

"A Novel Drug Delivery System for Targeted and Controlled Drug Delivery: Recent Advances and Future Perspectives"

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GRAPHICAL ABSTRACT

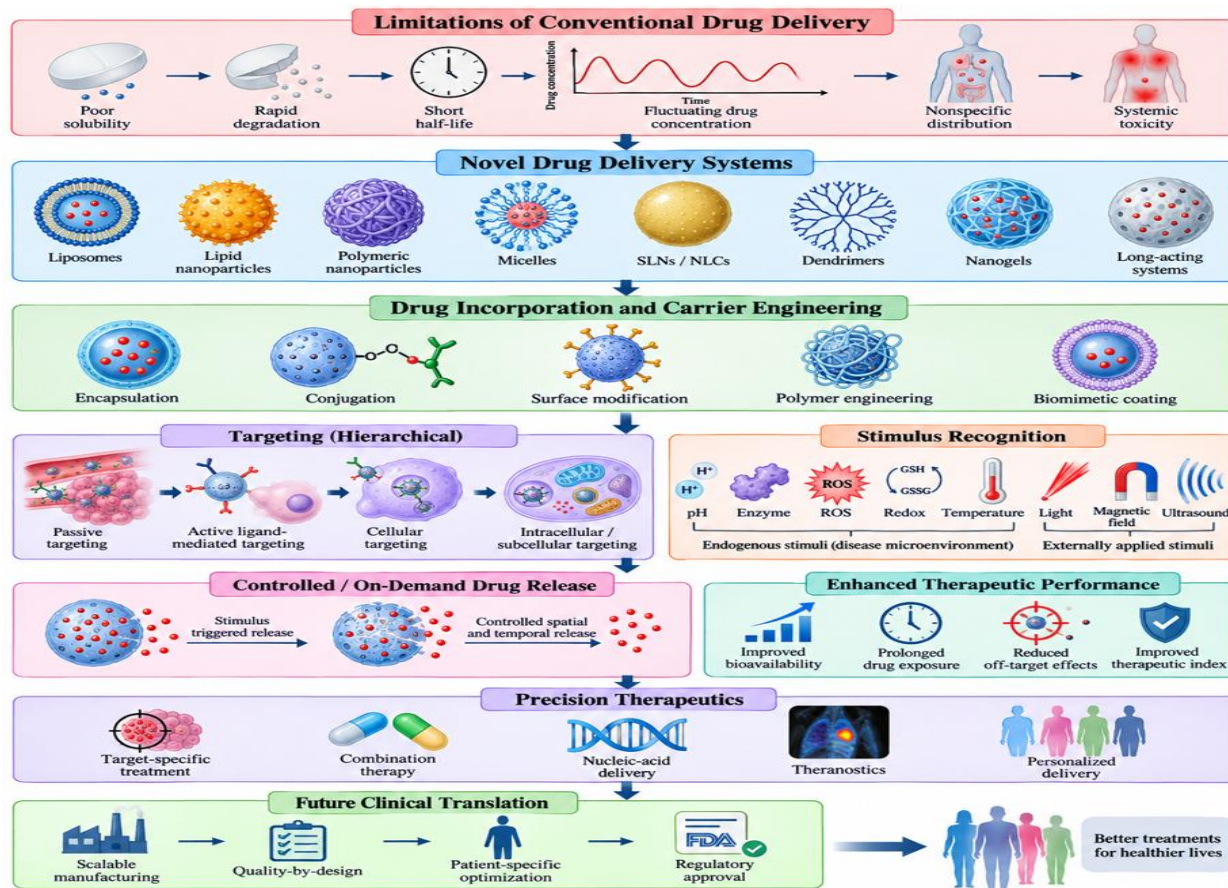


Figure 1. Graphical Abstract: Integrated strategy for targeted and controlled drug delivery.

Figure 1. Graphical Abstract [1]

Abstract—Novel drug delivery systems (NDDS) have emerged as an important area of pharmaceutical research because conventional dosage forms frequently encounter limitations related to poor solubility, instability, rapid elimination, nonspecific distribution, fluctuating plasma concentrations, and dose-related toxicity. Modern delivery technologies seek to overcome these limitations by controlling the spatial and temporal distribution of therapeutic agents. The evolution of NDDS has progressed from sustained-release formulations and depot systems toward multifunctional platforms capable of targeted transport, controlled release, intracellular delivery, and stimulus-responsive drug liberation. Liposomes, polymeric nanoparticles, lipid nanoparticles, polymeric micelles, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, nanogels, implantable systems, microneedles, and hybrid carriers have been investigated for improving therapeutic performance. Targeting can be achieved through passive accumulation, ligand-mediated recognition, tissue-specific administration, or intracellular and subcellular mechanisms. In parallel, endogenous stimuli such as pH, enzymes, reactive oxygen species, glutathione, and hypoxia, as well as external stimuli including light, temperature, magnetic fields, and ultrasound, have been exploited to achieve controlled or on-demand release. Recent advances in lipid nanoparticles have particularly expanded the application of drug delivery toward messenger RNA and other nucleic-acid therapeutics. At the same time, biomimetic carriers, theranostic systems, long-acting formulations, and multifunctional nanoplateforms are being developed to integrate therapeutic and diagnostic functions. Despite substantial progress, clinical translation remains constrained by biological barriers, protein-corona formation, heterogeneous target expression, unpredictable biodistribution, immunological responses, formulation instability, manufacturing complexity, scale-up requirements, and regulatory considerations. Future development is therefore expected to focus not merely on increasing formulation complexity but on achieving predictable pharmacokinetics, reproducible manufacturing, clinically meaningful targeting, patient-specific optimization, and improved safety. This review critically discusses the evolution, major platforms, targeting mechanisms, controlled-release strategies, recent technological developments, clinical translation, challenges, and future perspectives of targeted and controlled NDDS.

