Parenteral Nanocarriers for mRNA and Gene Therapy: Emerging Trends and Future Perspectives: A Narrative Review

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ABSTRACT

This narrative review critically discusses the recent advances in parenteral nanocarrier systems for mRNA and gene therapy. Focusing on delivery mechanisms, clinical translation, and regulatory challenges, it integrates findings from contemporary research to highlight emerging technologies and translational hurdles. The review emphasizes key nanocarrier systems including lipid nanoparticles, polymeric and hybrid carriers, and explores safety, scalability, and future prospects in precision nanomedicine.

Keywords: Cas delivery vectors, Crispr, Lipid nanoparticles, Parenteral mrna delivery, Polymeric nanocarriers, Self-amplifying RNA

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Introduction

In contemporary medicine, messenger RNA (mRNA) and gene therapy have become revolutionary techniques. mRNA therapies have shown great promise in treating genetic diseases and developing vaccinations.[1] Compared to traditional small-molecule medications, gene therapy offers more specificity and therapeutic precision by directly modifying genetic material.[2] The COVID-19 pandemic's recent success with mRNA vaccines has brought attention to how crucial parenteral delivery systems are. Because nucleic acid treatments are prone to enzymatic breakdown, fast clearance, and immunogenic reactions, their systemic distribution is difficult.[3] Because it offers quick absorption and precise tissue distribution, parenteral administration—intravenous (IV), intramuscular (IM), or subcutaneous (SC)—is therefore seen to be the most efficient method. Lipid nanoparticles (LNPs), polymeric carriers, dendrimers, and hybrid systems are examples of advanced nano formulations that improve cellular absorption and safeguard nucleic acids.[4] The effectiveness and safety of gene therapy and mRNA treatments depend on these carriers' ability to handle crucial issues such endosomal escape, regulated release, and targeted delivery.[5] This review attempts to facilitate the transition of next-generation nucleic acid therapeutics into clinical practice by offering a thorough examination of recent developments in parenteral nano formulations for mRNA and gene therapy, emphasizing delivery mechanisms, clinical applications, regulatory considerations, and future prospects.

Methodology

This work is a narrative review based on literature published between January 2015 and March 2025. Major databases including PubMed, Scopus, ScienceDirect, and Google Scholar were systematically searched using keywords such as "mRNA delivery," "gene therapy nanocarriers," "parenteral nano formulations," and "lipid nanoparticles."[6]

Both preclinical and clinical studies, as well as regulatory and manufacturing guidance documents from agencies such as the FDA and EMA, were included to ensure translational relevance. Inclusion criteria comprised peer-reviewed English-language publications addressing nucleic acid delivery via parenteral routes, nanocarrier design, or manufacturing and regulatory aspects. Exclusion criteria involved duplicate reports, non-English articles, or papers lacking primary data or mechanistic discussion.[7]

Selection Workflow: Initial database search yielded approximately 356 records. After screening titles and abstracts and removing duplicates, 112 studies were retained for full-text review, of which 74 met the inclusion criteria. Key quantitative and translational findings were extracted and tabulated to support comparative analysis and ensure transparent synthesis.

Preference was given to recent high-impact studies, landmark reviews, and clinical trial data to provide a balanced and integrative perspective. Where appropriate, quantitative comparisons—for example, between lipid- and polymer-based systems or viral vs. non-viral vectors—were summarized in tables for clarity.

This methodology ensures that the review presents an evidence-driven and transparent synthesis of advancements in parenteral nanocarrier systems for mRNA and gene therapy.

This review proposes a unifying Route–Carrier Decision Framework linking therapeutic objectives (such as vaccines, transient protein replacement, and durable gene correction) to parenteral routes (IV, IM, SC) and carrier classes (LNPs, polymers, liposomes, dendrimers, and viral vectors). By integrating biodistribution, duration, immunogenicity, re-dosing, and manufacturability considerations, this framework provides a rational basis for selecting optimal delivery strategies for mRNA and gene therapy.

mRNA and Gene Therapy

Evolution and significance - Gene therapy and messenger RNA (mRNA) are pioneering therapies that have developed recently in medicine. Gene therapy and mRNA treatments modify or replace defective genes and, unlike traditional medications, address the source of the illness.[8] The swift development of mRNA vaccines to counter COVID-19 and the approval of numerous gene therapies have demonstrated the treatment potential, and invigorated interest in gene therapy and mRNA around the world. They have the potential to treat previously untreatable infectious diseases, cancers, and inherited disorders.[9]

Importance of Parenteral Delivery for Nucleic Acids

Nucleic acids, or nucleic acid-based therapies including DNA, RNA, and oligonucleotides, have significant challenges regarding rapid systemic circulation clearing, limited cellular uptake, and in vivo enzymatic degradation.[10] It is debated that parenteral (IV, IM, and SC) is the most effective route for the delivery of nucleic acid-based therapies. Parenteral therapy provides the ability to administer a higher volume (for IM, SC), bypass pharmacodynamic degradation by the gastrointestinal (GI) tract, molecular metabolism, absorption issues when orally administered, and establish immediate systemic delivery.

