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Review Article

Emerging Frontiers in Formulation Development: Trends in Novel Drug-Delivery Systems for Enhanced Therapeutic Outcomes

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Abstract

The continuous evolution of the pharmaceutical sciences has led to significant advancements in the design and development of novel drug-delivery systems (NDDS) to improve therapeutic efficacy, patient compliance, and safety profiles. Conventional dosage forms often exhibit limitations such as poor bioavailability, rapid systemic clearance, and nonspecific distribution. To address these challenges, formulation scientists have integrated nanotechnology, polymer science, lipid-based carriers, and targeted delivery strategies into modern pharmaceutical development. Emerging platforms such as liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric micelles, hydrogels, and stimuli-responsive systems have transformed the delivery and release behavior of active pharmaceutical ingredients. This review consolidates recent advances in NDDS, highlighting formulation approaches, characterization techniques, regulatory considerations, and translational challenges. Emphasis is placed on the clinical potential of these systems in enhancing therapeutic outcomes across diverse disease conditions.

Keywords: Novel drug-delivery systems; Nanotechnology; Liposomes; Polymeric nanocarriers; Mucoadhesive systems; Targeted drug delivery; Controlled release; Pharmacokinetics; Regulatory trends

1. Introduction

The global pharmaceutical industry is undergoing a paradigm shift from conventional drug-delivery approaches toward intelligent, responsive, and patient-centric systems. Traditional dosage forms often suffer from limitations such as poor aqueous solubility, rapid metabolism, low bioavailability, and off-target toxicity, ultimately compromising therapeutic effectiveness¹⁻³. Novel drug-delivery systems (NDDS) have been developed to overcome these challenges by modulating drug release kinetics, improving site-specific delivery, and enhancing pharmacokinetic performance.

Advances in polymer science, nanotechnology, and bioconjugation have played a pivotal role in the evolution of NDDS⁴. Early developments in the 1970s introduced liposomes as biocompatible carriers capable of encapsulating both hydrophilic and lipophilic drugs. Subsequent innovations led to the development of polymeric nanoparticles, dendrimers, micelles, and lipid-based nanocarriers, significantly advancing formulation

science⁵⁻⁷. Contemporary research focuses on hybrid and multifunctional systems incorporating stimuli responsiveness, surface functionalization, and targeted delivery capabilities.

The primary objectives of modern formulation development include enhancing solubility and stability of poorly water-soluble drugs, achieving controlled or sustained drug release, reducing systemic toxicity, and improving patient adherence. Additionally, formulation strategies now emphasize scalability, regulatory compliance, and cost-effectiveness to facilitate clinical translation^{8,9}.

1.1 Historical Perspective

The development of drug-delivery technologies can be broadly categorized into three generations. First-generation systems focused on immediate and sustained drug release using conventional polymer matrices. Second-generation systems introduced transdermal delivery and stimuli-responsive mechanisms. Third-

generation NDDS emphasize targeted and personalized delivery enabled by nanotechnology and molecular engineering^{10–12}. Over the past two decades, the integration of biodegradable polymers, lipids, and smart materials has enabled precise control over drug biodistribution and therapeutic response.

1.2 Need for Novel Formulation Strategies

Approximately 40% of newly discovered chemical entities exhibit poor aqueous solubility, making formulation development a critical determinant of successful drug therapy¹³. Conventional approaches such as salt formation, co-solvents, and surfactants are often insufficient for highly lipophilic compounds. NDDS overcome these limitations by encapsulating drugs within carrier systems that enhance dissolution, permeability, and stability.

Furthermore, patient-centric drug design, particularly for chronic diseases, requires dosage forms that reduce dosing frequency, minimize adverse effects, and improve convenience¹⁴. Nanocarriers, mucoadhesive systems, and biodegradable polymers have demonstrated significant potential in meeting these clinical objectives.

1.3 Regulatory and Translational Landscape

Regulatory agencies such as the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) emphasize safety, efficacy, and quality consistency in NDDS development. Guidelines including ICH Q8 (Pharmaceutical Development) and ICH Q9 (Quality Risk Management) advocate the application of quality-by-design principles in formulation development^{15,16}. In India, the Central Drugs Standard Control Organization has introduced specific regulatory considerations for nano pharmaceutical products¹⁷.

Successful translation of NDDS from laboratory to market requires scalable manufacturing processes, robust characterization, and compliance with evolving regulatory frameworks.