Index Terms—Novel drug delivery systems; targeted drug delivery; controlled release; nanocarriers; lipid nanoparticles; polymeric nanoparticles; stimuli-responsive delivery; precision medicine.

I. INTRODUCTION

Drug delivery is a fundamental component of pharmaceutical therapy because the therapeutic activity of a drug depends not only on its pharmacological properties but also on the ability to reach the appropriate biological site at an effective concentration and remain there for an adequate period. Conventional dosage forms such as immediate-release tablets, capsules, injections, and conventional topical preparations generally provide limited control over the spatial and temporal distribution of therapeutic molecules. Consequently, rapid elimination, incomplete absorption, enzymatic degradation, poor aqueous solubility, nonspecific distribution, and concentration-dependent toxicity can compromise therapeutic outcomes.

The concept of NDDS developed in response to these limitations. Rather than simply administering a predetermined dose, NDDS technologies attempt to modify drug disposition through controlled release, improved solubilization, protection against degradation, prolonged circulation, altered tissue distribution, or selective delivery. Contemporary NDDS research encompasses a broad spectrum of systems ranging from polymeric matrices and long-acting depots to nanoscale carriers and intelligent stimulus-responsive platforms. [2]

Nanotechnology has substantially expanded the possibilities of NDDS because nanoscale materials can be engineered with specific particle sizes, surface properties, morphologies, compositions, and drug-loading characteristics. These parameters influence circulation, cellular interactions, tissue penetration, drug release, and elimination. Nanocarriers can also accommodate therapeutic molecules with very different physicochemical characteristics, including poorly water-soluble compounds, proteins, peptides, and nucleic acids. [3]

Targeted drug delivery represents a further refinement of this concept. Conventional systemic administration exposes multiple tissues to the active molecule, whereas targeted delivery seeks to increase the relative exposure of a therapeutic agent at a selected tissue, cell, or intracellular compartment. Targeting can occur through passive mechanisms related to tissue physiology or through active mechanisms involving molecular recognition between carrier-associated ligands and cellular receptors. However, successful

targeting requires more than ligand attachment because the carrier must first survive circulation, reach the relevant tissue, overcome biological barriers, and interact with the intended target. [4]

Controlled drug delivery addresses the temporal component of therapy. Instead of releasing the complete drug dose immediately after administration, a delivery system can regulate release through diffusion, polymer degradation, matrix erosion, swelling, membrane permeability, chemical cleavage, or stimulus-induced structural changes. Long-acting systems can therefore maintain drug exposure for extended periods and potentially reduce dosing frequency, an especially important consideration in chronic disease management. [5]

A major contemporary development is the emergence of stimuli-responsive or intelligent drug delivery systems. These systems are designed to detect specific physiological or pathological conditions and alter their properties accordingly. Endogenous triggers include pH, enzyme activity, redox conditions, reactive oxygen species, glucose, hypoxia, and intracellular metabolites. External triggers can include light, temperature, ultrasound, magnetic fields, and electric fields. Such systems aim to achieve spatiotemporal control over therapeutic release. [6]

The clinical importance of advanced delivery technology has been demonstrated by the successful translation of several liposomal and lipid-based products. Liposomes have been used clinically for multiple therapeutic applications, while lipid nanoparticles have enabled the clinical use of mRNA-based medicines and vaccines. These examples demonstrate that advanced delivery systems can become pharmaceutical products when formulation performance, manufacturing, safety, and regulatory requirements are appropriately addressed. [7]

Nevertheless, the translation of experimental NDDS remains considerably more difficult than their formulation at laboratory scale. Nanocarriers encounter a sequence of biological barriers beginning immediately after administration. Protein adsorption can generate a dynamic protein corona, followed by interactions with immune cells, organs of clearance, vascular barriers, extracellular matrix, cellular membranes, endosomal compartments, and intracellular trafficking pathways. These biological processes can substantially alter the behavior originally predicted from in vitro characterization. [8]

Therefore, the current scientific challenge is not simply to develop increasingly sophisticated carriers but to establish delivery systems whose behavior is predictable, reproducible, scalable, clinically meaningful, and safe. This review examines the evolution of targeted and controlled drug delivery, major carrier classes, molecular and cellular mechanisms, therapeutic applications, formulation strategies, recent advances, clinical translation, limitations, and future directions.

II. BACKGROUND AND EVOLUTION OF NOVEL DRUG DELIVERY SYSTEMS

The evolution of drug delivery systems can be broadly understood as a transition from dose administration toward control of drug disposition. Early pharmaceutical formulations primarily focused on providing a stable and convenient dosage form. Immediate-release preparations remain indispensable because they can rapidly establish therapeutic concentrations, but their performance may be inadequate when prolonged exposure or localized treatment is required.

