug delivery, and nervous system and bone repair. Recent advancements, such as 3D printing, predictive modeling, and drug delivery with *in situ*-forming systems, are enhancing the usefulness of implants (Fayzullin et al., 2021).

The Gliadel wafer has become the most validated implantable drug delivery system in practice. In a phase III trial, Gliadel wafers were found to be beneficial in the postoperative care of patients with recurrent glioblastoma multiforme, due to the wafers' ability to extend survival. In 1996, the FDA accelerated the approval process on Gliadel wafers as a result of the phase III trial study. In comparison, a newer implant controlled the release of temozolomide to orthotopic brain tumors and also demonstrated the ability to control tumor growth and recurrence (Kartal et al., 2026). Additionally, more than 85% of the animals who received this particular implant survived for a period of 3 months. Outside of cancer treatment, drug delivery systems are becoming more common in eye care and hormone therapy. They take on a variety of forms, such as rods, rings, and sheets, and are fabricated from polymers. There is a preference for reservoir-type systems due to the sustained release of the drug and the absence of an initial burst. However, the reservoir itself is not biodegradable. Membranes synthesized with PCL that are used to control the release of the drug have been shown to sustain drug release for 190 days. When combined with 3D printing, this has the potential to change the field (Bota et al., 2007).

7.3 Microneedle-based delivery

MN arrays are an innovative transdermal delivery system for drugs, vaccines, and other compounds. MN systems consist of multiple microneedles, capable of bypassing the most significant barrier to transdermal delivery, the stratum corneum. MN arrays or systems are pressed onto the skin to painlessly and rapidly deliver compounds to the viable dermis and/or epidermis. MN arrays utilized for transdermal delivery of controlled release medications can provide a significant improvement over traditional oral dosing regimens by providing a more controlled release and circulation of the drug, avoiding the peaks and troughs that are commonly associated with oral doses (Wu et al., 2024). There are several MN technologies, including solid, hollow, coated, dissolving, and hydrogel-forming MNs, which are capable of different drug release mechanisms and are designed for different therapeutic use cases (Gao et al., 2025; Madkhali, 2022; Galarza-Arévalo et al., 2026).

A powerful emerging strategy integrates MNs with nanoparticle-based drug carriers. MN patches combined with nanoparticles synergize to yield a powerful transdermal drug delivery system. MNs facilitate the transport of nanoparticles beyond the outer layers of skin. Conversely, nanoparticles add

unique features to the system, such as the ability to carry the drug in a protected, controlled, and smart manner (Xu et al., 2025b). The NPs@MAPs strategy greatly minimizes the disadvantages of oral drug delivery systems. It has the capability of achieving either systemic or localized pharmacological response. The combination of nanocarriers with transdermal MNs enhances drug transport across the skin 2- to 10-fold, depending upon the nanocarrier and drug system. Multilayer MN systems for vaccine delivery have generated a lot of clinical interest. Dissolving MNs with liposome carriers for the Hepatitis B vaccine have been shown to increase the efficiency of intradermal delivery of vaccines. Clinical advances have also been shown through MN-assisted iontophoresis to improve the transdermal delivery of the rabies vaccine. MN arrays that are coated and loaded with doxorubicin-coated nanoparticles have been shown to improve the drug's activity and reduce the side effects that are commonly associated with doxorubicin injections (Chutoprapat et al., 2022; Cheng et al., 2023).

7.4 Transdermal delivery technologies

There is increasing interest in the use of transdermal delivery of drugs systemically and locally for acting drugs to avoid the hepatic first-pass metabolism and sustained delivery of a drug to enhance patient compliance. While this delivery system has significant advantages, it also has severe disadvantages. For example, it has an impermeable barrier, which limits the use to a narrow class of small, lipophilic drug molecules. Transdermal delivery systems also offer a very appealing alternative to other delivery systems (Karthikeyan and Sivanewari, 2024). Most of these delivery systems offer greater flexibility of drug penetration through skin-by-skin hydration, modifying the systems to be more deformable, more disruptive to the stratum corneum, and by optimizing the surface charge of the systems and the particle size. A variety of approaches have also been used to design vesicular nanocarriers, lipid nanocarriers, emulsion nanocarriers, and polymeric nanocarriers for dermatological applications. Considerable advances have been made in nanocarrier technology, especially lipid nanocarriers such as liposomes, ethosomes, and inorganic nanoparticles. These technologies are changing transdermal delivery of drugs, especially in the area of improved delivery systems for targeted treatments with controlled release and in the area of facilitated drug penetration through the skin (Unnikrishnan et al., 2023; Shahalaei et al., 2024).

Systems with vesicles that have even greater deformability have been much more successful in penetrating unbroken skin. Ethosomes, flexible vesicles that are pretty rich in ethanol, can penetrate the skin better than conventional liposomes because of ethanol elasticity, which can also contribute to the small particle size and a more negative surface charge; comparative studies have shown that optimized ethosomal gels have a significantly higher permeation flux than commercially available gels and better drug deposition (Almuqbil and Aldhubiab, 2025). Further advanced designs of electronic skin (e-skin) architectures incorporate nanocarriers with responsive materials in order to enable therapeutic functions on demand: organohydrogel e-skin systems that embed silver nanoparticles have shown a considerable increase in stability, and in antimicrobial and responsive properties, acting as a connector between nanocarriers and tailoring medicine. The use of nanocarriers to transdermal systems can potentially increase the transport of the drug across the skin by 2 to

10 times relative to the drug and nanocarrier components; systems are aimed to increase drug permeability and bioavailability of the drug while improving the adherence of the patch to the skin and decreasing the adverse effects of the drug on other systems (Wang L. et al., 2025; Mondal et al., 2025).

7.5 Pulmonary drug delivery

The large surface area (approximately 100 m²) of the lungs and the structures that comprise the pulmonary system are advantageous for drug delivery systems that are either targeted locally to the lungs or systemically to other parts of the body. Drug delivery to the lungs, compared to intravenous and oral drug delivery methods, can be designed to maximize the drug concentration in the lungs while minimizing the systemic concentration and reduce the toxic effects of the drug (Mishra and Singh, 2020). Furthermore, intravenous and oral drug delivery methods require the drug and its formulation to avoid degradation in the gastrointestinal tract and liver, whereas drug delivery to the lungs avoids these methodologies. Pulmonary delivery systems are also advantageous to patients as they eliminate the use of a needle for drug delivery. The systems designed for pulmonary drug delivery, such as nebulizers or dry powder inhalers, are based on the most common design classifications of inhalation technologies (Preeti et al., 2023).

The use of nanoparticles has significantly improved the delivery of drugs via the lungs. Particles that are 1–5 µm in diameter are known to settle in the lungs. Once they settle in the alveoli, they can break apart into their primary constituents. Furthermore, the surfaces of nanoparticles can be modified to express various bioactive substances. These bioactive substances can be used to target different cell types in the lungs. Nanocarriers have also been gaining popularity for use in dry powder inhaler systems (van Rijt et al., 2014). In order to improve the safety and efficacy of gene delivery, the nanoparticles need to be able to encapsulate plasmid DNA and siRNA. Of the many emerging siRNA and mRNA delivery systems, siRNA therapy has been used to target VEGF in order to aid in the treatment and management of lung cancer. Furthermore, nanoparticles that utilize PEG to stabilize siRNA and mRNA have been utilized to create novel antiviral therapies and inhalable insulin. Additional examples of nanoparticle-based systems include mannitol-stabilized, sustained-release PLGA microcapsules. This delivery system is aimed to be a patient-friendly alternative to traditional insulin delivery systems. Liposomal amikacin (Arikayce®) is one of the first validated examples of a nanoparticle-based, inhaled therapy. Finally, at the forefront of nanoparticle research utilizing SPIONs is the development of systems that can utilize external magnetic gradient fields to achieve targeted delivery of aerosolized particles to the lungs (Osorio et al., 2024; Bartkowski et al., 2024; Donthi et al., 2023).

7.6 Oral targeted drug delivery

Although oral drug delivery is the most popular method for patients and the most commonly used method by physicians, it has disadvantages because of the environment in the gastrointestinal (GI) tract. The GI tract has a low pH (1.0–3.0), damages drugs with enzymes, has mucus layers, expresses P-glycoprotein efflux at the intestinal epithelium, and undergoes hepatic first-pass metabolism.

The GI tract also has barriers to bioavailability. These barriers also affect permeability and solubility. The GI pH, enzymes, and mucus also affect the dissolution and absorption of the therapeutic drug. Nanocarriers with different moieties can be used to target the drug to the area of interest with bioactive and biodistributed effects. Nanocarriers can also be used to modify the drug's half-life by allowing it to cumulate in the area of interest. This offers prolonged therapeutic effect and decreases the toxic effects that may occur systemically (Liu Y. et al., 2025; Hua, 2020).

Mucopenetrating and mucoadhesive nanoparticles in relation to GI drug absorption are both competing and complementary approaches that can be used to great effect. Mucoadhesive nanoparticles use mucus layer adhesion to increase the efficiency of drug delivery by increasing the residence time at an absorption site. Mucopenetrating nanoparticles improve the distribution and penetration of the mucus gel layer to the epithelial layer and, therefore, the accessibility to the underlying epithelium. In both of these cases, absorption-enhancing strategies can be used with the surface coating of nanoparticles with either chitosan or alginate and can be targeted to different regions of the GI tract (Zheng et al., 2025). The biopolymers that form the basis of these mucoadhesive drug delivery systems also provide an excellent framework through which the nanoparticle, microsphere, or hydrogel drug delivery systems are sustained and retained to specific sites within the GI tract. The primary bonding in these mucoadhesive systems is hydrogen bonds or ionically cross-linked systems, which upon contact with mucin increase the viscosity of the systems and thus provide an excellent framework for the sustained and retained delivery of the drug. An excellent example of this emerging area in the delivery of oral biologics is the use of a polymeric nanoparticle system. The technology enables glucose-responsive delivery of oral insulin and has been shown to provide delivery of oral insulin with 20% improvement in bioavailability along with sustained delivery of oral insulin that produces a superior subcutaneous delivery of insulin in rodent models (Liu Y. et al., 2025; Lal et al., 2023).

7.7 Colon-specific drug delivery

Colon-targeted drug delivery systems focus on releasing drugs specifically within the large intestine through colonic environment-based GI tract system-exerted features such as the mildly buffer to neutral alkaline GI tract system luminal pH, which is around 7–8, the rich and active GI tract microbiome, the peristaltic movements of the intestine under pressure, and a limited enzymatic system compared to the other systems of the GI tract (Philip and Philip, 2010). Formulating systems for delivery to the colon provide design flexibility to meet the challenge of the local delivery system for clinically needed symptomatic relief in patients with inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS); they also aid in the management of colorectal cancer and the systemic delivery of peptides and biologics. This is done through the use of triggered drugs (prodrugs), time-sensitive delivery systems, pH-sensitive delivery systems, pressure and microbiota-triggered delivery systems, and multiple delivery systems. Multiparticulate delivery systems also surpass single-particle delivery systems (Yang et al., 2014).