1.4 Objectives

This review aims to provide a comprehensive overview of emerging novel drug-delivery system platforms, with emphasis on formulation principles, characterization techniques, translational challenges, and regulatory considerations. The review also highlights future prospects of NDDS in personalized and precision medicine.

2. Overview of Novel Drug-Delivery Systems

Novel drug-delivery systems (NDDS) comprise a diverse range of formulation platforms designed to enhance the pharmacological performance of therapeutic agents by modifying drug release kinetics, biodistribution, targeting efficiency, and biological interactions¹⁸. These systems enable improved therapeutic efficacy while minimizing systemic toxicity and adverse effects. NDDS are particularly beneficial for drugs with poor solubility, narrow therapeutic indices, or rapid metabolism.

Based on carrier composition, route of administration, and functional mechanism, NDDS can be broadly classified into lipid-based systems, polymeric carriers, mucoadhesive systems, transdermal systems, targeted nanocarriers, and stimuli-responsive delivery platforms¹⁹. Each category presents distinct formulation advantages and challenges depending on the physicochemical characteristics of the active pharmaceutical ingredient and the intended therapeutic application. Classification of novel drug-delivery systems and their advantages as represented in table 1.

Table 1: Classification of novel drug-delivery systems and their advantages

Category	Examples	Key Advantages
Lipid-based systems	Liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs)	High biocompatibility, enhanced permeability, improved solubility of lipophilic drugs
Polymeric carriers	Polymeric nanoparticles, nano capsules, polymeric micelles	Controlled and sustained drug release, surface functionalization, biodegradability
Mucoadhesive systems	Buccal, nasal, ocular, vaginal delivery systems	Prolonged residence time, enhanced absorption, bypass of first-pass metabolism
Transdermal systems	Patches, microneedles, iontophoretic systems	Non-invasive delivery, sustained plasma levels, improved patient compliance
Targeted nanocarriers	Ligand- or antibody-modified nanoparticles	Site-specific drug accumulation, reduced systemic toxicity
Stimuli-responsive systems	pH, enzyme-, temperature or redox-responsive carriers	On demand drug release, improved therapeutic precision

Note: The above table data adapted from established NDDS classifications and formulation studies^{18,19}.

Each NDDS category exhibits unique formulation considerations related to carrier composition, drug-loading capacity, stability, scalability, and regulatory acceptance²⁰. Subsequent sections discuss major NDDS

platforms in detail, with emphasis on formulation strategies, recent advancements, and therapeutic applications.

3. Lipid-Based Drug-Delivery Systems

Lipid-based drug-delivery systems represent one of the most extensively investigated and clinically validated approaches in formulation science. These systems utilize physiological and biocompatible lipids to enhance the solubility, stability, and bioavailability of poorly water-soluble drugs. Lipid carriers also enable controlled release and targeted delivery through structural and surface modifications^{20–22}. Among lipid-based systems, liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) have gained widespread regulatory and commercial acceptance.

3.1 Liposomes

Liposomes are spherical vesicular systems composed of one or more phospholipid bilayers surrounding an aqueous core. Their unique structure allows encapsulation of both hydrophilic drugs within the aqueous compartment and lipophilic drugs within the lipid bilayer, making them highly versatile carriers²³. Liposomes protect encapsulated drugs from enzymatic

degradation and can modify pharmacokinetic behavior by controlling drug release and distribution.

Several liposomal formulations have received regulatory approval, including liposomal doxorubicin and liposomal amphotericin B, demonstrating improved therapeutic efficacy and reduced toxicity compared to conventional formulations²³. Advances in liposome technology have led to the development of long-circulating or “stealth” liposomes achieved by surface modification with polyethylene glycol (PEG), which reduces opsonization and reticuloendothelial system clearance²⁴.

Targeted liposomes functionalized with antibodies, peptides, or small-molecule ligands are being actively explored for site-specific delivery in cancer, infectious diseases, and ocular disorders. These systems enhance cellular uptake through receptor-mediated endocytosis while minimizing off-target effects. Encapsulation of hydrophilic and lipophilic drugs within liposomal vesicles and subsequent controlled release shown in fig 1.