The introduction of sustained-release systems represented an important step toward temporal control. Matrix tablets, reservoir systems, microspheres, implants, and depot injections were developed to slow drug liberation and maintain therapeutic concentrations for longer periods. Modern long-acting delivery systems include injectable suspensions, PLGA microspheres, oil-based depots, in situ-forming implants, preformed implants, and polymer-drug conjugates. These approaches can reduce dosing frequency and potentially improve treatment adherence. [9]

The development of colloidal carriers subsequently created opportunities to modify the distribution of drugs within the body. Liposomes became particularly important because their phospholipid architecture can accommodate both hydrophilic and hydrophobic molecules. Their composition, size, surface properties, membrane characteristics, and drug-loading method can be modified to influence circulation and release. Several liposomal products have progressed to clinical use, establishing liposomes as one of the most clinically validated nanocarrier classes. [10]

Polymeric nanoparticles provided another important platform. Biodegradable polymers can be designed to

encapsulate drugs and release them through diffusion or polymer degradation. Their surfaces can additionally be modified with ligands or polymers to influence circulation and targeting. Despite extensive preclinical research, however, polymeric nanoparticles have achieved considerably less clinical penetration than liposomal systems, highlighting the importance of manufacturing and translational considerations. [11]

The emergence of lipid nanoparticles substantially broadened the scope of drug delivery. Unlike conventional formulations designed primarily for small molecules, lipid nanoparticles have become important carriers for nucleic acids. Their composition commonly includes ionizable lipids, phospholipids, cholesterol, and polyethylene glycol-associated lipids. This architecture facilitates nucleic-acid encapsulation, protection from degradation, cellular uptake, and intracellular release. [12]

The development of targeted systems introduced molecular recognition into carrier design. Ligands such as antibodies, peptides, aptamers, carbohydrates, and receptor-specific molecules can be incorporated

into delivery systems to improve interaction with selected cell populations. However, target expression can vary with disease stage, tissue type, patient characteristics, and cellular heterogeneity. Consequently, active targeting is increasingly being integrated with other delivery mechanisms rather than considered a stand-alone solution. [13]

The latest generation of NDDS incorporates stimulus-responsive behavior. In these systems, carrier architecture is designed to respond to a disease-associated or externally imposed signal. pH-sensitive, enzyme-sensitive, redox-sensitive, temperature-sensitive, light-responsive, magnetic, and ultrasound-responsive systems have all been investigated. Dual- and multi-responsive systems attempt to increase selectivity by requiring more than one stimulus before substantial drug release occurs. [14]

The field has therefore progressed from simple controlled-release matrices toward multifunctional delivery systems integrating targeting, controlled release, intracellular trafficking, imaging, and therapeutic action.

Table 1. Evolution of drug delivery systems toward targeted and controlled delivery [15]

Development stage	Representative technology	Primary objective	Major limitation
Conventional delivery	Tablets, capsules, injections	Administration of therapeutic dose	Limited control over distribution
Sustained release	Matrix tablets, reservoir systems	Prolonged drug release	Limited tissue selectivity
Long-acting systems	Microspheres, depots, implants	Extended therapeutic exposure	Formulation and administration complexity
Vesicular systems	Liposomes, niosomes	Drug protection and altered distribution	Stability and manufacturing challenges
Nanocarriers	Polymeric nanoparticles, lipid nanoparticles, micelles	Improved delivery and pharmacokinetics	Biological barriers
Active targeting	Ligand-functionalized carriers	Cell/receptor recognition	Target heterogeneity
Stimuli-responsive systems	pH-, enzyme-, redox-, light-responsive systems	On-demand drug release	Trigger variability
Multifunctional systems	Hybrid, biomimetic and theranostic platforms	Integrated targeting, therapy and diagnosis	Complexity and translation

III. MAJOR NOVEL DRUG DELIVERY PLATFORMS

3.1 Liposomes

Liposomes are vesicular systems composed predominantly of phospholipid bilayers surrounding an aqueous internal compartment. Their amphiphilic architecture permits incorporation of hydrophilic molecules within the aqueous phase and lipophilic

molecules within the lipid membrane. Modification of lipid composition, vesicle size, membrane rigidity, surface charge, and surface coating provides opportunities to alter pharmacokinetics and release behavior. [16]

The pharmaceutical importance of liposomes is supported by their clinical history. Liposomal formulations have been developed for anticancer, antifungal, analgesic, and other therapeutic

applications. Their ability to alter drug distribution can reduce exposure of some healthy tissues and improve the therapeutic index of selected drugs. [17]

Surface modification has further expanded liposomal functionality. Long-circulating formulations can be produced using hydrophilic surface coatings, while ligands can be attached for receptor-mediated interactions. Stimulus-responsive liposomes can incorporate membrane components or chemical linkers that respond to pH, enzymes, temperature, or other triggers.

Despite their advantages, liposomes can undergo physical and chemical instability, drug leakage, aggregation, lipid oxidation, hydrolysis, and changes in vesicle characteristics during storage. Manufacturing at commercial scale also requires precise control of critical quality attributes. [18]

3.2 Polymeric Nanoparticles

Polymeric nanoparticles consist of nanoscale structures formed from natural or synthetic polymers. Frequently investigated materials include biodegradable polymers such as PLGA and related polymeric systems. Therapeutic compounds may be encapsulated within the polymer matrix or associated with the particle surface. Their release kinetics can be adjusted by modifying polymer molecular weight, polymer composition, particle size, drug loading, matrix porosity, and degradation behavior. Surface modification provides additional opportunities for targeting and prolonged circulation. [19]

A major advantage of polymeric nanoparticles is their versatility. They can accommodate small molecules, proteins, peptides, and nucleic acids and can be engineered to respond to physiological or external stimuli. Nevertheless, relatively limited clinical translation compared with liposomes indicates that formulation sophistication must be accompanied by robust manufacturing, reproducibility, safety evaluation, and regulatory development. [20]

3.3 Lipid Nanoparticles

Lipid nanoparticles have become one of the most influential developments in modern drug delivery. Their clinical importance increased substantially with the successful delivery of mRNA. The carrier protects nucleic acids from extracellular degradation and facilitates cellular uptake and intracellular release.