The use of pH-sensitive polymer coatings to target the colon is the leading method clinically. The development of pH-responsive smart delivery systems has resulted in the use of various polymers

and polysaccharides to include polymethacrylates, polysaccharides, and chitosan. These materials undergo a pH-dependent physicochemical change to swell, dissolve, or erode for the controlled release of therapeutic agents. The bioavailability of the drug increases, and the pH-dependent delivery system also decreases the toxicity of the drug to the system. Eudragit® S, which dissolves at a pH above 7, is utilized in colon targeting (Lee et al., 2020). Some of the drugs that have been delivered with colon-specific delivery systems using Eudragit are 5-aminosalicylic acid, insulin, and prednisolone. To overcome the variability of the GI transit time associated with the use of single-polymer Eudragit® S100 delivery systems, interpolymer complexes related to Eudragit® copolymers have been developed. An elegant example of one such system of delivery utilized a pH-sensitive Eudragit S100 coating over hydrogen sulfide donor liposomes loaded with a drug for ulcerative colitis. In the acidic pH (pH 2) of the stomach, the liposomes formed aggregates to minimize the unwanted release of the sulfide donor hydrogen liposome over the 8-day period. This resulted in a five-fold decrease of the unwanted release in comparison to the free form of the drug (Chai et al., 2025; Nunziata et al., 2025).

Polysaccharide-based coatings that use bacterial enzymatic degradation provide a method for site-specific release other than pH-responsive systems. Development of colon-targeted drug delivery systems has become a greater focus in recent years as they have become more useful in the treatment of IBD, IBS, colorectal cancer, and many other colon-related illnesses. There are many systems that provide colon-targeted drug delivery. Some of these systems are pH-based, time-based, microbe-based, prodrug-based, pressure-sensitive, and nanoparticle systems (Kurl et al., 2023). Each system has its benefits. Nanoparticle systems are especially useful in addressing many of the challenges posed by colon-targeted delivery, such as variable pH, microbial systems, and enzymatic and time-based systems. PLGA/Eudragit S100 nanoparticles are useful for treatment of colorectal cancer because of their pH-controlled systems. These nanoparticles reduce the rate of drug release at neutral pH (7.4); however, they increase the rate of drug release at the pH (5.5) of colorectal cancer environments. These nanoparticles also improve the cytotoxicity of Caco-2 cells in comparison to the drugs offered in the control. The combination of these technologies exemplifies the benefits of targeting the colon and using stimuli-based approaches in a single delivery system (Wang et al., 2020).

8 Emerging technologies in precision drug delivery

The following technologies do not self-mediate. Rather, they are tools created to provide design and prediction models to make rational, patient-specific, in-demand delivery systems more probable. The previous sections explain precision drug delivery systems, such as the used materials, targeting ligands, and the macroscopic platforms. Recently, innovations in computational, microengineering, and robotics technologies have begun to alter the design, testing, and application of these systems. Six of these disruptive technologies were extracted and are represented in the following subsections. These include the use of artificial intelligence (AI) to assist design, the application of machine learning (ML) to predict release, digital twins (DTs), organ-on-chip (OoC) systems,

microfluidic technologies, and nanorobotics. These systems address the need to move precision medicine from the empirical and experimental design to a more predictive and data-centric approach (Lim et al., 2020). AI-assisted drug-delivery approaches are summarized in Table 7.

8.1 Artificial intelligence-assisted carrier design

AI is changing the entire landscape of drug delivery carriers. The development process was slow, frustrating, and costly and usually required many rounds of physically testing prototypes and adjusting based on results and guess work to finalize a carrier. AI is changing this by allowing the development of carriers to be more data-driven and based on some predictions (Suksaeree, 2025). When it comes specifically to AI and how it looks to change drug delivery systems based on nanotechnology, it will help overcome the challenges associated with design and synthesis as well as optimize the nanoparticles. Traditional techniques to develop a nanoparticle-based system used guesswork and, thus, slowly developed a system that had low compatibility with the human body and, thus, was very inefficient. However, AI is changing the game especially to help overcome the barriers present in the body and increase the delivery of the drug at the needed location (Meng et al., 2024).

A variety of AI architectures have been incorporated into carrier design. Convolutional neural networks examine microstructural images to find relationships between particle morphology and release kinetics. Graph neural networks focus on characterizing the interrelations of polymers, surfactants, and active ingredients. Many biopharmaceutical constraints have been met using the diffusion model and variational autoencoders to intelligently predict excipients. Recently, several generative models have proposed new nanoparticle designs that met the requirements of the generative design model and were experimentally validated (Omidian, 2025). Data-centric nanocarriers tailored for direct drug delivery in combination with AI-powered nanoarchitectonics integrates design and an ML-driven framework. One example of a rapid prototyping framework for direct drug delivery is the combination of high-content screening and microfluidic-assisted preparation of several nanocarrier designs, where a formulation-dependent ML model is used to predict the biological response. An example for nucleic acid therapeutics is the three-step guided discovery of nanoparticles for the design of flexible ionizable lipid nanoparticles (Gonçalves, 2026). AI and ML have fully penetrated the nanomedicine development pipeline from the initial drug formulation and determination of the target all the way to the ultra-personalized optimal dose and toxicity prediction (Kantesaria and Panda, 2026). Examples of this are the EVONANO and FSC Systems, which allow the *in silico* design of nanoparticles and drug combinations (Throat and Bhattacharya, 2024; Mohan et al., 2024).

Beyond predictive screening, the field is advancing to generative and inverse design, where desired properties are specified and structures are generated accordingly. One example of this line of thinking is the AI-Guided Ionizable Lipid Engineering (AGILE) platform. The platform uses a graph-neural network model that was pre-trained on a combinatorial library that allowed screening of 1,200 ionizable lipids and made predictions in a virtual space of 12,000 variants. This work allowed lipid variants to be synthesized that would have pretty specific delivery preferences to cell types that

TABLE 7 AI-assisted drug-delivery approaches.

Approach	Function	Representative example	Reported outcome	Maturity
CNN/GNN prediction	Structure-property/activity prediction	GNN virtual screening	Rapid <i>in silico</i> screening	Research
Generative/inverse design	Goal-directed carrier design	AGILE (ionizable lipids)	1,200→12,000-variant library, validated candidates	Emerging
Reinforcement learning	Autonomous formulation optimization	AlphaFlow	Optimized ≤40-parameter synthesis and outperformed conventional	Emerging
Gradient boosting (LightGBM/XGBoost)	Drug-release prediction	PLGA release models	Predicts release from formulation features	Research
Gaussian-process regression	Size/zeta-potential prediction	Particle-property models	Formulation optimization	Research
Explainable AI (SHAP/LIME)	Interpret structure-property drivers	SHAP on LNP descriptors	Identified electrostatic/ratio drivers	Emerging
Digital twins/ <i>in silico</i> trials	Simulate patient response	Virtual patient models	<i>In silico</i> trial feasibility	Early

would be extremely difficult to determine using a trial-and-error process (Xu et al., 2024). These types of goal-oriented processes turn the design process on its head and begin with the ultimate transfection or release goal and then derive the molecular structure, as opposed to the standard design process which is moving from the molecular structure to the outcome (Shen et al., 2025).

Without the need for preset experimental grids, reinforcement learning (RL) allows for systems to formulate in a closed-loop and self-optimizing manner. Integrating an RL agent with a self-driving microfluidic platform, AlphaFlow is able to fully discover and optimize multi-step nanoparticle synthesis workflows involving up to 40 parameters. AlphaFlow is able to do this with significantly less data and improved workflows, even compared to standard workflows (Volk et al., 2023). Even with these developments, AI-assisted design continues to be data-constrained rather than algorithm-constrained. Training sets are sparse, split across various labs, and biased toward favorable published results. As a result, AI models are restricted to a limited chemical scope. Validation is still largely retrospective and *in vitro*. No AI-designed nanocarrier has received regulatory approval. For the foreseeable future, the technology is better suited to narrowing candidate libraries and optimizing the number of required wet-lab experiments, as opposed to fully automating experimental design. Other similar autonomous and semi-autonomous systems have been used for polymeric long-acting injectables and other lipid-based nanoparticle systems. These systems have the ability to rapidly learn and implement new experiments to successfully find the optimal formulation with significantly improved lab productivity (Bannigan et al., 2023).

8.2 Machine learning for drug release prediction

A good example of how ML is being successfully applied in the field of precision drug delivery is the prediction of drug release kinetics in polymeric and lipid-based carriers. In the past, drug

release kinetics was modeled with empirical equations, such as Korsmeyer–Peppas (Rebouch et al., 2019) and Weibull, that often could not describe the complex and nonlinear nature of actual release behaviors. ML problems involve complex, nonlinear relationships; therefore, drug release from PLGA microspheres and the rational design of formulations can be addressed with ML. This, of course, will help decrease the number of laboratory experiments needed to be performed (Shen et al., 2023).

There have been a lot of new advancements with PLGA-based systems and our public dataset creation. A public dataset with 321 *in vitro* release studies and 89 drug-PLGA microsphere formulations has great potential to create public ML models to fill existing gaps. The dataset and ML models have built great systems to predict 24-h cumulative drug release using formulation descriptors and preliminary *in vitro* release measurements. These systems have shown that the best models are based on ensemble trees, whereas neural networks, single trees, and linear models underperformed (Song et al., 2026). The model based on Light Gradient Boosting Machines performed better than the others. These systems have shown the potential of creating PLGA-based, long-acting, injectable formulations for public use in a safe and reproducible manner, in accordance with the Quality-by-Design framework. A similar approach was taken and improved upon the original systems. A classification approach using a stacked model was used to predict the release occurrence within a 3-day window. This was subsequently included as a feature in a regression model to predict the entire release profile. Among the models tested, XGBoost performed the best with respect to the mean absolute error. The model was validated against PLGA microspheres containing a different drug, which was never included in the training data for the model, and demonstrated the validity of the model to predict release behavior (Li et al., 2020).

ML-based release prediction methods are being used in other areas in addition to predicting PLGA release. Gaussian process regression showed superior performance to other models for predicting the size and zeta potential of PLGA nanoparticles, achieving a high-test R^2 and low mean squared error. Other,

similar models, such as neural networks, have been developed to reconstruct entire *in vitro* release curves for drug delivery systems incorporating PLGA. These models provide a way to avoid traditional kinetic models when screening formulations (Yang and Sun, 2022).