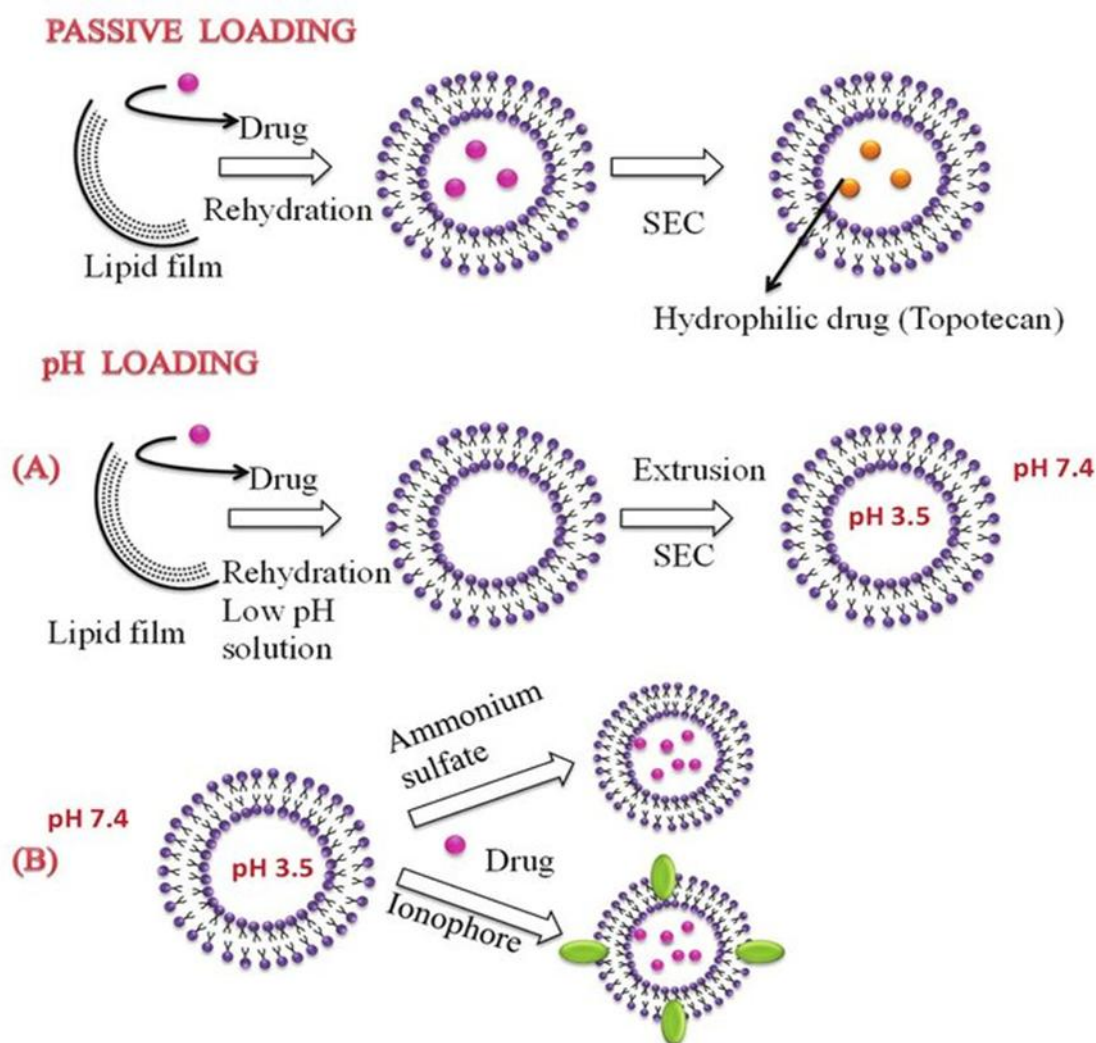


Figure 1: Schematic illustration showing encapsulation of hydrophilic and lipophilic drugs within liposomal vesicles and subsequent controlled release²⁴.

3.2 Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles were developed as an alternative to polymeric nanoparticles to overcome issues related to polymer toxicity and organic solvent use. SLNs are composed of solid lipids such as stearic acid, glyceryl behenate, or cetyl palmitate, stabilized by surfactants^{25,26}. These systems offer advantages including high physical stability, controlled drug release, protection of labile drugs, and feasibility for large-scale production.

SLNs have been extensively investigated for oral, topical, ocular, and parenteral drug delivery. However, their major limitations include limited drug-loading capacity and potential drug expulsion during lipid crystallization upon storage. Optimization strategies involving lipid selection, surfactant concentration, homogenization techniques, and cryoprotectants have been employed to mitigate these challenges²⁷.