Ionizable lipids play a particularly important role because their charge state can change according to environmental pH. This behavior can facilitate nucleic-acid encapsulation during formulation while supporting intracellular trafficking and endosomal escape after administration. [21]

The expanding application of LNPs includes infectious-disease vaccines, cancer immunotherapy, protein replacement, gene editing, and treatment of genetic disorders. Current research increasingly investigates tissue-specific and cell-specific LNPs to move beyond predominantly liver-associated delivery toward extrahepatic applications. [22]

3.4 Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

SLNs consist of a solid lipid matrix stabilized by surfactants, whereas NLCs generally contain mixtures of solid and liquid lipids. The less ordered structure of NLCs can provide increased space for drug incorporation and may reduce drug expulsion during storage.

These systems are particularly attractive for poorly water-soluble molecules and can be adapted for oral, topical, transdermal, ocular, and parenteral delivery. Surface engineering can additionally modify interaction with biological membranes and target tissues.

However, lipid polymorphism, drug partitioning, lipid crystallization, particle aggregation, and storage stability remain important formulation considerations.

Table 2. Major NDDS platforms and their characteristics [23]

NDDS platform	Structural principle	Main delivery advantage	Major development consideration
Liposomes	Phospholipid bilayer vesicle	Encapsulation of hydrophilic and lipophilic drugs	Stability and scale-up
Polymeric nanoparticles	Biodegradable polymer matrix	Controlled release and versatile drug loading	Manufacturing and long-term safety

Lipid nanoparticles	Ionizable/structural lipid assembly	Intracellular nucleic-acid delivery	Tissue targeting and stability
SLNs	Solid lipid matrix	Protection and prolonged release	Lipid crystallinity
NLCs	Solid-liquid lipid matrix	Improved loading and reduced drug expulsion	Physical stability
Polymeric micelles	Amphiphilic self-assembly	Solubilization of hydrophobic drugs	Dilution stability
Dendrimers	Highly branched macromolecule	Multivalent surface functionality	Toxicity and clearance
Nanogels	Cross-linked hydrated polymer network	Macromolecule delivery and stimulus response	Structural stability
Long-acting depots	Polymer/lipid/implant matrix	Extended exposure	Administration and dose reversibility

IV. TARGETED DRUG DELIVERY STRATEGIES

Targeted delivery seeks to increase the fraction of therapeutic exposure reaching the intended biological compartment. Three broad approaches are commonly considered: passive targeting, active targeting, and intracellular/subcellular targeting.

4.1 Passive Targeting

Passive targeting depends primarily on physiological characteristics of the target tissue and physicochemical properties of the delivery system. Nanoparticle size, shape, surface characteristics, circulation time, vascular permeability, tissue perfusion, and clearance can all influence tissue distribution.

In cancer research, the enhanced permeability and retention concept has historically provided an important rationale for nanoparticle accumulation within tumors. However, the extent of this phenomenon varies substantially among tumors and patients. Contemporary research has therefore emphasized the importance of understanding actual human biodistribution rather than assuming that all tumors provide equivalent nanoparticle accumulation. [24] Passive targeting should consequently be regarded as a biological opportunity rather than a guaranteed mechanism of selective delivery.

4.2 Active Targeting

Active targeting incorporates a molecular recognition component onto the carrier surface. Antibodies, antibody fragments, peptides, aptamers, carbohydrates, and receptor-specific ligands can be used to promote interactions with selected cell types. The intended mechanism generally involves ligand receptor recognition followed by cellular uptake. This strategy can be particularly useful when the target

receptor is highly expressed on diseased cells but comparatively limited on surrounding healthy tissue.

However, active targeting does not eliminate systemic biological barriers. A ligand-functionalized carrier must first reach the target tissue before molecular recognition can occur. Furthermore, heterogeneous receptor expression, ligand accessibility, receptor internalization, immune interactions, and the formation of protein coronas can modify targeting efficiency. [25]

4.3 Intracellular and Subcellular Targeting

Modern drug delivery increasingly focuses on events occurring after cellular uptake. For many therapeutic molecules, particularly nucleic acids and some proteins, cellular entry alone is insufficient. The carrier must undergo appropriate intracellular trafficking and release the therapeutic cargo at the correct compartment.

Endosomal escape is particularly important for many nanoparticle systems. Other approaches seek delivery to the cytoplasm, nucleus, mitochondria, lysosomes, or other intracellular compartments. Stimuli-responsive systems can exploit intracellular pH, glutathione, reactive oxygen species, enzymes, ATP, hypoxia, and other biochemical characteristics to trigger drug release. [26] This transition from tissue targeting to intracellular precision delivery represents an important direction in modern NDDS research.

V. CONTROLLED AND STIMULI-RESPONSIVE DRUG RELEASE

Controlled release is designed to regulate the rate and duration of drug liberation, whereas stimuli-responsive delivery links release to a specific biological or physical trigger.

5.1 pH-Responsive Delivery

Differences in pH between biological compartments provide an attractive trigger for controlled drug release. The gastrointestinal tract, tumor microenvironment, endosomes, lysosomes, and some inflammatory tissues exhibit distinct pH conditions.

pH-sensitive polymers, acid-labile chemical bonds, ionizable groups, and pH-dependent changes in carrier structure can therefore be incorporated into delivery systems. A properly designed system can remain relatively stable during circulation while increasing drug release under a defined acidic condition. [27]

5.2 Redox-Responsive Delivery

Redox-responsive systems exploit differences in reducing conditions between extracellular and intracellular environments. Disulfide-containing linkers are frequently investigated because they can undergo cleavage under appropriate reducing conditions.

Such mechanisms can be particularly useful for intracellular delivery, where increased concentrations of reducing molecules such as glutathione can act as an endogenous trigger.

5.3 Enzyme-Responsive Delivery

Disease-associated enzymes can provide biological specificity. Enzyme-sensitive peptides or linkers can be incorporated into nanoparticles, hydrogels, polymers, or prodrug systems so that carrier degradation or drug liberation occurs following enzymatic cleavage.

