

# Recent Advances in Nano formulation for Targeted Drug Delivery

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## Abstract:

Nanoformulations are reshaping targeted drug delivery by improving payload stability, enabling controlled release, and achieving tissue- or cell-specific localization. From advances in lipid nanoparticles (LNPs) that enabled the mRNA vaccine revolution to engineered extracellular vesicles (EVs), biomimetic coatings, stimuli-responsive materials, and nanoparticle-enabled CRISPR delivery, the 2023–2025 period has seen accelerated translation and new technical strategies for organ-selective delivery. This review summarizes design principles, notable technological innovations (2023–2025), applications, and translational bottlenecks—focusing on strategies that increase specificity, safety, and manufacturability. We highlight key recent studies and propose directions likely to drive clinical translation over the next five years.

**Keywords:** nanoformulation, targeted drug delivery, lipid nanoparticles, extracellular vesicles, CRISPR delivery, biomimetic coatings, stimuli-responsive nanoparticles.

## 1. Introduction

Nanoformulations—engineered carriers at the 1–500 nm scale—remain central to modern targeted therapeutics. By changing surface chemistry, shape, composition, and responsiveness to local environments, nanoformulations can alter pharmacokinetics, bypass biological barriers, and selectively deliver small molecules, biologics, nucleic acids, or gene-editing cargos to target cells. The success of LNP-based mRNA vaccines during the COVID-19 pandemic accelerated interest and investment in nanoscale delivery systems, catalyzing a wave of innovations from lipid chemistry to organ-selective targeting approaches and clinical trials for nucleic acid therapeutics.<sup>1-2</sup>

## 2. Design Principles and Types of Nanoformulations

Nanoformulations can be categorized by material and function: lipid-based systems (liposomes, LNPs), polymeric nanoparticles, inorganic nanoparticles (gold, silica), dendrimers, micelles, and biological carriers (extracellular vesicles, cell-membrane coated particles). Key design parameters include size distribution, surface charge, ligand display for active targeting, stealthing (e.g., PEGylation or alternative polymers), payload encapsulation efficiency, and triggers for controlled release (pH, redox, enzymes, light, heat). Rational design seeks to balance circulation time, target accumulation, endosomal escape (for intracellular cargo), and biodegradation/clearance.

## 3. Preparation and Manufacturing Advances (2023–2025)

Scale-up and reproducibility are frequently cited as practical barriers. Progress in microfluidic mixing, continuous-flow production, and Quality-by-Design (QbD) frameworks has improved batch-to-batch consistency for LNPs and polymeric nanoformulations. Additionally, greener/biofabrication approaches—using plant-derived or biotemplated processes—are gaining traction to reduce environmental burden and simplify regulatory pathways. Advances in characterization techniques (e.g., high-throughput dynamic

light scattering, cryo-EM for structural validation) support regulatory-grade control of critical quality attributes.<sup>3-4</sup>

## 4. Key Technological Advances

### 4.1. Next-generation Lipid Nanoparticles: organ- and cell-selective LNPs

LNPs have been optimized beyond generic liver tropism. New ionizable lipid chemistries, helper lipid ratios, and selective organ-targeting (SORT) strategies—where lipid composition is tuned to alter biodistribution—enable preferential accumulation in organs such as the spleen, lung, or even selective uptake by immune cell subsets. Importantly, the first systemic CRISPR-Cas9 therapies delivered by LNPs entered the clinic in 2023–2024, confirming the utility of LNPs for systemic gene-editing applications and underscoring progress in safety and payload protection.<sup>5</sup>

### 4.2. Extracellular Vesicles (EVs) and Engineered Cell-Derived Carriers

EVs—naturally secreted vesicles with inherent cell-targeting properties—have seen rapid methodological advances in isolation, cargo-loading (electroporation, hydrophobic insertion, genetic engineering of donor cells), and surface engineering. 2024–2025 literature emphasizes EV bioengineering to present targeting ligands or to hybridize EVs with synthetic lipids to combine biocompatibility and tunable pharmacokinetics. These carriers show promise for hard-to-reach tissues and for reducing immunogenicity relative to synthetic particles.

### 4.3. Biomimetic Coatings and Cell-Membrane Cloaking

Coating nanoparticles with membranes from red blood cells, platelets, or tumor cells provides immune evasion and homotypic targeting. 2023–2025 work refined methods to preserve membrane proteins during coating, improving circulation times and enhancing accumulation in target tissues. Hybrid designs that combine synthetic core functionality (e.g., triggered release) with natural surface cues are increasingly studied.<sup>6</sup>

### 4.4. Stimuli-Responsive and “Smart” Nanoformulations

Intelligent carriers that respond to tumor microenvironmental cues—acidic pH, elevated glutathione, proteases—or external stimuli (ultrasound, photothermal) enable controlled release and spatiotemporal activation. Recent designs have integrated multi-stimuli responsiveness (e.g., pH + enzyme) and modular linkers that permit cargo release only upon sequential triggers, increasing on-target activity while minimizing off-target exposure. Clinical translation paths are being explored for externally actuated modalities (e.g., focused ultrasound to open the blood-brain barrier).