3.3 Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers were developed to address the drawbacks associated with SLNs. NLCs consist of a mixture of solid and liquid lipids, creating an imperfect crystalline matrix that enhances drug-loading capacity and minimizes drug expulsion during storage²⁸. The structural flexibility of NLCs allows tailoring of release profiles and improved long-term stability.

NLCs have demonstrated superior performance compared to SLNs in dermal, oral, and ocular drug-delivery applications. Their ability to accommodate higher drug concentrations and provide sustained release makes them particularly suitable for chronic therapeutic regimens. The selection of lipid combinations plays a crucial role in determining particle size, encapsulation efficiency, and release kinetics.

4. Polymeric and Nanocarrier Systems

Polymeric nanocarriers constitute a major class of novel drug-delivery systems due to their structural versatility, biodegradability, and capacity for surface modification. These systems enable precise control over drug release kinetics, protection of active pharmaceutical ingredients from degradation, and improved targeting efficiency. Common polymeric nanocarriers include polymeric nanoparticles, micelles, dendrimers, and hydrogels²⁹.

4.1 Polymeric Nanoparticles

Polymeric nanoparticles typically range from 10 to 1000 nm in size and are prepared using biodegradable polymers such as poly(lactic-co-glycolic acid), polycaprolactone, and chitosan. These systems can be formulated as nanospheres or nano capsules, depending on whether the drug is uniformly dispersed within the polymer matrix or confined within a core surrounded by a polymeric shell³⁰.

Polymeric nanoparticles provide sustained and controlled drug release by modulating polymer composition, molecular weight, and degradation rate. Surface modification with hydrophilic polymers or targeting ligands further enhances circulation time and site-specific delivery. These systems have been widely explored for anticancer, ocular, and vaccine delivery applications.

4.2 Polymeric Micelles

Polymeric micelles are formed by the self-assembly of amphiphilic block copolymers in aqueous environments. The hydrophobic core serves as a reservoir for poorly water-soluble drugs, while the hydrophilic shell provides steric stabilization and prolonged circulation time³¹.

Polymeric micelles have demonstrated particular utility in cancer therapy due to their ability to exploit the enhanced permeability and retention effect. Clinical investigations of micellar paclitaxel formulations have reported reduced hypersensitivity reactions compared to conventional surfactant-based formulations³². However, issues related to micelle stability and premature drug release remain key formulation challenges.

4.3 Dendrimers

Dendrimers are highly branched, monodisperse macromolecules characterized by a well-defined three-dimensional architecture and numerous surface functional groups. Their unique structure allows precise control over drug loading, surface charge, and targeting moieties³³.

Polyamidation dendrimers have been extensively investigated for delivery of anticancer drugs, nucleic acids, and imaging agents. Functionalization of dendrimer surfaces with ligands such as folic acid or antibodies enhances receptor-mediated uptake and therapeutic selectivity. Despite their advantages, concerns regarding cytotoxicity and synthesis complexity must be carefully addressed during formulation development.

4.4 Polymeric Hydrogels

Polymeric hydrogels are three-dimensional, cross-linked polymer networks capable of absorbing large amounts of water or biological fluids. Their swelling behavior and mesh size can be tailored to achieve controlled drug release profiles³⁴.

Stimuli-responsive hydrogels respond to environmental triggers such as pH, temperature, or ionic strength, enabling on-demand drug release. These “smart” hydrogels have gained increasing interest in injectable depot formulations, wound healing, and tissue engineering applications³⁵. Biocompatibility and mechanical stability remain critical considerations in hydrogel-based drug-delivery design. Polymeric hydrogel network structure and drug release mechanisms as shown in fig 2.