A previously acknowledged disadvantage of achieving high performance with such models is that they remain opaque to users. Methods in Explainable Artificial Intelligence (XAI) like Shapley Additive Explanations (SHAP) and Local Interpretable Model-Agnostic Explanations (LIME) attempt to negate this by giving users the ability to see how different features of the inputs cause different outcomes of the predictions. In nanoparticle design and delivery modeling, tree-based models and SHAP analyses have been used to explain delivery performance in cancer modeling. In modeling ionizable-lipid systems, SHAP analyses have been used to identify which electrostatics (in particular the partial charge of the ionizable lipid) and the ratio of the lipid and RNA, explain the systems, and also the synergistic result of the interacting features, which in turn provides the model its predictive value. It is evident that this type of modeling is becoming a necessity not only for researchers and scientists but also for regulatory bodies that use AI-based design assistance and modeling (Lavecchia, 2025). The main limitation here is still data quality. Publicly available release datasets are small, mixed in method and sampling interval, and are rarely standardized, which restricts transferability between laboratories. Importantly, these models predict *in vitro* release, which does not correlate well with *in vivo* release. As of now, the main application will be in formulation and Quality-by-Design. Broader clinical use is dependent on standardized reporting and validated in the *in vitro*–*in vivo* correlation.

Progress in AI-assisted drug delivery has been positive, but algorithms are not the primary limitation. Data remain an issue (Blanco-Gonzalez et al., 2023). AI models are constrained by datasets which are small, methodologically heterogeneous, and biased toward characterizations that are easier to describe and publish. These constraints affect the generalizability of models. Validation of these models is largely retrospective and *in vitro* (Cheng and Shi, 2025). AI-designed models and systems lack regulatory approval. For design systems to gain regulatory approval, explainable AI methods, such as SHAP and LIME, are critical. These systems of design will remain constrained and not fulfill their potential, within the Quality-by-Design framework. Beyond that point, AI-assisted drug delivery systems have the potential to keep wet lab work to a minimum (Zhu, 2025). Quality attributes and critical process parameters will be defined by these systems. Broader adoption of AI-assisted drug delivery systems will be predicated on models that are ready for regulatory approval and have interpretable data, as well as design validation that is *in vivo* and prospective (Sahu et al., 2026).

8.3 Digital twin concepts

DTs are very useful for the development of drugs and medicine because they are tools that can virtually replicate and sync with physical models or systems. Like DTs, simulators that replicate human systems may help pharmacologists understand the relationships among patients, the drugs, and the responses to the drugs. DTs are virtual replicas of physical objects. They may or may

not be synchronously connected and may be used to simulate the behavior of the physical objects. Digital patient twins, or virtual replicas of patients, are composed of patient data, population data, and/or data from wearables or other medical devices. Digital patient twins are used to develop new digital health data ecosystems that integrate AI (Chen J. et al., 2023).

Regarding precision drug delivery, DTs allow modeling of patient-specific drug uptake, dispersion, and therapeutic response. Using a patient-based physiology and feedback model, an example of a patient DT for transdermal drug delivery may be constructed in order to standardize the treatment for the patient; DTs may also be constructed for a patient class. More advanced DTs may include the pain scale feedback as well as biomarker feedback, thereby enabling *in silico* trials for a virtual patient population. DTs open new frontiers in personalized medicine; examples include the construction of DTs for patients that predict personalized drug dose within a margin of 7% of the dose from actual clinical practice (Porwal et al., 2025). For DT oncology, cancer-specific digital twins or “cancer avatars” are constructed from a synthesis of a cancer patient’s tumor images, cancer genome, and pluripotent pharmacology; these DTs also simulate both the evolution of tumors and the response of tumors to different treatment regimens and pharmacology. Important retrospective work has compared actual tumor evolution to that of the DT, including breast cancer and melanoma; this work has opened new frontiers in the design and implementation of clinical treatment protocols for cancer. Even though the use of DTs to guide drug delivery in clinical medicine is very new, they may also be used in the combination of real-time biosensing to enable individualized treatment of drug delivery (Zhang Y. et al., 2025). DTs are still a long way from being a standard part of clinical care. They require information from research settings about a patient that is difficult to find outside of research settings, and their validation has mostly been done in a retrospective way. Currently, there is no validation process for DTs and their *in silico* testing for drug delivery. At this time, the best use for DTs is in designing research trials and simulating dosing, rather than being a part of direct patient care.

8.4 Organ-on-chip platforms

OoC systems, or microphysiological systems, are devices that simulate the physical and chemical characteristics of human tissues and organs. These systems are designed to meet the needs of researchers studying drug delivery systems. OoC systems were designed with the goal to reproduce organ structures by way of microdevices that conduct research on organ systems. These devices can replicate environments that allow cells to interact via the recreation of 3D *in vivo* microenvironments (which carry the size and scale of the typical cellular environment that is present in the body but is done in a bioreactor). The cells can interact in the way that they would in nature. Many of these OoC devices are being used to test the effects of drugs and the toxicity of these drugs (Quan et al., 2020).

OoC platforms narrow a key translational gap for therapeutics based on nanoparticles. Traditional models and human biology differ greatly. This adds to the already high attrition rate of drugs with good preclinical results that show poor efficacy in humans. This gap is even more significant in assessing nanoparticle-based

therapeutics. The efficacy, toxicity, biodistribution, clearance, and immunogenicity of nanoparticles are based on their interactions with human microenvironments. The OoC technology integrates living cells with controlled microenvironments and microfluidic systems to simulate microenvironments in which fine, biomechanical forces can be incorporated to create a more applicable model of pathophysiological conditions than traditional, static models (Sampaio et al., 2025). The first applications of this technology were focused on delivering more realistic and human-based models for toxicological assessments. An excellent example is the model developed by Huh et al. of a breathing, lung-on-a-chip, which is capable of assessing the toxicological effects of the absorption of silica nanoparticles that induce oxidative stress in the lung epithelium. More recently developed vascularized OoC systems have enabled direct studies of the interactions of nanoparticles with endothelial cells on the chip. Researchers modeled tumor microvessels and respiratory exercise, on lung-on-chip systems, to study the effect of silica nanoparticles on pulmonary inflammation. The latest advancements in this field are multi-organ interconnected OoC systems. These systems allow simultaneous assessment of the behavior of nanomedicine in multiple organs and systems of the body (Geng et al., 2023; Wilson et al., 2024). Despite the potential that OoC platforms hold, they currently suffer from a lack of uniformity between devices and labs, less throughput compared to traditional screenings, and a missing functional immune compartment. This last issue is meaningful since immune recognition is what clears the nanoparticles. Regulatory qualification to replace animal testing is still in progress, so for the predictable future, OoC platforms will be a screening method to eliminate risks to the subjects for the next phase.

8.5 Microfluidic drug delivery systems

Microfluidic technologies offer superior control over fluid mixing at the microscale and nanoscale, enabling the synthesis and characterization of nanoparticle drug delivery systems. Control at the nanoscale means that mass transport is also basically defined. These features make microfluidic technologies the ideal choice for screening nanoparticle drug delivery systems. The lab-on-a-chip and microfluidic technologies enable the rapid characterization of the nanoscale delivery system while maintaining tunability of the delivery systems. These technologies also allow for rapid biological assessments, yielding faster results and determinations on system effectiveness. The advances also assist in enhancing monodispersity and reproducibility when dealing with liposomes, PNPs, and metallic nanocarriers. By utilizing microfluidic technologies, one may also assess the pharmacokinetics and pharmacodynamics of the delivery systems in conjunction with OoC models (Javid-Naderi and Shaegh, 2025; Zhang et al., 2026).

The rise of mRNA vaccines has greatly advanced the microfluidic synthesis of LNPs and their medicinal nanocarriers. Likewise, the ability to manipulate the physics of fluid transport and particle synthesis at the microscale with microfluidic systems creates novel methods for the production of LNPs. The remarkable success of LNP mRNA vaccines for COVID-19 has also proven that microfluidic systems can be scaled with great precision to

produce parallel or numerically controlled micro drug delivery systems. Especially in microfluidic systems, precise control of flow rates can adjust the physical and chemical attributes of the LNPs. The flow rate ratio has the greatest impact on an LNP's size and the degree of size dispersion. Increasing the rate of the aqueous phase in the microfluidic flow cell also increases the shear stress and narrows the width of the precursor phase, resulting in significantly decreased mixing times for the flow and, thus, the formation of the nanoparticles, which decreases their size (Mutlu et al., 2026; Graham et al., 2025; Kashkooli et al., 2024).

Beyond LNPs, the fabrication methods used to create PNPs using microfluidics have also been developed. Flexibility of substrate selection can be applied to choose from a wide array of polymers used to create nanoparticles such as PLGA, polycaprolactone, or other biocompatible and biodegradable polymers. Like the case for LNPs, microfluidics provides a simple and effective means to control the size and size distribution of PNPs. The trend is toward direct integration of microfluidic platforms with the biological evaluation tools. For example, in many of these emerging platforms, the microfluidic systems integrate functionality for *in vitro* 3D models for real-time pharmacokinetics (PK), advanced OoC systems, and monitoring the physiological responses of nanocarriers to the embedded platforms. A clear example of these next-generation microfluidic systems is a 3 organ model which integrates gut, vascular, and neural systems to provide real-time tracking of toxicity and the transport of metabolites between the integrated organ systems (Moradi Kashkooli et al., 2024; Zhou et al., 2014). Microfluidics is one of the more advanced technologies as it produces the LNP-mRNA COVID-19 vaccines at a worldwide level. However, microfluidics applications beyond lipid systems are less developed. The transition from single-chip production to industrial-scale production is a complicated task and would require large-scale, extensive parallelization, which reintroduces variability from batch to batch. Furthermore, channel fouling, high device costs, and the need for specialized, complex analytics pose severe practical limitations. A reasonable expectation is that in the near to mid-term, market focus will be more in the realm of lipid-based systems and a slow addition of polymer and some hybrid systems.

8.6 Nanorobotics and micro-robotics

Nanorobotics and microrobotics are the most advanced field in precision drug delivery. They utilize wireless robotic systems scaled to the micro and nanometer size range. Traditional nanocarriers rely on passive diffusion and circulation-dependent accumulation. Actively controlled microrobots navigate to diseased locations on their own. Magnetic microrobots are a new drug delivery platform and present great promise for drug delivery systems (Qin et al., 2025). They are able to navigate by the control of external magnetic fields. Microrobots address the common drug delivery issues of poor tissue penetration and drug distribution. Improvements in the design and fabrication of magnetic microrobots and drug loading through advanced methods have resulted in improvements and flexibility for drug delivery systems. The incorporation of these advanced technologies will assist microrobots in the delivery of improved therapeutics while optimizing precision targeting (Tzavara et al., 2025).