The major advantage is the potential for disease-associated biochemical recognition without requiring an external device. However, enzyme expression can vary among patients and tissues, and therefore the reliability of enzyme-triggered delivery must be experimentally established for each application.

5.4 Externally Triggered Delivery

External stimuli provide an opportunity to regulate drug release at a selected time and location. Light, temperature, ultrasound, magnetic fields, and electrical stimulation have been investigated as external triggers. External triggering is attractive because the stimulus can potentially be applied according to the treatment schedule. However, tissue penetration, equipment requirements, treatment geometry, safety, and reproducibility must be considered before clinical translation. [28]

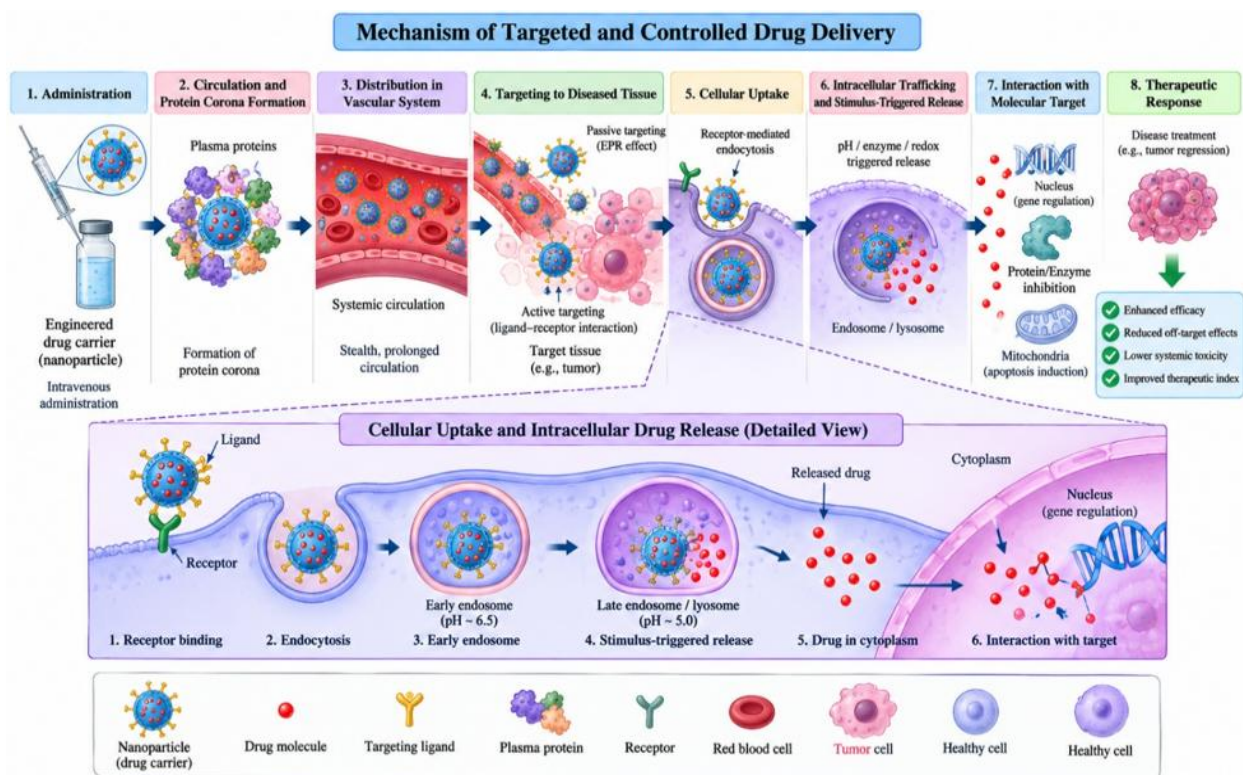


Figure 2. Mechanism of targeted and controlled drug delivery [29]

VI. PHARMACOLOGICAL AND THERAPEUTIC APPLICATIONS

6.1 Cancer Therapy

Cancer has remained one of the principal fields for advanced drug delivery because conventional anticancer drugs can exhibit severe systemic toxicity and limited selectivity. Nanocarriers can modify drug distribution, protect active molecules, facilitate combination therapy, and provide opportunities for tumor-associated targeting.

Liposomes, polymeric nanoparticles, micelles, lipid nanoparticles, antibody–drug conjugate-related systems, and stimuli-responsive carriers have been investigated for cancer therapy. Multifunctional systems may combine chemotherapy with nucleic-acid delivery, immunotherapy, phototherapy, or imaging. However, tumor heterogeneity and variable vascular permeability remain major barriers to consistent targeting. [30]

6.2 Infectious Diseases

NDDS can improve antimicrobial therapy by protecting unstable drugs, increasing local concentrations, improving intracellular delivery, and prolonging residence time. Nanocarriers have been investigated for antibacterial, antifungal, antiviral, and antiparasitic applications.

Lipid-based systems can improve delivery of poorly soluble antimicrobial agents, while nanoparticles can potentially transport therapeutics into cells harboring intracellular pathogens. The increasing importance of nucleic-acid technologies has also expanded research into nanoparticle-mediated delivery of vaccine and antiviral components. [31]

6.3 Inflammatory and Autoimmune Disorders

Inflammatory diseases may benefit from localized or stimulus-responsive delivery because prolonged systemic administration of potent anti-inflammatory agents can produce undesirable effects. pH-, enzyme-, ROS-, and inflammation-responsive systems are being explored to release drugs preferentially within pathological microenvironments.