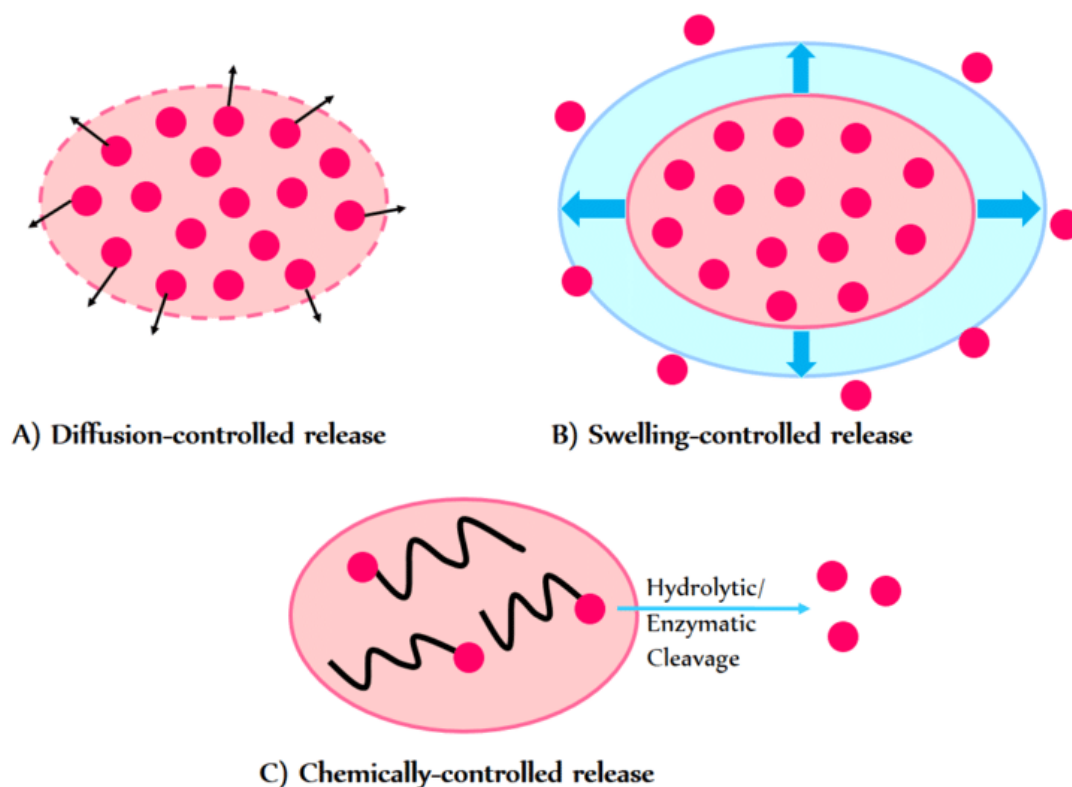


Figure 2: Schematic representation illustrating polymeric hydrogel network structure and drug release mechanisms governed by diffusion, swelling, and polymer degradation³⁵.

5. Mucoadhesive Drug-Delivery Systems

Mucoadhesive drug-delivery systems are designed to enhance drug residence time at mucosal surfaces by exploiting interactions between the formulation and mucus layers. These systems improve drug absorption, prolong therapeutic action, and reduce dosing frequency, making them particularly useful for buccal, nasal, ocular, and vaginal routes of administration³⁶.

Mucoadhesion is achieved through physical and chemical interactions such as hydrogen bonding, electrostatic attraction, and polymer chain interpenetration with mucin glycoproteins. Polymers commonly employed in mucoadhesive formulations include chitosan, Carbopol, hydroxypropyl methylcellulose, sodium alginate, and polyacrylic acid due to their strong adhesive properties and biocompatibility^{37, 38}.

Chitosan-based mucoadhesive systems have demonstrated enhanced permeability by transiently opening tight junctions, particularly beneficial for peptide and protein delivery. Studies have shown that mucoadhesive nanoparticles and microspheres significantly improve oral and nasal bioavailability of drugs compared to conventional formulations³⁷.

Recent advancements include thermo-responsive and in situ gelling mucoadhesive systems that undergo a sol-to-gel transition upon exposure to physiological conditions. These systems ensure prolonged local retention and controlled drug release. Mucoadhesive platforms are increasingly explored for non-invasive systemic delivery and localized therapy, especially in ophthalmic and nasal drug-delivery applications³⁹.

6. Transdermal Drug-Delivery Systems

Transdermal drug-delivery systems (TDDS) deliver therapeutic agents across the skin into systemic circulation, thereby avoiding gastrointestinal degradation and first-pass hepatic metabolism. These systems offer sustained drug release, stable plasma drug concentrations, improved patient compliance, and reduced systemic side effects⁴⁰. TDDS are particularly beneficial for chronic conditions requiring long-term therapy.