To aid microrobot movement in biological fluids and tissues, several physical actuation modalities have been developed. Magnetic and acoustic field-driven microrobots have the potential to be widely used in biomedical applications. Hybrid magneto-acoustic microrobots may develop better and safer drug delivery systems in precision medicine. There are even more potential advantages with each development. Because of being completely wireless and having an easier time getting to and working in hard-to-reach parts of the body, they have great biocompatibility and can easily work in and engage tissue (Weerathna et al., 2025). Ultrasonic waves are very common in noninvasive medicine and can effectively provide forces in the nanoscale region. Acoustic activated nanorobots are easily actuated in biological fluids. There are acoustic tweezers, where particles are trapped in an acoustic field to be propelled later, and bubble activation, where the nanorobots are propelled by bubble creation. These methods greatly improve the nanorobots' ability to permeate biological systems and be localized with precision (Wang T. et al., 2025). Magnetic actuation has been successfully applied in ocular and otic drug delivery where control with great precision is required in small, confined spaces within the body. When combined with nanorobotics, the use of external magnetic fields facilitates the guided propulsion of bio-robots through the body's vitreous humor. This enables the delivery of drugs to the retina without the tissue damage that typically accompanies the invasive delivery of drugs. This system also allows for the delivery of larger drug payloads. As described in this review, the drug loading and release system that works with these magnetic robots can also be modified to respond to different stimuli. In fact, magnetic microrobots can utilize a number of different methods, including the use of pH or temperature changes or enzymatic activity, to respond to stimuli in order to release their drug payloads. Safety, large-scale production, and adequate precision in microrobotic movement within complex biological systems are the main challenges that face the clinical implementation of these systems. In the future, an even more advanced system may originate from the integration of biological and robotic systems to create biohybrid micro/nanorobots for targeted drug delivery and other applications. Convergence of robotic and biological systems for tissue engineering and drug delivery will be even more advanced, however, with significant challenges relating to stability and biocompatibility (Saha et al., 2024; Kumari et al., 2023). Emerging computational, microengineering, and robotic technologies in precision drug deliveries are summarized in Table 4.

9 Therapeutic applications

Each application below shows the precision delivery principle under separate biological obstacles and shows how the specifications of material, targeting, and release strategy are designed to address the constraints of the specific disease. This section looks at how smart biomaterials are applied to various diseases after covering what factors comprise smart biomaterials (materials, targeting strategies, stimuli-responsive mechanisms, and delivery platforms). The adaptive drug delivery mechanisms have a significantly varying range of potential in different disease contexts, determined by the challenges and barriers present in different microenvironments. The following section looks at

smart biomaterials delivery systems in six different domains: cancer therapy, regenerative medicine, therapy for cardiovascular diseases, therapy for neurological disorders, infectious disease therapies, and therapies using genetically modified nucleic acid constructs (Nag et al., 2024).

9.1 Cancer therapy

This section discusses how smart biomaterials are used with different diseases after looking at each component of smart biomaterials (materials, targeting strategies, stimuli-responsive mechanisms, and delivery platforms). Each adaptive drug delivery mechanism is different when used with different diseases, based on the constraints and barriers that the mechanism is likely to encounter in a given microenvironment. This section next describes smart biomaterial delivery systems in the context of cancer therapy, regenerative medicine, cardiovascular therapy, neurological therapy, infectious disease therapy, and therapies involving engineered nucleic acid constructs (Nitta and Numata, 2013).

The variety of nanocarrier designs for cancer treatment continues to broaden. Responsive nanoparticles that can be guided or that will react to specific biological cues are being developed as a highly effective platform for focused polymeric nanocarriers. Other smart nanocarriers include dendrimers, liposomes, protein nanoparticles, and cell membrane nanoparticles, as well as mesoporous silica nanoparticles, gold nanoparticles, iron oxide nanoparticles, quantum dots, and CNTs. These can respond to and interact with internal and external stimuli such as pH, temperature, and different types of optics, as well as various enzymes. In addition, several multimodal smart nanoparticles have the potential to integrate both therapy and diagnostics (Bhairam et al., 2026). One of the major breakthroughs of responsive nanocarriers in smart nanomedicine is the integration of drug delivery, medical imaging, and photothermal therapy, while the other has shown the delivery of glutathione-responsive cisplatin to lung cancer, the targeting of circulating breast cancer cells, and the targeting of colon cancer therapy for improved polyphenol bioavailability. The cell- and biomimetic-styled technologies are expanding targeting precision. For instance, cellular nanodisks have demonstrated the ability to be directly functionalized for targeting chemotherapeutics to specific tumors (Jabeen and Atif, 2024; Patra et al., 2024).

9.2 Cardiovascular disorders

Cardiovascular disease, notably atherosclerosis and myocardial infarction, includes a range of complications and is increasingly becoming an area of interest regarding nanoparticle-based drug delivery. Systemic pharmacotherapy cannot successfully achieve the concentrations of drugs that are required at the sites of interest, i.e., in the diseased vascular tissues. Atherosclerosis involves the formation of lesions in the arteries as a result of the chronic inflammation of vascular tissues, accumulation and lipid and cellular components, and formation of plaques (Omidian et al., 2023). It remains a leading cause of morbidity and mortality due to cardiovascular disease. Nanoparticle drug delivery systems have the potential to target the cellular components that contribute to the

progression of the disease. The use of targeted methodologies that are aimed at disease-associated biomarkers and the microenvironment of the plaques of atherosclerosis offers the potential to achieve therapeutic goals and increase the efficacy of the treatment, while limiting effects that are unwanted or that occur away from the target site (Jumadi et al., 2026).

Considerable research done on targeting strategies in this disease area has focused on the population of inflammatory cells that lead to the progression of plaques. A key feature of atherosclerotic plaque inflammation is the persistent recruitment of monocytes. This recruitment antagonizes the resolution of inflammation. The ability to silence monocyte recruitment has the potential to reduce inflammation and ventricular remodeling of the heart post-myocardial infarction. To that end, researchers have utilized yeast-derived cells to create nanoparticles that encapsulate the MCP-1/CCL-2 inhibitor, Bindarit (Soehnlein and Libby, 2021). It is important to note that the inflammation of plaques is a complex problem. To that end, researchers have created multifunctional theranostic platforms in order to address this complexity. Drug-loaded, metal-organic, cage-doped, manganese dioxide nanoparticles have facilitated the co-delivery of not only oxygen but also hydrogen sulfide to inflammatory cells. This has been shown to reduce the formation of foam cells as well as relieve the inflammatory burden of plaques in preclinical studies (Nasri et al., 2025). The early stages of clinical work in this area have shown both promise and disappointment. One trial reported that a liposomal nanoparticle system that co-delivered low-dose clopidogrel and aspirin to 270 patients with coronary artery disease showed a positive safety profile and reduced the incidence of major adverse cardiovascular events (Yang et al., 2025). However, in a separate trial of atherosclerosis, the use of liposomal nanoparticles of prednisolone showed no significant decrease in inflammation (van der Valk et al., 2015). This demonstrates that successful targeting in preclinical studies does not guarantee a positive outcome in clinical work if care is not taken in the design of the studies and the dose of the drug (Varanko et al., 2020; Milligan et al., 2022).

9.3 Neurological diseases

The combination of the challenges associated with the BBB and neurodegenerative diseases like Alzheimer's and Parkinson's makes this area particularly challenging for precision drug delivery. The BBB restricts the vast majority (>98%) of small molecules and essentially all biologics from reaching the brain tissue. However, brain-specific drug delivery via BBB crossing with the use of nanotechnology and specially designed therapeutic nanoparticles is a game changer. Novel therapeutic nanoparticles may offer the means to increase the effectiveness of neurodegenerative disease treatments in the future (Jumadi et al., 2026; Jaber et al., 2026). The heterogeneous pathophysiology of Alzheimer's, with features like neuroinflammation and oxidative stress, involves many different stages. Because of this, a variety of classes of nanocarriers have been examined. Each type of nanoparticle (lipid, polymer, and inorganic) can play a special role in drug delivery for Alzheimer's. Strategies to target nanoparticles to neuro-afflicted tissue emphasize surface modifications to improve permeability. Gold-based metallic nanoparticles, in particular, have a notable advantage because of their

biocompatibility and their history with the FDA, along with ease of crafting and building conjugates for nanoparticles with therapeutics and DNA/RNA, peptides, antibodies, and aptamers. Off-the-shelf liposomal systems have been fabricated with biomimetic cell membranes. These systems are particularly promising for multitarget disease modification. One of these systems constructed a hybrid cell membrane, fused platelets and CCR2, and liposomes to which two different drugs were loaded. These liposomes were also coated to achieve a target and multi-task therapeutic design, which reduced both neuroinflammation and cognitive deficits in transgenic models of familial Alzheimer's disease and also reduced amyloid plaque aggregation. Other more recent liposomal constructs have been used to enable the delivery of therapeutic mAbs aimed at treating Parkinson's disease. Advances in nanocarriers have led to the development of innovative noninvasive transport strategies. These strategies have yet to compromise the integrity of the BBB; however, they have relied on receptor-mediated transcytosis and focused ultrasound (Varanko et al., 2020; Milligan et al., 2022; Kochman et al., 2026).

9.4 Infectious diseases

The growing awareness of the global threat of antimicrobial resistance has sparked a lot of interest in using nanoparticles to treat infections. It is an effective means to boost the treatment of microbial resistance compared to conventional small-molecule antimicrobials. Since resistance to antimicrobials is increasing, researchers are finding new means for treating these diseases. The technological advancement of nanoparticles and the understanding of infectious diseases have improved antimicrobial treatments. A great deal of work has gone into using nanoparticles in the design of liposomes, dendrimers, and polymeric particles and inorganic nanoparticles. These have been applied successfully against infectious diseases along the lines of rapid detection of microorganisms, antimicrobial vaccines, and controlled delivery of a combination of antibiotics (Mohammadi et al., 2017; Hayat et al., 2025).