Such strategies may be particularly valuable in inflammatory bowel disease, inflammatory skin disorders, arthritis, and other conditions characterized by localized biochemical abnormalities. [32]

6.4 Central Nervous System Disorders

The blood–brain barrier represents one of the most significant challenges in drug delivery. Nanocarriers have been investigated to improve transport across or around this barrier through receptor-mediated transcytosis, surface modification, intranasal administration, and other approaches.

Nevertheless, CNS delivery requires careful evaluation of particle size, surface chemistry, protein interactions, neurotoxicity, clearance, and actual tissue distribution. Improved brain accumulation alone does not necessarily demonstrate therapeutic benefit.

6.5 Genetic and Nucleic-Acid Therapeutics

The development of lipid nanoparticles has transformed the feasibility of delivering nucleic-acid therapeutics. mRNA, siRNA, gene-editing components, and other nucleic acids require protection from degradation and efficient intracellular delivery.

The clinical success of LNP–mRNA products demonstrate that an appropriately engineered carrier can convert an unstable biological molecule into a practical therapeutic platform. Current research is moving toward tissue-specific and cell-specific delivery for cancer, rare diseases, protein replacement, and genome editing. [33]

VII. ADVANCED FORMULATION AND DELIVERY STRATEGIES

Modern NDDS development increasingly involves combinations of materials and mechanisms rather than single-component carriers.

Hybrid systems: Hybrid nanocarriers combine two or more material classes, such as lipid–polymer, polymer–inorganic, or vesicle-based architectures. The objective is to combine complementary advantages, for example the structural stability of polymers with the biological compatibility of lipids.

Biomimetic systems: Biomimetic delivery platforms attempt to exploit naturally occurring biological structures. Cell-membrane-coated nanoparticles, exosome-based systems, protein-based carriers, and other biologically inspired platforms may reduce certain biological barriers and provide endogenous targeting characteristics.

Nanogels: Nanogels combine nanoscale dimensions with the hydrated characteristics of hydrogel networks. Their responsiveness to pH, temperature, enzymes, or redox conditions makes them attractive for controlled delivery of both small molecules and biological macromolecules.

Microneedle systems: Microneedles provide minimally invasive transdermal delivery by temporarily disrupting the stratum corneum. Recent systems incorporate nanoparticles, stimuli-responsive materials, dissolving polymers, and other advanced structures. Such approaches can potentially improve patient acceptability while avoiding some limitations

associated with oral or conventional parenteral administration. [34]

Long-acting delivery systems: Long-acting formulations can maintain therapeutic exposure for weeks or months depending on the platform and drug. Injectable nanosuspensions, PLGA microspheres, oil-based depots, implants, and in situ-forming systems are being investigated for chronic therapies.

Long-acting delivery can reduce dosing frequency, but dose reversibility and management of adverse effects become important considerations because drug exposure may persist after administration. [35]

Table 3. Major targeting and controlled-release mechanisms. [36]

Strategy	Trigger/mechanism	Primary objective	Major consideration
Passive targeting	Tissue physiology and carrier properties	Altered tissue accumulation	Patient and disease heterogeneity
Active targeting	Ligand–receptor recognition	Enhanced cellular association	Target expression
pH responsiveness	Environmental acidity	Site-specific release	pH variability
Redox responsiveness	Reducing environment	Intracellular release	Biological variability
Enzyme responsiveness	Disease-associated enzymes	Biochemical activation	Enzyme heterogeneity
ROS responsiveness	Elevated reactive oxygen species	Pathology-associated release	Oxidative environment variability
Thermal responsiveness	Temperature change	Triggered release	Temperature control
Light responsiveness	Photochemical activation	Localized release	Tissue penetration
Magnetic responsiveness	Magnetic field	Remote control	Equipment and localization
Ultrasound responsiveness	Acoustic energy	Localized release/permeation	Exposure parameters

VIII. MOLECULAR AND CELLULAR MECHANISMS GOVERNING NDDS PERFORMANCE

The biological performance of an NDDS is determined by a sequence of interconnected events rather than by particle composition alone.

After administration, nanoparticles immediately encounter biological fluids containing proteins, lipids, electrolytes, immune cells, and other biomolecules. Adsorption of biomolecules onto the particle surface generates a dynamic protein corona that can alter the effective biological identity of the carrier. Consequently, the surface initially engineered by the formulation scientist may differ substantially from the surface recognized by cells in vivo. [37]

Circulation time is another critical determinant. Rapid uptake by macrophages and clearance through organs such as the liver and spleen can reduce the quantity of

carrier reaching the intended tissue. Particle size, morphology, surface charge, hydrophilicity, and composition all contribute to these processes.

Once a carrier reaches the target tissue, extracellular matrix density, vascular permeability, interstitial pressure, and cellular architecture influence tissue penetration. A nanoparticle may therefore demonstrate excellent targeting in vitro while showing limited tissue penetration in vivo.

Cellular uptake can occur through several forms of endocytosis. After internalization, the carrier may enter early endosomes, late endosomes, lysosomes, or other intracellular compartments. For many therapeutic cargos, particularly nucleic acids, successful delivery requires escape from endosomal compartments before degradation.

Stimulus-responsive systems can be designed to exploit intracellular conditions. Acidic endosomal environments can activate pH-sensitive carriers, while

intracellular glutathione can trigger reduction-sensitive systems. Elevated ROS or intracellular enzymes can also serve as release signals. [38]

The final stage involves release of the active therapeutic molecule and interaction with its molecular target. Thus, the therapeutic performance of an NDDS represents the combined outcome of pharmacokinetics, biodistribution, tissue penetration, cellular uptake, intracellular trafficking, release kinetics, and pharmacodynamics.