The major challenge in transdermal delivery is the low permeability of the stratum corneum, which acts as a formidable barrier to drug penetration. Recent technological advancements have focused on overcoming this barrier using both passive and active enhancement strategies.

6.1 Transdermal Patches and Microneedle Systems

Early transdermal patches relied on passive drug diffusion through the skin. While effective for small, lipophilic molecules, this approach is inadequate for macromolecules and hydrophilic drugs. To overcome these limitations, advanced techniques such as iontophoresis, electroporation, sonophoresis, and microneedle-based systems have been developed⁴¹.

Microneedles are minimally invasive micro-projections that create transient microchannels in the skin, facilitating enhanced drug permeation without reaching nerve endings or blood vessels. Microneedle arrays have demonstrated significant success in the delivery of vaccines, insulin, and biologics, representing a major translational advancement in transdermal drug delivery⁴².

6.2 Microemulsions and Nano emulsions

Microemulsions and nano emulsions are thermodynamically stable or kinetically stable colloidal systems composed of oil, water, surfactants, and co-surfactants. These systems enhance transdermal drug delivery by increasing drug solubility and altering the lipid structure of the stratum corneum, thereby improving drug permeation⁴³.

Nano emulsion-based gels have been extensively investigated for topical and transdermal delivery of antimicrobial, anti-inflammatory, and antifungal agents. Optimized nano emulsion formulations have shown improved cutaneous drug deposition and therapeutic efficacy compared to conventional dosage forms⁴⁴.

7. Targeted and Stimuli-Responsive Drug-Delivery Systems

Targeted and stimuli-responsive drug-delivery systems represent the next generation of NDDS, designed to enhance therapeutic precision by delivering drugs selectively to diseased tissues or cells while minimizing systemic exposure and adverse effects. These systems integrate targeting ligands or smart materials that

respond to internal or external triggers, thereby improving therapeutic efficacy and safety⁴⁵.

7.1 Passive and Active Targeting Strategies

Passive targeting exploits physiological differences between healthy and diseased tissues, most notably the enhanced permeability and retention (EPR) effect observed in tumor vasculature. Nanocarriers preferentially accumulate at tumor sites due to leaky blood vessels and impaired lymphatic drainage. Liposomal doxorubicin remains a landmark example of successful passive targeting, demonstrating reduced cardiotoxicity and improved antitumor efficacy⁴⁶.

Active targeting involves surface modification of drug carriers with ligands such as antibodies, peptides, aptamers, or small molecules that bind selectively to receptors overexpressed on target cells. Ligand-functionalized polymeric nanoparticles and liposomes have shown enhanced cellular uptake through receptor-mediated endocytosis, leading to improved therapeutic outcomes in cancer and inflammatory diseases⁴⁷. Comparison of passive targeting via the enhanced permeability and retention effect and active targeting through ligand receptor interactions were shown in fig 3.