Specifically, for local infection management, addressing the problem of balancing drug concentration at the infection site and the level of drug exposure to the rest of the body (which can lead to the development of drug resistance) is possible using nanoparticle platforms. More local treatment is preferred to strengthen the drug concentration and avoid resistance. Therapeutic nanoparticles, particularly liposomes, PNPs, dendrimers, and inorganic nanoparticles, are especially promising. These nanoparticles help focus antibiotics to the bacteria, help in the interaction of the drug with the bacteria to overcome resistance, and help in the vitally important anti-virulence activity to promote a "drug-free" approach to antimicrobial treatment (Gao et al., 2018). Nanoparticles provide valuable drug delivery systems as they have a large surface area, are able to be functionalized, and can be combined with various antibacterial agents. They can provide a sustained and controlled release of the active pharmaceutical agent. They can shield a drug from being degraded and can serve as a means of excipient to improve the drug delivery to targeted sites in the body. One of the most important examples is the use of PLGA nanoparticles to incorporate a controlled release system into vaccines to improve the vaccine and immune response. The World Health Organization has identified antimicrobial resistance as one of the 10 most significant threats to global health. This is due to the evolution of

bacteria, fungi, viruses, and parasites to evade antimicrobial treatments. With standard procedures either preventing infection or slowing down antimicrobial resistance, the new advancements in nano-vaccine technologies target the resistance at its core by focusing on the molecular mechanisms of antimicrobial resistance (Fathi and Oyelere, 2016).

9.5 Gene and nucleic acid delivery

The delivery of genes and nucleic acids through smart biomaterials is an emerging area of great interest and development. This has been facilitated by the global COVID-19 crisis using LNPs combined with mRNA, causing a wave of greater interest and a wider application of nucleic acid therapies. The use of LNPs as a carrier system for new-generation nanomedicine is very promising since it offers a high level of efficacy and a low cost of production for a greater range of therapies, vaccines, and cancer treatments. The use of nucleic acid therapies, mainly using mRNA, is becoming even more useful for the treatment of a wider range of diseases. The use of mRNA vaccines during the COVID-19 crisis has strongly reinforced this advance in therapy. Unstable mRNA requires the use of protective carriers, such as LNPs, which prevent their degradation and allow cellular uptake (Wang et al., 2023; Amici et al., 2023).

The last decade has seen the advent of a number of classes of LNP-based approved nucleic acid therapeutics. The developments mark the first instances of the LNP-based RNA therapeutics of their types reaching the market and the first approved LNP-based therapeutics of any kind. The use of the technology has allowed for the first use of for-FDA approval of RNA therapeutics, specifically mRNA and siRNA, as delivery vehicles for nucleic acid drugs encapsulated in LNPs. The technology has also helped develop the first siRNA therapeutics, which are based on lipid-nucleic acid systems (Kiaie et al., 2022). The first licensure of an siRNA therapeutic based on the SNALP technology occurred in August of 2018, when patisiran was approved by the FDA. The field is moving on from the liver, the main organ in which the majority of LNPs accumulate, to target other organs and tissues. Nontargeted LNPs remain the major option for most LNP products. Targeted LNPs represent the next step in providing LNP-based therapeutics and are centered on recent advances in drug delivery that focus on lipid technology innovations, as well as organ-targeting LNPs that employ active targeting methods to reduce unwanted side effects (Singh et al., 2026). In addition to linking ligands, there are other passive-targeting mechanisms that take advantage of the biological environments that are being researched. One of these methods includes vehicle delivery of nanoparticles in a protein corona-mediated, extra-hepatic manner, inspired by classic ligand-mediated active targeting. In this instance, nanoparticle targeting can occur even if a specific ligand is not conjugated to the carrier, demonstrating the integration of other passive targeting methods and the early active targeting concepts in the field of nucleic acid delivery (Chen et al., 2024).

9.6 Regenerative medicine applications

Smart biomaterials represent a new class of biomaterial systems employed in regenerative medicine. These intelligent systems serve

as structural support elements for regenerating tissues and as controlled delivery systems for bioactive agents involved in tissue repair. Smart biomaterials operate as scaffolding systems for tissue regeneration and for the controlled delivery of therapeutic agents based on their ability to respond to a defined set of environmental stimuli (pH, temperature, light, electric and magnetic fields, and enzymes) (Zhang W. et al., 2025). These materials may be designed to modulate the scaffold's degradation rate in a controlled manner, thus affecting the delivery of therapeutic agents. They may also be designed to exhibit varying levels of electrical conductivity and initiate the release of therapeutic agents in a manner that is dictated by the material's permeability (Vallet-Regí et al., 2026).

In regenerative therapy, the controlled delivery of growth factors addresses their clinical challenges. Growth factors are unstable with a short half-life. They are easily inactivated in a physiological environment, degrade quickly, and have low biocompatibility, which limits their clinical application. One solution to the instability is the rapid development of delivery systems using biomaterial-based scaffolds (Al-Sahlawi et al., 2024). They have included the use of biodegradable polysaccharides to deliver growth factors and speed up tissue repair and regeneration. Further to passive scaffolds, active biomaterials have been designed to influence the immune microenvironment of regeneration. The field of smart biomaterials has progressed from passive scaffolds to active, immune-modulating systems capable of shaping the regenerative microenvironments. This includes the development of materials that are responsive to pH, temperature, and enzymes in a way that allows intelligent interaction with biological signals. Often, the focus of this type of research is the control of macrophage polarization. The scaffolds, with their physicochemical properties and controlled release of immunomodulating factors, have many applications from cancer immunotherapy to the regeneration of myocardial tissue and scar inhibition (Khan et al., 2025).

Regenerative outcomes benefit from precise control of release kinetics. Burst release of photo-crosslinkable osteogenic growth peptides (OGPs) was prevented by a scaffold composed of co-crosslinked photo-crosslinked gelatin and OGPs. With UV irradiation, the scaffold obtained sustained release of the growth peptides, which was desirable for supporting bone regeneration. The application of nanotechnology to regenerative medicine has reached a level of clinical practice, especially with the precision control of release kinetics of regenerative medicine, which is also a strong focus in the field (Maeso et al., 2026). Nanotech is used in regenerative medicine for improved interactions with cells and biomaterials to facilitate tissue repair. Many tissue engineering practices using a combination of scaffolds at the nanoscale level along with nanoparticles for drug and growth factor delivery, as well as nanofibers to support the overall structure design, are seeing much clinical success. The combination of scaffolding and active regenerative medicine is still a new concept, especially with the incorporation of gene delivery. Therapeutic scaffolds are biomimetically designed to integrate tissue with active gene delivery through the expression of genes at the site of injury to overcome physiological limitations linked to repair, will the suggested long-lasting effects, to support complex wounds which are especially challenging to heal, are traumatic, and chronic in nature (Zennifer et al., 2022).

10 Translational and clinical perspectives

Laboratory-demonstrated precision will only matter in the clinic if it survives the barriers of production, regulation, and reimbursement. This last barrier to realized precision delivery will be evaluated in this section. This section provides a translational perspective on smart biomaterial-based delivery systems, integrating insights from the data collected. [Section 10.1](#) summarizes the approved products and those that have been clinically evaluated. [Section 10.2](#) looks at the regulations around the assessment, [Section 10.3](#) describes the manufacturing barriers to reproducibility, and [Section 10.4](#) outlines the scale-up and commercialization issues that affect the delivery of clinically validated systems to patients. When read together, these sections show the areas of successful and stalled translational activity and the reasons for these.

The previous sections have detailed the development of smart biomaterials from passive nanocarriers to more sophisticated formulations involving active components that respond to specific stimuli, incorporate ligands, and utilize advanced algorithms. This section focuses on clinical realities. Here, we examine the smart biomaterials already in use. We take into account the main challenges and practical considerations for getting these materials from the lab into the clinic, focusing on the history of smart biomaterials, the main regulatory challenges, the main challenges to developing scalable manufacturing for smart biomaterials, and the main pathways to the commercialization of smart biomaterials ([Aravindan et al., 2024](#)).

10.1 Clinical success stories

For 7 years now, the history of nanomedicine has begun to be written. This journey has been laden with real revolutions and notable failures and has contributed, to a large extent, to the use and limitations of targeting with nanocarriers. One of the first anticancer drugs to be approved using nanocarriers was the PEGylated nanoliposome formulation of doxorubicin (Doxil), approved by the FDA in 1995, and by the EMA in 1996 with the formulation of Caelyx ([Tiwari and Pathak, 2011](#)). The incessant dedication of nearly five decades of researchers to liposomes and the advances of science allowed the development of remote drug loading, extrusion for homogeneous size, liposomes of long blood circulation, PEGylated liposomes, liposomes with triggered release, and liposomes with ligands of target; established lipidic nanoparticles became the first nanomedicine delivery system to undergo translation from a conceptual idea to a clinical application ([Galarza-Arévalo et al., 2026](#)).

The clinical reality of EPR-dependent nanomedicines has fallen short of the initial excitement surrounding them, but the last 3 decades of clinical practice have established nanomedicine as a viable cancer treatment option, featuring both good and bad cases. Following the approval of Doxil ([Barenholz, 2012](#)), the first 10 years saw a lot of optimism and hope for clinical success. However, Doxil and other targeted nanoparticles eventually met a growing skepticism after failing to achieve a number of clinical endpoints, most of which were attributed to substantial disillusionment and reliance on material-based engineering, with little regard for the

complex, advanced pathophysiology associated with cancer. A good example of this disruption in the pathophysiology of cancer is the unexpected, unfulfilled, and poor clinical expectations for Doxil. Evidence of the EPR effect in Doxil led many to hypothesize that doxorubicin conjugated to liposomes would outperform free doxorubicin in metastatic breast cancer. This hypothesis was quickly dispelled when doxorubicin liposomes and doxorubicin were shown to have an equivalent tumor response ([Salvioni et al., 2019](#)). Nonetheless, a number of nanomedicine formulations that advanced to the clinical setting demonstrated sustained commercial success in the oncology area. The advancement of nucleic acid nanomedicines demonstrates a recent and remarkable success. The progress from Doxil to Onpattro illustrates the advancement of lipid-based nanoparticle systems designed for gene therapies. The evolution of these systems led to the utilization of LNPs that significantly facilitated the fast clinical implementation of COVID-19 mRNA vaccines ([Wang et al., 2024](#)). Nab-paclitaxel (Abraxane) has a distinct profile. Solvent-based paclitaxel is the comparator for nab-paclitaxel. Patients in the paclitaxel arm had a lower response rate (19%) compared to those in the nab-paclitaxel arm (33%). Nab-paclitaxel also had a longer time to tumor progression (23.0 vs. 16.9 weeks; $P = 0.006$) ([Gradishar et al., 2005](#)). However, the increase in time to tumor progression was likely due to the formulation beneficial to dose-schedule intensity, resulting in decreased myelosuppression due to the removal of the castor oil-based solvent, rather than enhanced preferential accumulation of nab-paclitaxel to tumor sites. In advanced non-small cell lung cancer, one of the few studies to directly compare nab-paclitaxel to paclitaxel, nab-paclitaxel had a higher response rate (33% vs. 25%, $P = 0.005$) ([Socinski et al., 2012](#)). After these studies, it was shown that formulation design (which included drug delivery systems, but not particulate systems) of the drug to nanoscale level (which enhanced targeting and delivery of the drug to sites of interest) has played a much larger role than improved design of the particulated systems of the drug. Clinically approved smart drug-delivery products are listed in [Table 8](#).