IX. RECENT ADVANCES IN TARGETED AND CONTROLLED DRUG DELIVERY

Recent research has increasingly moved toward multifunctional systems capable of combining targeting and controlled release with diagnostic or therapeutic functions.

9.1 Site-Specific Lipid Nanoparticles

Although LNP technology has achieved substantial clinical success, many LNP formulations show preferential distribution to the liver following systemic administration. Current research therefore seeks to modify lipid composition, surface chemistry, particle characteristics, and targeting ligands to promote delivery to extrahepatic tissues and specific cell populations.

Site-specific LNPs are being explored for delivery to immune cells, endothelial cells, tumors, and other tissues. Such approaches may expand the therapeutic scope of mRNA and other nucleic-acid technologies. [39]

9.2 Stimuli-Responsive Biomacromolecular Systems

Recent biomacromolecular delivery systems increasingly combine natural and synthetic polymers with multiple stimulus-responsive mechanisms. pH,

redox, enzymes, temperature, and external triggers can be integrated within a single carrier.

Multi-stimulus systems theoretically provide greater selectivity because release can depend on more than one biological condition. However, the additional complexity creates a need for detailed characterization of trigger thresholds, kinetics, degradation, and reproducibility. [40]

9.3 Theranostic Delivery

Theranostic systems combine therapy with diagnostic or imaging functionality. A single platform may carry a therapeutic agent while simultaneously enabling imaging, disease localization, treatment monitoring, or treatment-response assessment.

The clinical appeal of theranostics lies in the possibility of connecting diagnosis and therapy within a single precision-medicine framework. However, combining diagnostic and therapeutic components also increases manufacturing and regulatory complexity. [41]

9.4 Artificial Intelligence and Data-Guided Formulation Design

The growing complexity of NDDS formulation has encouraged the use of computational methods and artificial intelligence for formulation optimization. Data-driven approaches can potentially identify relationships between composition, process parameters, particle characteristics, drug loading, stability, and biological performance.

AI-assisted approaches may eventually support prediction of formulation behavior and reduce experimental iterations. Nevertheless, reliable prediction depends on high-quality datasets, standardized characterization, appropriate validation, and mechanistic interpretation.

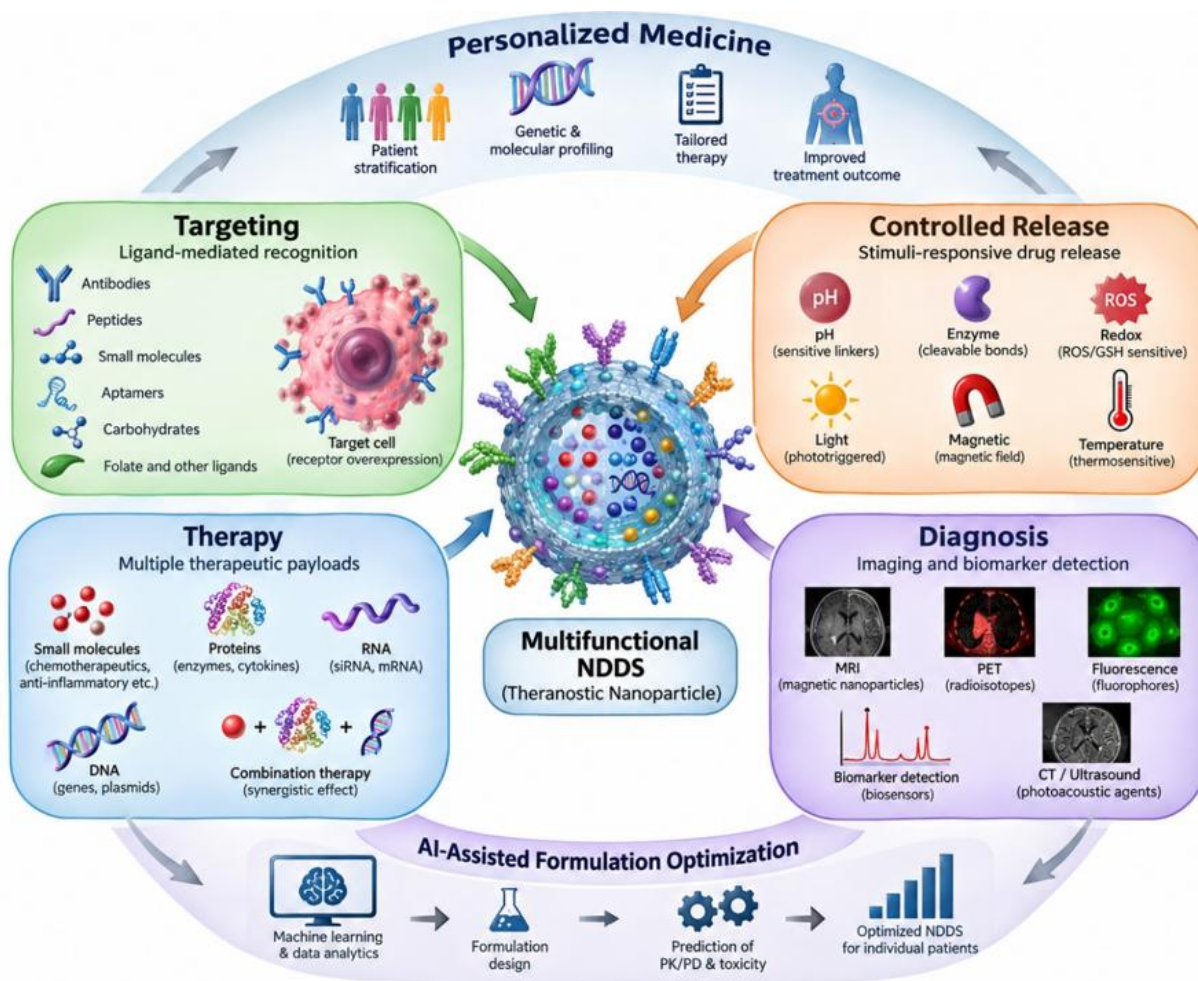


Figure 3. Recent advances in multifunctional NDDS.[42]

X. CLINICAL TRANSLATION OF NOVEL DRUG DELIVERY SYSTEMS

The existence of clinically approved liposomal products demonstrates that nanomedicine can successfully progress from laboratory formulation to commercial pharmaceutical product. Clinical translation is supported when formulation characteristics can be adequately controlled and when the modified delivery system provides a meaningful therapeutic advantage.