This schematic (Figure 1) depicts encapsulation of mRNA and DNA in lipid nanoparticles, liposomes, and polymeric nanocarriers delivered via IV, IM, and SC routes to achieve cellular uptake and gene expression.

Nano formulation Platforms for mRNA and Gene Therapy

Numerous nano-formulation approaches have been created with the goal to enhance the delivery and therapeutic efficacy of mRNA and gene manipulation.[11] Given the popularity of COVID–19 mRNA vaccines, lipid nanoparticles (LNPs) provide the furthest advance and are the most widely used systems clinically. The ionizable lipids have enabling characteristics, specifically their ability to promote endosomal escape and cytoplasmic release of nucleic acids, greatly benefiting nucleic acid delivery methods.[12] Despite the clinically promising characteristics of LNPs, concerns about liver accumulation, as well as stability at cold-chain conditions, and possible immune effects are on-going. While polymer formulations (for example branched polyethyleneimine (PEI), poly (β-amino esters), PLGA, and chitosan derivatives) can provide delivery systems with controlled release, biodegradability, and/or tenable chemistry, they also have inherent cytotoxicity and lower transfection efficiency in vivo.[13] Although liposomes and lipoplexes were some of the earliest nanocarriers to come into use clinically, provided biocompatibility, and the ability to encapsulate both hydrophilic and lipophilic agents, they have often had issues with stability and limited systemic efficacy. Dendrimers (such as PAMAM) and hybrid nano-carriers with lipid - polymer or lipid - dendrimer systems provide a number of benefits, such as enhanced loading capacities and targeting specificity, but also generate some caveats like associated long-term toxicity and scalability.[14] Even with their immunogenicity, limited payloads, and manufacturing limitations, viral vectors (AAVs, lentiviruses, adenoviruses), while still considered a gold standard for transfection efficiency and sustained gene expression, remain excessively clinically cumbersome for wider use. [15] Even if they only provide short-lived expression, the alternative non-viral vectors LNPs, polymers, liposomes, and dendrimers provide a much safer, scalable, and modular solutions for gene modification, with safety, effectiveness, and scalability still being balanced technologies. Together, these nano-formulation platforms are not yet fully developed, but are progressing towards complimentary technologies with therapeutic needs dictating the mechanism used.

Lipid Nanoparticles (LNPs)

One of the most sophisticated and clinically proven non-viral delivery methods for mRNA is lipid nanoparticles (LNPs). Ionizable lipids form the functional backbone of LNPs, enabling endosomal escape and cytoplasmic release. Early-generation analogs, known as lipidoids, share similar cationic architectures but differ in biodegradability and design flexibility. share structural similarity but differ in chemical tunability and biodegradability." that turn cationic in acidic endosomes, they shield mRNA from nuclease destruction, promote uptake, and allow endosomal escape. They also allow tunability of lipid composition, PEGylation, cholesterol, and helper lipids to optimize biodistribution and reduce immunogenicity. But there are still issues, such as immune stimulation, liver buildup, and strict cold-chain stability regulations.

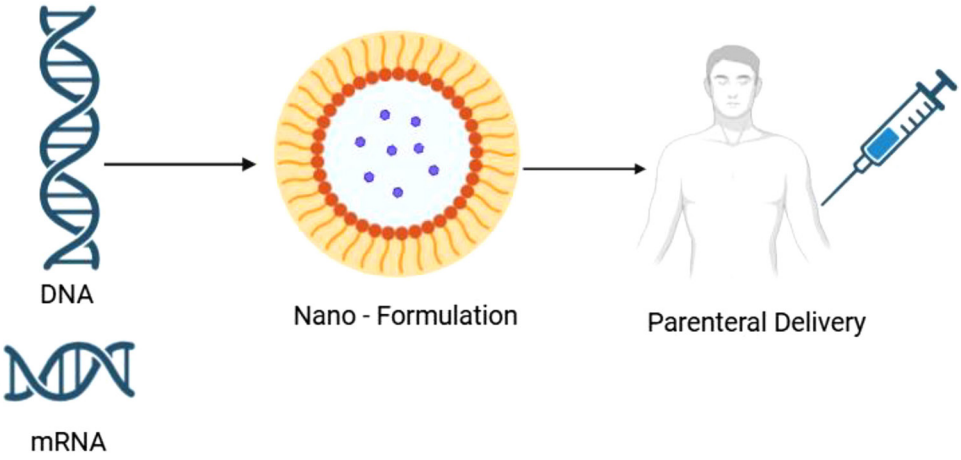

Fig 1 | Schematic representation of mRNA and gene therapy delivery via parenteral nanocarriers