10.2 Regulatory considerations

Regulatory assessments for nanomedicines differ significantly from those for traditional small-molecule drugs. This is caused by having far more multicomponent structures and complex, *in vivo*, multifunctional behaviors. Nanoscale drug delivery systems are much more complicated than traditional small drug molecules. Because of this complexity, the regulation of these delivery systems is much more challenging and is often behind the pace for new products in the area of medicine ([Stucchi et al., 2026](#)). Nanotechnology delivery systems, in particular, are being used as drug delivery systems to promote regulated and modified drug release to help address the problems of drug dosing and side effects in drug delivery, for which traditional. Similar findings have been reported for Abraxane, which exhibits improved pharmacokinetic properties, including drug clearance, retention, and half-life, compared with traditional drug-delivery systems ([Desai, 2012](#)).

There are two major regulatory authorities responsible for the oversight of nanomedicines in the large global pharmaceutical

TABLE 8 Clinically approved smart drug-delivery products.

Product	Carrier type	Payload	Indication	Approval status
Doxil/Caelyx (Barenholz, 2012)	PEGylated liposome	Doxorubicin	Kaposi sarcoma, ovarian cancer, and multiple myeloma	FDA 1995 (first approved nanomedicine)
Abraxane (Gradishar et al., 2005)	Albumin-bound (nab) nanoparticle	Paclitaxel	Metastatic breast, NSCLC, and pancreatic cancer	FDA 2005
Genexol-PM (Lee et al., 2008)	Polymeric micelle (mPEG-PDLLA)	Paclitaxel	Breast cancer and NSCLC	Approved South Korea 2007 (not FDA)
Onpattro (patisiran) (Adams et al., 2018)	Lipid nanoparticle (LNP)	siRNA	Hereditary transthyretin amyloidosis (hATTR)	FDA 2018 (first approved siRNA drug)
Comirnaty (Polack et al., 2020)	Lipid nanoparticle (LNP)	mRNA	COVID-19 vaccine	FDA 2021 (EUA 2020)
Spikevax (Baden et al., 2021)	Lipid nanoparticle (LNP)	mRNA	COVID-19 vaccine	FDA 2021 (EUA 2020)

markets. Each has their own philosophy and tools. The U.S. FDA and EMA as examples of global regulatory authorities establish and develop evaluation and approval frameworks for nanomedicines. These agencies are generally most interested in the pharmacology and biodegradation and environmental and nanomaterial toxicity and biocompatibility of nanomaterials. There are currently regional policy and framework differences that affect the global integration of the nanomedicine market (Rodríguez-Gómez et al., 2025). The FDA and the EMA are comprehensive studies that demonstrate that the FDA approves medications in a manner that is less time-consuming and with greater flexibility for the use of less complete data and use of surrogate endpoints than the EMA, which emphasizes long-term safety. The FDA approved 46 novel drugs in 2025, and the EMA had 38 active substances that fulfilled the criteria for a positive recommendation. An example of the regulatory maze that is similar for all nanomedicines is the difficulty in establishing therapeutic equivalence for generic or follow-on nanoformulations (Bowman and Gatof, 2015). The data requirements for the approval of nanomedicine follow-on products and the assessment of their therapeutic equivalence to the reference product are unknown to many stakeholders. In the EU, therapeutic equivalence may be approved by one of three different, simplified procedures, which may be generic, hybrid, or biosimilar. Regulators openly identify challenges in the reproducible and robust manufacture, scale-up, and stability of nanomedicine products. One challenge is drug loading and release, size and size distribution, and surface chemistry. Regulators are in the process of developing a guide for the standardization of analytical techniques for common quality attributes (Shore et al., 2024).

The nature of a smart biomaterial impacts the regulatory pathway that it must follow and the burden of proof it must meet, especially in relation to the product's risk classification. In the United States, products classified as lower risk are able to demonstrate substantial equivalence to a predicate device in the 510(k) process, while novel, low-to-moderate risk, predicate-less devices can utilize the *de novo* pathway (Aboy et al., 2024). The most challenging and highest-risk products must utilize the premarket approval process to provide evidence of safety and efficacy. The use of smart biomaterials adds complexity to this framework due to the product's combination nature; smart biomaterials are typically products that combine a therapeutic agent with a device or

delivery system. The product's classification is important and impacts the selection of the reviewing center, which in turn creates an impact on the evidence requirements and the review process. Invested time and resources in early and direct communication with the relevant regulatory authority to establish the classification of a product can greatly outweigh the impact of the time and resources spent due to a downstream product re-classification (Rawat et al., 2026). The still evolving guidance of the FDA and the ISO/EMA standards creates a divergence that impacts the requirements for product submissions. The use of smart biomaterials adds complexity to the framework. The FDA's Breakthrough Devices Program and other expedited pathways will shorten the process for reviewers but will not shorten the time required to generate the research to support the device (Teixeira et al., 2026).

10.3 Manufacturing challenges

One major hurdle to mass production of a medicine with nanoparticles that is compliant with Good Manufacturing Practice (GMP) regulations is the leap from laboratory production to industrial-scale production. This is particularly difficult with nanomedicine because of the extra complexity of combining multiple components (Operti et al., 2022). Nanomedicines and their manufacturing processes are significantly more complex than their small, single-component, traditional pharmaceutical counterparts. For this reason, and because nanomedicines contain multiple components at the nanoscale, the manufacturing processes used for traditional pharmaceuticals cannot be used. For this reason, the testing and release requirements for nanomedicines are also greater than the requirements for traditional pharmaceuticals (Bi et al., 2025).

Discrepancy among product batches is a large recurring issue for manufacturers. Translating successful developments from lab synthesis to large-scale synthesis that are effective and consistent within the confines of GMP is a large concern for chemistry, manufacturing, and controls (CMC). Regulatory bodies demand precise control and characterization of inter-batch variability of critical quality attributes (CQAs), describing the following: morphology, particle size and size distribution (polydispersity index), surface charge (zeta potential), composition, drug loading,

encapsulation efficiency, and *in vitro* release profile. These descriptions, as even minute changes in the particle size of a formulation (10 nm), can significantly change the pharmacokinetics and the biodistribution (Desai et al., 2025). Quality-by-Design frameworks are increasingly integrated with process analytical technology (PAT). In this approach, CQAs are ascertained during the production process, rather than at the completion of the finished batch. This approach aligns best with the continuous microfluidic processes. In such processes, deviations like changes in particle size or polydispersity can be adjusted in-process, as opposed to being discovered during release testing. This means quality control is ascertained in-process as opposed to being performed during the final inspection. Batch-to-batch variability (BV) of a formulation, high cost of scale-up, and immunological recognition of a product resulting in accelerated blood clearance are critical barriers across the field of nanomedicine. Traditional synthesis process of small batches seldom meets the demands of large-scale production. Emulsification, nanoprecipitation, and microfluidic synthesis innovations developed in the laboratory are difficult to replicate large-scale synthesis. Continuous manufacturing combined with microfluidic technologies is preferred to produce homogenous particle size but also brings the challenges of meeting client demands of large-scale production and regulatory compliance, which increase the cost of production with the need for advanced analytical equipment and extensive quality control. These challenges can be overcome in part with new approaches such as nanocrystallization, extrusion, supercritical fluid technologies, and microfluidics which have different impacts on cost, scalability, and reproducibility of nanomaterials. The application of GMP and Quality-by-Design frameworks is effective in ensuring batch-to-batch uniformity for nanomaterials (Alemie et al., 2025).

The replicability of precision at larger scales is crucial to assessing the impact of precision seen at the lab bench. Many high-potential materials face their greatest hurdle at this stage. Viability shown under lab conditions does not address the challenges faced at scale under GMP standards (Tripathi et al., 2024). These challenges dictate a validation and documentation framework for each process step, along with a variety of rigid process constraints. Reproducibility at scale is particularly problematic for precision delivery systems, such as multicomponent carriers, polymers, targeting ligands, and stimuli-responsive linkers. Here, maintaining consistent particle size, surface chemistry, and drug loading from lot to lot becomes even more difficult (Suksaeree et al., 2026). This is an increasing problem for carrier systems which are laden with cells and which also carry biologics. These systems also face the problem of guaranteeing a uniform distribution of the payload at the large scales required for commercial production. Combining the challenges of terminus sterilization with the constraints outlined poses a problem to the design of such systems. The Quality-by-Design framework is the most systematic response to the reproducibility challenges and the challenges of modern biomanufacturing (Fuchs et al., 2020).

10.4 Scale-up and commercialization

Aside from the challenges faced in manufacturing that hinder reproducibility, the commercial viability of smart biomaterial-based

delivery systems also highly depends on the economic factors, market considerations, and infrastructural systems that ultimately establish if a clinically validated nanomedicine will be available to patients in a meaningful time frame. An increasing number of assessments to enable the scale-up process, such as the manipulation and preparation of nanomaterials, batch production size, stability testing, and applicable methods, as well as proper filing and record-keeping, will allow the reliable manufacturing of nanomedicine. The production of nanomedicine in large batches will offer opportunities to conduct comprehensive preclinical and clinical trials. Recent advancements in microfluidic tools and multiparameter, computer-integrated modeling and optimization approaches are paving the way for the controlled assembly of nanomedicine with the desired batch size for clinical trials (Hrapović et al., 2026; Tiboni et al., 2021).

Moving from small- to large-scale production incorporates process dynamics that are different from those at small volumes. Some of these dynamics are mixing, shear, solvent removal, heat, and mass transfer. Because these are all different at large volumes, even if a process has been optimized at small scale, it usually has to be considerably modified to produce consistent product at scale (Chen et al., 2026). Before large amounts of capital are spent, manufacturing at the pilot scale is the best way of optimally scaling the process and using equipment that is similar to commercial equipment. Smart development biomaterials and nanomedicines can also be cited as a cost constraint because the development of the product is expensive because of the research and the multiple steps of complex manufacturing and lengthy clinical development. Additionally, the cumulative building costs of the product restraints the per-dose price, which limits the use of the product in cost-limited health systems. Even after a product is approved, it will not be available without the payer coverage, which is a reimbursement barrier. N.A. has well-established reimbursement systems and a mature market, whereas other parts of the world have less developed markets and are less profitable (Bi et al., 2025). Representative clinical-stage smart nanomedicines are mentioned in Table 9.