Liposomal formulations provide an important example. Their clinical development has required control of lipid composition, particle size, drug-loading method, encapsulation efficiency, release behavior, stability, sterility, and other critical quality attributes. Regulatory experience with marketed

liposomes provides valuable guidance for future nanocarrier development. [43]

LNP-based mRNA delivery represents another major milestone. Clinical use of LNP–mRNA vaccines demonstrated the feasibility of delivering nucleic acids using engineered lipid systems. This success has accelerated research into LNP-based therapeutics for infectious diseases, cancer, protein replacement, and genetic disorders. [44]

Long-acting delivery systems provide a parallel pathway for clinical translation. Injectable microspheres, nanosuspensions, implants, and depot formulations have demonstrated the practical value of prolonged drug release. Their development emphasizes the importance of predictable release kinetics, dose uniformity, injection performance, storage stability, and control of long-term drug exposure. [45]

XI. CHALLENGES AND LIMITATIONS

Despite substantial advances, several barriers continue to limit widespread clinical translation.

Biological barriers: Nanocarriers encounter protein corona formation, immune recognition, clearance, vascular barriers, extracellular matrix limitations, cellular uptake barriers, and intracellular degradation. These processes can substantially alter delivery efficiency compared with in vitro expectations. [46]

Target heterogeneity: Disease-associated targets may not be uniformly expressed across patients or even within the same lesion. Consequently, a targeting ligand that performs effectively in one biological model may produce inconsistent results in another.

Manufacturing and scale-up: Small-scale laboratory methods do not necessarily translate directly to industrial production. Changes in mixing, solvent removal, temperature, shear, raw materials, or equipment can alter particle size, encapsulation, morphology, and release behavior.

Stability: Nanocarriers may experience aggregation, drug leakage, lipid oxidation, polymer degradation, particle growth, or changes in surface properties during storage. Stability therefore remains an important determinant of product feasibility.

Safety: The long-term effects of some nanomaterials remain incompletely characterized. Potential immunogenicity, accumulation, oxidative stress, organ toxicity, and degradation products require careful evaluation.

Regulatory complexity: Multicomponent and multifunctional systems can be more difficult to characterize than conventional drug products. A clear relationship between formulation attributes and clinical performance is essential for regulatory development.

XII. FUTURE PERSPECTIVES

The future of NDDS is likely to emphasize precision, predictability, personalization, and translational practicality rather than formulation complexity alone.

One important direction is the development of tissue- and cell-specific carriers. Current LNP research demonstrates that modification of lipid composition and surface properties can alter organ and cellular distribution. Future platforms may increasingly incorporate biological information to identify patients most likely to benefit from a particular targeting mechanism. [47]

Another major opportunity is the integration of controlled delivery with personalized medicine. Patient-specific disease characteristics, receptor expression, pharmacokinetics, biomarkers, and genetic information could eventually guide carrier selection and dose optimization.

AI-assisted formulation development may further accelerate this process by identifying relationships between formulation variables and biological outcomes. Such approaches could reduce experimental burden while supporting systematic quality-by-design development.

The development of biomimetic systems is another promising direction. Exosomes, cell-membrane-coated nanoparticles, protein-based carriers, and other biological or bioinspired platforms may offer opportunities to exploit naturally evolved transport mechanisms. However, manufacturing consistency and characterization remain essential challenges.

Multi-responsive delivery is also likely to continue developing. Systems capable of responding to combinations of pH, enzymes, ROS, redox conditions, temperature, or externally applied stimuli may provide more precise release than single-trigger platforms. Nevertheless, increased complexity must be balanced against reproducibility and clinical practicality. [48] Finally, future NDDS development should increasingly use clinically relevant models and translational pharmacology at early stages. Improved prediction of biodistribution, tissue penetration, clearance, and human pharmacokinetics may reduce the gap between promising laboratory systems and successful clinical products.

XIII. CONCLUSION

Novel drug delivery systems have transformed pharmaceutical formulation from simple dose administration toward controlled regulation of drug disposition. Liposomes, polymeric nanoparticles, lipid nanoparticles, micelles, lipid-based carriers, long-

acting systems, stimuli-responsive platforms, and multifunctional nanocarriers provide diverse strategies for improving therapeutic delivery.

The most significant future advances are likely to arise from the integration of targeting, controlled release, intracellular delivery, biomimicry, nucleic-acid delivery, theranostics, and personalized medicine. However, successful translation will depend on more than technological novelty. Predictable biological behavior, reproducible manufacturing, adequate stability, safety, clinically meaningful therapeutic benefit, and regulatory feasibility must be incorporated into formulation development from the beginning.

The ultimate objective of NDDS research should therefore be the development of delivery systems that provide measurable therapeutic advantages with controllable manufacturing and predictable clinical behavior. Such an approach can facilitate the transition of targeted and controlled drug delivery from sophisticated experimental platforms toward reliable therapeutic technologies.

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CONFLICT OF INTEREST

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