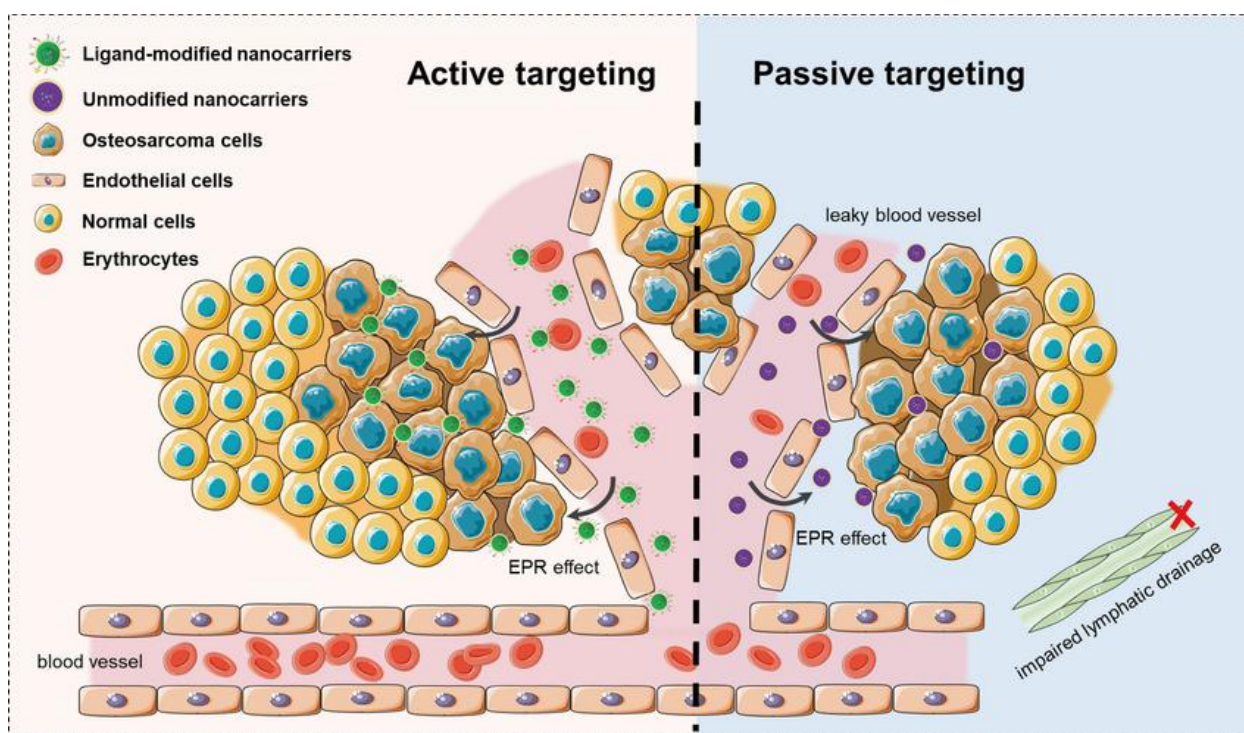


Figure 3: Schematic illustration comparing passive targeting via the enhanced permeability and retention effect and active targeting through ligand-receptor interactions⁶². Copyright 2023, Springer Nature.

7.2 Stimuli-Responsive Drug-Delivery Systems

Stimuli-responsive or “smart” drug-delivery systems are engineered to release therapeutic agents in response to specific physiological or external stimuli such as pH, temperature, redox potential, enzymes, light, magnetic fields, or ultrasound⁴⁸.

pH-responsive systems are particularly effective in tumor and infection environments, where extracellular pH is

slightly acidic. Thermo-responsive polymers, including poly(N-isopropylacrylamide), undergo sol-gel transitions near physiological temperatures, making them suitable for injectable depot formulations. Externally triggered systems using magnetic fields or ultrasound provide additional spatial and temporal control over drug release⁴⁹.

7.3 Gene and RNA-Based Drug-Delivery Systems

The rapid advancement of gene therapy and nucleic acid-based therapeutics has significantly increased interest in efficient delivery systems for DNA, siRNA, and mRNA. Lipid nanoparticles have emerged as the most clinically successful carriers for nucleic acid delivery, as evidenced by their use in mRNA-based vaccines⁵⁰.

Lipid nanoparticles protect nucleic acids from enzymatic degradation and facilitate endosomal escape, enabling cytosolic delivery. Hybrid polymer-lipid nanocarriers and ionizable cationic lipids are being actively optimized to improve tissue specificity, transfection efficiency, and safety profiles⁵¹.

8. Challenges and Regulatory Perspectives

Despite significant advancements in novel drug-delivery systems, several scientific, technological, and regulatory challenges continue to limit their widespread clinical translation and commercialization. Addressing these challenges is critical for the successful integration of NDDS into routine therapeutic practice.

One of the primary challenges in NDDS development is reproducibility and scalability. Manufacturing nanocarriers with consistent particle size, surface charge, and drug-loading efficiency at an industrial scale remains technically complex. Batch-to-batch variability can significantly affect therapeutic performance and regulatory approval⁵².

Long-term stability represents another major concern, particularly for lipid- and polymer-based nanocarriers. Physical instability, polymorphic transitions, aggregation, and chemical degradation during storage may compromise product quality and efficacy. Appropriate excipient selection, formulation optimization, and packaging strategies are essential to ensure stability throughout the product lifecycle⁵³.

Safety and toxicity evaluation of nanomaterials is a critical regulatory requirement. Although many nanocarriers are composed of biocompatible materials, chronic exposure may result in immunogenicity, oxidative stress, or organ accumulation. Comprehensive *in vitro* and *in vivo* toxicological studies are therefore required to establish safety profiles⁵⁴.