### 4.5. Nanoparticle-Enabled CRISPR and Gene Editing Delivery

Non-viral nanoparticle systems for CRISPR (LNPs, polymeric carriers, EVs) have matured: improved encapsulation of Cas proteins or mRNA/gRNA complexes, enhanced endosomal escape chemistries, and improved targeting to specific organs. Notably, the shift from ex vivo to systemic in vivo editing—demonstrated in early clinical trials—marks a major translational milestone. Nanoparticle strategies now emphasize transient delivery (reducing off-target editing) and tissue-restricted editing by combining targeting ligands with organ-biased formulations.<sup>7</sup>

## 5. Applications and Case Studies<sup>8</sup>

### 5.1. Vaccines and Immunotherapies

LNP-mRNA platforms continue to diversify beyond infectious disease vaccines into cancer vaccines, personalized neoantigen vaccines, and immune-modulating therapies. Combination strategies pairing nanosystems with checkpoint inhibitors or oncolytic approaches were prominent in the literature (2023–2025), with preclinical studies showing improved antitumor responses using nanoparticle-delivered mRNA for tumor antigens.

### 5.2. Oncology: Targeted Chemotherapy and Combination Modalities

Nanoformulations are being used to deliver cytotoxic drugs with improved tumor penetration (via TME-responsive release), radiosensitizers, and immune stimulants. Multifunctional nanoparticles that co-deliver

chemo + siRNA or chemo + immunostimulant payloads demonstrated synergistic effects in animal models and selected early-phase clinical studies.

### 5.3. Genetic Diseases and Gene Editing

The advent of LNP-based CRISPR delivery targeting liver-expressed genes (e.g., transthyretin, metabolic genetic disorders) progressed into clinical testing by 2024, indicating that nanoparticle-based systemic gene editing is feasible and that safety monitoring and transient expression are manageable. This opens avenues for treating monogenic disorders that are difficult to address with traditional small molecules.

### 5.4. CNS and Mucosal Delivery Strategies

Brain delivery remains challenging. Advances include LNPs with surface modifications enabling transcytosis, nose-to-brain nanoparticle strategies, EVs with brain tropism, and externally actuated BBB opening (ultrasound). Recent 2023–2025 reviews and preclinical reports describe incremental progress toward systemic mRNA or protein delivery to the brain, but translation remains cautious.

## 6. Translation, Regulatory, and Safety Considerations

While scientific innovations abound, translation depends on scalable manufacturing, robust characterization, safety (immunogenicity, long-term toxicity), and regulatory frameworks. The rapid clinical uptake of mRNA LNPs has accelerated regulatory familiarity with ionizable lipid platforms, but new chemistries (novel lipids, biomimetic surfaces) will require rigorous safety testing. Standardization of EV isolation and characterization remains a major regulatory obstacle. Environmental considerations and reproducible manufacturing are increasingly part of regulatory discussions.

## 7. Challenges and Open Questions

1. **Off-target biodistribution and long-term safety.** Even organ-biased particles can accumulate in non-target tissues; chronic toxicity data are limited.
2. **Endosomal escape efficiency.** Efficient cytosolic delivery of nucleic acids remains a rate-limiting step for many intracellular targets.
3. **Manufacturing and standardization for biological carriers.** EVs and cell-derived systems face reproducibility and scale challenges.
4. **Immunogenicity and repeat dosing.** Immune recognition (anti-PEG antibodies, anti-lipid responses) can limit repeated administrations.
5. **Regulatory harmonization for novel materials.** New lipid chemistries and hybrid biomimetic systems require tailored pathways for approval.

Addressing these issues requires coordinated efforts across material science, pharmacology, manufacturing engineering, and regulatory science.<sup>9</sup>

## 8. Future Perspectives

- **Precision LNPs and SORT-like strategies** will enable more organ- and cell-subset-selective therapies, expanding nucleic acid therapeutics beyond the liver.
- **Hybrid biologic–synthetic carriers** (engineered EVs, membrane-coated particles) will mature as scalable production and standardization improve, providing superior biocompatibility.
- **Clinical expansion of nanoparticle CRISPR therapies**—as early trials report safety and editing efficacy—will likely stimulate more disease-targeted programs.
- **Integration of AI and computational design** to predict biodistribution and rationally design lipid/polymer chemistries for desired organ tropism.
- **Externally controlled activation** (focused ultrasound, light) may permit high-precision activation of payloads in deep tissues, reducing systemic exposure.

## 9. Conclusion

The field of nanoformulation for targeted drug delivery moved from proof-of-concept into early clinical application for several transformative modalities—most notably LNP-based systemic delivery of nucleic acids and nascent EV engineering strategies. Innovations in organ-biased LNPs, biomimetic coatings, stimuli-responsive release, and nanoparticle-enabled gene editing are converging to make truly targeted therapeutics feasible for a broader set of diseases. However, sustained clinical impact will depend on solving manufacturing, safety, and regulatory challenges—areas that must be addressed in parallel with material innovation.

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