The argument for the economics of nanomedicine, despite the obstacles, has proven strong, particularly with the market growth predicted to be strong. From 2024 to 2025, the nanomedicine market revenue is predicted to increase from \$331.61 billion to \$375.87 billion, at a compound annual growth rate of 13.3%. Certain growth trends will be the development of multifunctional nanoparticles that combine therapeutics and imaging, expansion of nanoparticle-based diagnostics, increased usage in regenerative medicine, and growing applications and use of nanomedicine to target and treat neurological disorders (Germain et al., 2020). The year 2026 is predicted to be a year of transformation for the nanomedicine industry, especially with the growth of advanced and established nanomedicine and imaging agents, the expanded use and adoption of mRNA-based nanomedicine beyond the vaccine, the advanced use of nanorobotics, and a host of other breakthroughs. The integration of AI, ML, and novel advanced highly accelerated and enhanced computational modeling will ease the burden of drug discovery and development. Unfortunately, for smaller players in the industry, there will be a host of challenges to the broader commercialization of nanomedicine (Bawa, 2007). Synthesis of nanomaterials, characterization, and scaling will

TABLE 9 Representative clinical-stage smart nanomedicines.

Candidate	Carrier/trigger	Payload	Indication	Status (highest phase reached)
ThermoDox	Thermosensitive liposome (heat-triggered)	Doxorubicin	Hepatocellular carcinoma	Phase III- HEAT/OPTIMA trials: did not meet primary endpoints (Rachamala, 2025)
NK105	Polymeric micelle	Paclitaxel	Metastatic breast cancer	Phase III; did not meet the non-inferiority endpoint (Srivastava et al., 2026)
CRLX101	Cyclodextrin-polymer nanoparticle	Camptothecin	Renal cell carcinoma (Srivastava et al., 2026)	Phase II; development largely halted
CALAA-01	Transferrin-targeted siRNA nanoparticle (Srivastava et al., 2026)	siRNA	Solid tumors	Phase I; first targeted siRNA in humans, discontinued

TABLE 10 Key translational and commercialization challenges for smart biomaterial drug-delivery systems and current mitigation strategies.

Translational challenge	Underlying issue	Mitigation/current direction	Ref.
GMP manufacturing	Laboratory-scale performance does not guarantee GMP-compliant, validated production	Early GMP-compatible process design; process analytical technology	(Al et al., 2025)
Reproducibility/batch variability	Multicomponent nanocarriers multiply sources of variance in size, loading, and surface chemistry	Quality-by-design; design-of-experiments; real-time monitoring	(Ansari et al., 2024)
Sterilization	Gamma/ethylene oxide can alter degradation kinetics and payload integrity	Co-select method with material; re-validate post-sterilization properties	(Haim et al., 2019)
Scale-up	Mixing, shear, mass-transfer dynamics differ between the bench and plant scale	Pilot-scale validation before capital commitment	(Li et al., 2016)
Cost	Capital-intensive development → high per-dose pricing	Platform/modular manufacturing; process efficiency	(Baldea et al., 2017)
Regulatory approval	510(k)/De Novo/PMA and combination-product classification set differing evidentiary burdens	Early agency engagement; correct classification; accelerated pathways	(Gupte et al., 2025)
Reimbursement	Approval does not guarantee patient access	Health-economic evidence; early payer engagement	(Akhmetov and Bubnov, 2017)

require expensive integrated advanced infrastructure that will also be a barrier to their entry. Responding to advanced manufacturing and strict quality control has already been evidenced in the recent commercial industry developments. Full GMP approval for complex nanomedicine formulations has been achieved by contract development and manufacturing organizations. There remains a strong commitment for continued clinical investment with the National Cancer Institute sponsoring a Phase 1 study in 2025 to develop smart therapeutic biomaterials for commercial applications (Malyshev et al., 2024). Commercialization challenges for smart biomaterial drug delivery systems and current mitigation strategies are summarized in Table 10.

11 Current challenge and Future Directions

After analyzing the frameworks, tools, and workflows for smart biomaterial-based precision drug delivery, this section addresses the challenges that inhibit clinical utilization. It describes the phenomena

that this discipline will have to confront. The issues of toxicity, biological variability, and unrealized full customization, discussed in this section, are not merely technical details. They will ultimately determine whether the solutions proposed in this review will enable the envisioned patient-specific delivery of drugs (Liu et al., 2016).

11.1 Safety and toxicity concerns

There have been many advancements in carrier design, but the long-term safety of engineered nanomaterials is still not fully understood. Nanotoxicology is still trying to catch up with the development of nanocarriers. Nanoparticles are widely used in nanomedicine, but their small size and their unique properties are the cause for safety concerns. The dimension, shape, the functional groups present on the surface, and the dose all are important in determining the toxicity of nanoparticles (Xuan et al., 2023). Chemically synthesized nanoparticles tend to be more toxic, possibly because of the presence of the chemical residues from the synthesis, while biosynthesized particles tend to have surface groups that are biocompatible, suggesting lower

toxicity. Several studies have shown that nanoparticles can be highly damaging to health if the body is not sufficiently protected and the nanoparticles are allowed to come into contact with the body by ingestion, inhalation, or through the skin. The level of toxicity is highly dependent on characteristics like the size of the particle; the surface area, shape, and the size of the particle when resolved; how the particles are grouped or measured; and how pure the particles are. The toxicity of nanoparticles is induced when reactive species are formed and cytotoxicity, genotoxicity, and neurotoxicity effects are initiated (Singh et al., 2020).

The need for material-specific toxicological profiles makes developing safety guidance for the various classes of nanocarriers even more difficult. To gauge risks for various types of nanoparticles (SPIOs, dendrimers, mesoporous silica particles, gold nanoparticles, and CNTs), it is necessary to understand their biocompatibility and their distribution and degradation in the body and to understand the type of nanomaterial and its impact on different cells, including those of the immune system (Kurul et al., 2025). There are also limitations with existing methods to evaluate the risk. In the field of nanotoxicology, particular methods can rely heavily on *in vitro* cell tests. These tests can fail to capture the complexity of drug activity in addition to organ toxicity and multiple cellular-level toxicities, as evidenced in the preclinical and clinical phases (Li et al., 2012). There are no established methods to determine the toxicity of nanoparticles; thus, the field of nanotoxicology is evolving and developing. The unresolved questions regarding the potential hazards of nanomaterials (e.g., high surface area, increased reactivity, and tunable electronic and optical properties) which contribute to their therapeutic efficacy are, in essence, the basis of the physicochemical props of nanomaterials and the best response to those concerns. These responses may include risk assessment, design for safety, surface modification, and the harmonization of regulatory frameworks. This also includes the safe use and disposal of nanomaterials (Kyriakides et al., 2021).

A factor that is important, but frequently neglected, is the protein corona. Upon entering the bloodstream, nanoparticles, within seconds, are coated by plasma proteins, thereby developing another biological identity that is different from its designed surface, determining its biodistribution and clearance (Tenzer et al., 2013). It may be possible that the protein corona may also conceal targeting ligands which are attached and designed to be exposed on the surface. The size and charge of the nanoparticle are contributing factors to how the corona is formed, as well as the surface chemistry. These are the major contributing factors for the differences that are observed when *in vitro* and *in vivo* results are compared (Walkey and Chan, 2012).

This is how we assess long-term risks: biodegradable carriers like PLGA and lipid carriers degrade to native metabolites over time and are processed enzymatically. However, carriers like gold, silica, and carbon are persistent in tissues as they undergo little or no degradation. This means for long-term safety, the end-products of degradation and the pathways they take are more important than the acute cytotoxicity, when compared to chronic or repeated dosing routines.

11.2 Biological variability

The major obstacles to precision drug delivery include biological variability both within and between patients, which undermine the

targeting methods described in this review. One example is the EPR effect, which forms the basis of passive tumor targeting. In the last 5–10 years, it has been increasingly appreciated that there is extensive inter- and intra-patient variability of EPR-mediated tumor targeting, which has contributed to the varied outcomes of clinical trials conducted to investigate the use of nanomedicines (Islam et al., 2025). In particular, to cope with this variability, it is necessary to move beyond the traditional passive tumor-targeting methods and develop new approaches to nanomedicine, which will provide a more tailored solution. When the extent of the problem is assessed, the clinical data indicate that on average, less than 1% (approximately 0.7%) of the administered dose of a nanocarrier actually reaches the solid tumor, illustrating the inadequacy of the reliance on passive targeting, a problem that stems from the highly variable nature of the EPR effect, which is present across the tumor type, site, tumor size, vascular architecture, and patient pathologies (Wu, 2021).

The EPR effect adds a layer of complexity to inter- and intra-patient variability seen across the development of drug therapies and, thus, cannot be considered a static property, even within a single patient. Heterogeneity among patients is further exacerbated with more aggressive double-dose nanotaxane therapy, and higher EPR-based tumor accumulation was found to correlate with therapy success when tracked over time with imaging (Wu, 2021). TME pathophysiological features and stromal properties, such as density and the ECM, as well as hypoxia and interstitial fluid pressure, represent significant heterogeneity and must be addressed to offer enhanced and individualized frameworks of targeted nanomedicine. In response, the field is employing patient stratification as a complementary approach, along with non-EPR-based delivery (Subhan et al., 2023). Such strategies may place an emphasis on the tumor endothelium, transcytosis, or cell-mediated delivery and may reside within the same tumor. Such approaches will facilitate the development of next-generation nanomedicines that seek to move beyond the limitations of EPR-optimized delivery while remaining flexible and targeted for a highly diverse patient population. In light of the significant inter- and intra-patient heterogeneity, there is an overwhelming consensus among researchers that the EPR effect is evaluated on a patient-by-patient basis. In such cases, it is suggested that EPR-positive patients, in whom a significant accumulation of nanodrugs is observed, be targeted and treated with nanodrug formulations (Sun et al., 2022). Companion imaging is one way to make that determination. Ferumoxytol, which is an SPIO of approximately 30 nm that has recently been approved to treat iron deficiency anemia, can be used as an imaging surrogate. Because in tumor imaging therapeutic nanoparticles often co-localize, even when they have different physicochemical properties, quantitative ferumoxytol-enhanced MRI can be used as a proxy to estimate the extent of EPR-mediated deposition in advance of treatment (Miller et al., 2015). In a clinical pilot study, imaging of ferumoxytol deposition by MRI predicted the response of the lesions to treatment with nanoliposomal irinotecan in patients with advanced solid tumors. This shows that the same imaging agent can be used as a generic companion diagnostic for different nanotherapeutics and that using the same agent can

avoid the regulatory and financial burden of a therapeutic agent being radio-imaged (Ramanathan et al., 2017). The method has important limitations owing to fundamentally different sizes of the imaging agent and the therapeutic agent and the small-scale studies. Nevertheless, this is a viable method to improve the situation for EPR heterogeneity, which has previously been an unknown and largely unquantifiable barrier for assessing the viability of a clinical study.