From a regulatory perspective, ambiguity in global regulatory frameworks remains a challenge. While agencies such as the US Food and Drug Administration, European Medicines Agency, and national regulatory authorities have issued guidance documents for nanotechnology-based medicinal products, harmonized global standards are still evolving. Regulatory agencies emphasize quality-by-design approaches, *in vitro*-*in vivo* correlation, and detailed physicochemical characterization of nanocarriers to ensure product quality and consistency⁵⁵.

Additionally, the cost and accessibility of advanced drug-delivery technologies pose significant barriers, particularly in low- and middle-income countries. The integration of cost-effective excipients, scalable manufacturing methods, and sustainable formulation

strategies is essential to ensure equitable access to innovative therapies⁵⁶.

9. Future Prospects and Emerging Technologies

The future of novel drug-delivery systems lies in the convergence of advanced materials science, digital technologies, and personalized medicine. Emerging formulation strategies aim to improve therapeutic precision, accelerate development timelines, and enhance patient-specific treatment outcomes.

9.1 Personalized and AI-Integrated Formulation Development

Artificial intelligence and machine learning are increasingly being integrated into pharmaceutical formulation development to enable predictive modeling and data-driven decision-making. AI-based tools facilitate optimization of excipient selection, particle size distribution, drug-loading efficiency, and stability profiles by analyzing large experimental datasets⁵⁷.

Machine learning algorithms are also being employed to predict pharmacokinetic behavior and *in vivo* performance of nanocarriers, thereby reducing reliance on trial-and-error experimentation. These advances support the development of personalized drug-delivery systems tailored to individual patient needs and disease characteristics.

9.2 Three-Dimensional Printing and Microfluidics

Three-dimensional printing technologies have emerged as powerful tools for fabricating patient-specific dosage forms with precise control over drug dose, geometry, and release kinetics. 3D printing enables the production of multi-layered and multi-drug systems, offering new possibilities for personalized therapy⁵⁸.

Microfluidic platforms provide highly controlled environments for nanoparticle synthesis, enabling precise manipulation of formulation parameters such as flow rate, mixing time, and temperature. These systems offer superior reproducibility and scalability compared to conventional batch processes, making them particularly attractive for industrial applications⁵⁹.

9.3 Theragnostic Drug-Delivery Systems

Theragnostic systems combine therapeutic and diagnostic functionalities within a single nanoplatform, enabling real-time monitoring of drug distribution and therapeutic response. These systems often integrate imaging agents such as gold nanoparticles, quantum dots, or iron oxide nanoparticles with drug molecules⁶⁰.

Theragnostic nanocarriers facilitate personalized treatment by allowing clinicians to assess treatment efficacy and adjust therapy accordingly. Despite their potential, challenges related to regulatory approval, safety, and cost remain to be addressed before widespread clinical adoption.

9.4 Sustainable and Biodegradable Nanocarriers

Sustainability has become an important consideration in modern pharmaceutical development. Green chemistry approaches are being explored to develop biodegradable

and environmentally friendly nanocarriers using natural polymers, lipids, and proteins⁶¹.

The adoption of sustainable excipients and solvent-free manufacturing techniques not only reduces environmental impact but also enhances biocompatibility and patient safety. Future research is expected to focus on integrating sustainability with high-performance drug-delivery design.

10. Conclusion

The evolution of novel drug-delivery systems has significantly transformed pharmaceutical formulation science by addressing the limitations associated with conventional dosage forms. Advances in lipid-based carriers, polymeric nanocarriers, mucoadhesive platforms, transdermal systems, and stimuli-responsive delivery technologies have demonstrated substantial potential in enhancing drug solubility, bioavailability, therapeutic efficacy, and patient compliance.

Targeted and smart drug-delivery systems enable site-specific drug action while minimizing systemic toxicity, thereby improving overall treatment outcomes. Emerging technologies such as lipid nanoparticles for nucleic acid delivery, artificial intelligence-assisted formulation design, microfluidics, and personalized drug-delivery platforms are expected to further accelerate innovation in this field.

Despite these advancements, successful clinical translation of novel drug-delivery systems requires overcoming challenges related to scalability, long-term stability, safety assessment, regulatory harmonization, and cost-effectiveness. Continued collaboration among academic researchers, pharmaceutical industries, and regulatory authorities will be critical to translating these advanced delivery platforms into clinically viable and accessible therapies. Overall, novel drug-delivery systems represent a cornerstone of future precision medicine and patient-centric pharmaceutical development.

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