11.3 Personalized drug delivery

The biological variability discussed previously has stimulated a change toward truly individualized drug delivery systems. These systems are created with the unique genetic, physiological, and disease characteristics of the individual patient. Personalized medicine provides the ability to create therapeutics that are specific to a target and allow for stratification of patients. However, personalized medicine by itself does not address the barriers to delivery that restrict the distribution of a therapeutic and its safety. Because of this, delivery systems are needed to incorporate the molecular stratification of a therapeutic and the requirements of physical and pharmacokinetic aspects of delivering the therapeutic to its target (Puccetti et al., 2024).

Nanotechnology-based drug delivery systems are an exciting area of research as a component of personalized medicine, involving the application of pharmacogenomics, gene editing, and nanoparticles. Development of new drug delivery systems that incorporate nanotechnology into pharmacogenomics will impact drug delivery systems and create new opportunities to address other problems in pharmacogenomics, including drug resistance and the use of nanoparticles. Integration of these technologies is allowing for a new generation of clinical applications (Durgam and Oroszi, 2025). These technologies are beginning to be used in the treatment of cancers such as leukemia and other solid tumors. Systems that use AI to design optimal pharmacotherapy based on patient testing, as well as 3D printing systems, have been developed to design optimal drug delivery systems that combine different drugs in a single pill with safe and effective dosing for children. The agenda for personalized medicine extends to drug delivery systems. Nanotechnology allows for tailoring drug delivery systems to the needs of individual patients in order to improve the effectiveness of a therapy. Nanotechnology also allows the design of drug delivery systems that focus the therapy on the affected diseased tissue while minimizing the effects of the therapy on healthy tissue (Eze et al., 2026).

11.4 Precision medicine integration

To realize the full potential of smart biomaterials, drug delivery systems need to integrate more with the rest of the precision medicine landscape (e.g., companion diagnostics, biomarker-oriented patient stratification, and the tracking of patients' responses to treatment) rather than being developed as separate therapeutic systems (Seyhan and Carini, 2019). Advanced precision medicine and, especially, precision oncology are destined to be disruptive and revolutionary. Instead of the traditional "one size fits all" approach, where a drug is given to all patients with a given cancer, the new approach is to develop highly effective and highly rational therapies that are more biologically aligned with the patient.

For this new approach to be successful, there also needs to be a parallel development of highly efficient and clinically relevant biomarkers and their companion diagnostics alongside drug delivery systems (Krzyszczuk et al., 2018).

Rapid evolution is seen in the regulatory and clinical infrastructures relevant to this integration. Essentially, companion diagnostics identify a treatment based on its relevant biomarker and identify which patient is most likely to benefit from that treatment. Although companion diagnostics were developed predominantly in the field of oncology, the focus and scope of these diagnostics are gradually broadening to include other disciplines, such as cardiology, neurology, and infectious diseases, as well as rare disorders. Designing companion diagnostics alongside drug candidates for therapeutic use is an increasingly accepted practice in order to achieve simultaneous regulatory approvals (Kadam et al., 2025). Balancing the needs of the industry, regulators have incorporated companion diagnostics with a focus on accelerating patient use. Alongside these developments, distinct improvements in data accessibility, AI, and advanced analytics have the potential to significantly enhance the quality of clinical decision-support systems and sophisticated frameworks for integrating real-world data with diagnostic services. Regarding smart biomaterial-based delivery systems, this means that design choices, such as the carriers and dosing used, can be determined based on an individual patient's diagnostics and biomarkers, rather than being uniformly applied to a population of patients with the same disease. This would include both inter-patient and intra-patient variability (Fahim et al., 2025).

11.5 Future research priorities

Looking to the future, the field is converging on personalized, precision-guided delivery. Many of the imminent directions are focused on biomarkers for patient selection, where nanomedicines are assigned to patients whose tumor or disease phenotype predicts a response; companion diagnostics that combine a therapeutic carrier and an available diagnostic to define eligibility; pharmacogenomics-driven therapeutic carriers that are formulated to the patients' metabolic and transport phenotypes; and the use of 3D printing to create flexible personalized dosage forms. The realization of these directions will require incorporating AI/ML design tools (Section 8), stimuli-responsive systems (Section 5), and translational safeguards (Section 10) into iterative development pipelines.

Despite the fact that pharmacologically complex platforms are being designed, a number of challenges that remain largely unsolved have to be addressed first. A significant issue is the gap between expected and actual performance seen in late-stage clinical trials for multiple stimuli-responsive and actively targeted platforms. This is the result of the variable EPR effect between patients and tumors, the difficulty of GMP-scale production for complex large constructs, long-term biosafety and immunogenicity being unknown, and no international regulatory harmonization for unit component testing. Addressing these issues will be critical for the wide clinical adoption of smart biomaterials.

Addressing the challenges discussed in this review identifies key areas of research that are necessary for the development of smart biomaterials. These therapeutics have the potential to make laboratory and early-stage clinical biomaterials more available and effective. To close this gap, more resources will need to be allocated

for developing new predictive models. As discussed in Section 8, OoC systems, DTs, and AI simulations are all examples of models that may make predictions of how these materials behave in humans and, therefore, decrease the expenditures associated with performing nonpredictive clinical trials (Liu M. et al., 2025).

Second, the combination of nanocarrier design with multi-omics, AI-enhanced biomarker discovery and nanotechnology is emerging as one of the most dynamic fields. Biomarkers help clinicians categorize patients to design targeted treatments, and ML is being used to sort out profiles and rank possible treatments in the order of most likely beneficial and least harmful, potentially integrating treatment suggestions into regular diagnostic processes, thereby aiding pharmaceutical companies in their biomarker and target discovery efforts. Developing comprehensive systems to evaluate AI technologies in this space is critical. The technology to deploy AI-based diagnostics is far ahead of the systems to assess its clinical integration. Therefore, preliminary systems for the adoption of AI diagnostics in research labs is critical (Bae et al., 2025).

Third, we need to focus on the standardization of nanotoxicology frameworks. This is important for making safety assessments for different biomaterials more consistent and reliable. Nanotoxicology studies focus on the hazards of nanoparticles and potentially harmful effects. This is done by characterizing particles, determining hazard and exposure pathways, assessing the biological distribution, and conducting genomic studies and regulatory assessments. This study integrated many of these components which are, unfortunately, not standardized in the field (Kumar et al., 2025). Fourth, because of the issues with the passive targeting of nanoparticles across different patients and tumor types, research should focus on mitigating the heterogeneity of the EPR effect. This can be done by incorporating patient stratification techniques, which include imaging assessments of the EPR effect prior to treatment, as well as different, non-EPR targeting strategies. Finally, to achieve the various levels of mechanistic detail and rational design in drug delivery systems across the continuum of stimuli and ligand-based systems and AI-driven carriers, it will be necessary for material scientists, clinicians, regulatory bodies, and computational researchers to collaborate. This will give the systems the potential and capacity to meet the initial goals of precision drug delivery for the right patient (Sridhar et al., 2025). Challenges and future directions in the clinical translation of smart biomaterials are summarized in Table 5.

12 Conclusion

This review reflects an important shift in pharmaceutical science. The examples range from the first sustained-release polymer matrices developed in the 1950s to contemporary nanocarriers that are stimuli-responsive, ligand-targeted, and optimized with the aid of computer algorithms. There have been fundamental changes to the ways in which drugs and drug delivery systems are developed. The emphasis has changed from the ways in which drugs and drug delivery systems accommodate the pharmacokinetics to the ways in which drug delivery systems

interact with the body. This review places smart biomaterials at the center of these changes. The systems use natural and artificial materials of all kinds, and they are no longer passive supports. Rather, they play an active role in the therapeutic process. These materials can be designed to respond to and to sense pH, redox, and other imbalances, as well as changes in temperature and external stimuli, including light, sound, and magnetic fields. These materials can be designed to respond and release therapeutic agents at specific locations in the body and to do so at specific times.

The precision targeting concepts covered in this review, mostly passive targeting via EPR effect and active targeting via antibodies, aptamers, and peptides as well as receptor-specific ligands, show that achieving site-specific delivery is difficult to attain via any single mechanism. An optimum delivery system will incorporate various targeting and release mechanisms, including dual passive and active targeting, multiple stimuli-responsive carrier systems and ligands, and functionalized systems that are responsive to stimuli. This same approach is evident in the macroscopic delivery systems discussed in this review. The injectable systems, implants, MNs, transdermal systems, and oral and colon delivery systems strive to overcome anatomical and physiological challenges. Many of the recent delivery innovations including the AI-guided design, OoC technology, microfluidic delivery, and nanorobotics, will help improve the interface between delivery systems and living organisms in ways that have not previously been possible.

This field covers many therapeutic areas including not just oncology but also cardiovascular and neurodegenerative diseases, as well as infectious diseases, gene therapies, and regenerative medicine. The range demonstrated in this field shows that smart biomaterials are a platform science and are not a specialized technology. Certainly, the information on the translation and the clinics here encourages tempered optimism. In the last 30 years, there has been a real success from Doxil to Onpattro to the COVID-19 mRNA vaccines, but there have been many hard experiences: The EPR effect, which was the first successful argument in cancer nanomedicine, showed that the effect is far more heterogeneous in various tumors and patients. Reproducibility of the manufacturing process beyond the laboratory continues to present challenges, and great variability persists in the regulatory frameworks across the global markets and the balance of concerns. These are not peripheral issues but will determine if the scientific sophistication is to have any reliable benefit.

Future growth in this field will probably be characterized less by the breakthroughs of new materials and more by how current techniques coalesce within the larger framework of precision medicine, including biomarker-driven patient selection; companion diagnostics; pharmacogenomics to inform dosing; and the predictive design of an AI paradigm, along with the biomaterials described in the present review. Meeting the challenges of translatable nanomaterials and the balance of inter- and intra-patient bio variability will be required for the integration of nanomaterials in medicine to succeed. When such challenges are addressed, intelligent biomaterials are ideally suited to the vision for smart drug delivery articulated at the start of this review and will deliver the right therapy, to the right place, at the right time, to the right patient, thus enabling the precise and controlled release of therapeutics to become common practice.

Author contributions

SS: Methodology, Software, Visualization, Writing – review and editing, Validation, Writing – original draft, Data curation, Investigation, Conceptualization. RB: Writing – review and editing, Visualization, Data curation, Software. CS: Software, Visualization, Writing – review and editing. JJ: Writing – review and editing, Visualization, Data curation.

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