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Liposomes and Lipoplexes

Liposomes are lipid bilayer vesicles that have proven formulation methods and biocompatibility. They can encapsulate hydrophilic payload inside and hydrophobic cargo in their membrane. They produce lipoplexes when they electrostatically complex with nucleic acids. Both commercial medication delivery and gene delivery investigations have made considerable use of them. However, compared to viral vectors, cationic liposomes often result in inferior gene transfer efficiency in vivo, can cause cytotoxicity and inflammation, and are unstable (cargo leakage, aggregation).[16]

Dendrimers and Hybrid Nanocarriers

Dendrimers are artificial macromolecules that are highly branched and have many terminals functional groups that allow for surface modification and great loading capacity. As non-viral carriers, they have been studied, particularly poly(amidoamine) (PAMAM) dendrimers and previous research.[17] Although scale-up, complexity, and possible toxicity are still obstacles, hybrid systems (such as lipid-polymer hybrids and lipid-dendrimer assemblies) seek to combine the advantages of several materials—stability, targeting, and biocompatibility.[18]

Viral vs. Non-viral Vectors

Viral vectors, such as AAV, lentivirus, and adenovirus, are considered the "gold standard" in gene therapy because of their high transduction effectiveness, long-lasting gene expression, and often cell targeting. However, there are hazards associated with limited payload, insertional mutagenesis, immunogenicity, and manufacturing complexity. Although non-viral vectors (such as LNPs, polymers, liposomes, and dendrimers) are safer, more scalable, and have greater design flexibility, they often only provide temporary gene expression and have a lower transfection effectiveness. "A comparative overview of different nanocarrier systems for mRNA and gene therapy is summarized in Table 1."

Parenteral Delivery: Routes, Barriers, and Formulation Considerations

For mRNA and gene therapy nano formulations, parenteral administration is still the recommended method since it can skip first-pass metabolism, circumvent the gastrointestinal tract, and provide quick systemic bioavailability.[24] The route selection, however, has a major impact on biodistribution, safety, and therapeutic effectiveness. Sterility, immunological recognition,

Table 1 | Comparison of Different Nanocarrier Systems for mRNA / Gene Therapy

S.No.	Nanocarrier System	Advantages	Disadvantages	Application
1.	Lipid Nanoparticles (LNPs) [19]	• Excellent encapsulation of nucleic acids (mRNA, siRNA) protecting from nuclease degradation. • Ionizable or cationic lipids allow endosomal escape. • Clinically validated (e.g., mRNA vaccines for COVID-19).	• Potential toxicity / immunogenicity of lipid components. • Clearance by RES (reticuloendothelial system), off-target accumulation (e.g liver). • Cold chain / stability challenges.	Widely used for vaccine delivery, protein replacement therapies, recently in clinical vaccines; excellent for transient expression were repeated dosing acceptable.
2.	Polymer-based Nanoparticles / Polyplexes	• High tunability: polymers can be modified chemically, tailored release kinetics. [20] • Good protection and stability of nucleic acids; possible targeting moieties. • Potential for lower immunogenicity if designed well.	• Some polymers (especially cationic ones) can be cytotoxic. • Often lower transfection efficiency compared to viral vectors. • Challenges in achieving good biodistribution and endosomal escape for certain tissues.	Useful in vaccine delivery, gene editing (e.g., with CRISPR components), when tuning of release or repeated dosing is needed, or where viral vectors are less preferable.
3.	Liposomes and Lipoplexes[21]	• Biocompatible and well understood; liposomes can carry both hydrophilic (in aqueous core) and hydrophobic cargo (in lipid bilayer). • Lipoplexes (complexes of lipids + nucleic acids) are relatively simple to prepare, can help with charge interactions. • Often lower immunogenicity compared to viral options.	• Cationic liposomes can be cytotoxic and recognized by immune system; can aggregate, fuse, and leak. • Stability can be an issue; shelf life, serum stability, leakage of cargo. • Generally lower in vivo transfection vs viral vectors in many cell types.	Good for localized delivery, vaccine adjuvants, when transient expression is sufficient; lipoplexes sometimes used for in vitro or ex vivo transfection; liposomes used when biocompatibility is critical.
4.	Dendrimers & Hybrid Nanocarriers	• Precise and branched architectures allow multivalency, high payloads, and functional modifications. [22] • Hybrids (lipid-polymer hybrids, lipid-dendrimer etc.) can combine benefits of different systems: e.g., stability from polymers + biocompatibility from lipids.	• Increased complexity in design and synthesis; scale-up may be difficult. • Potential issues with biodegradability, clearance, toxicity especially for large or highly charged dendrimers. • Cost can be higher.	Often explored in preclinical studies; for targeted delivery or special applications (e.g., cell-specific targeting, crossing barrier tissues); hybrids are promising for enhancing performance of simpler systems.
5.	Viral Vectors vs. Non-Viral Vectors[23]	**Viral**: High transfection efficiency; long expression (in some cases); good for applications requiring strong, durable gene expression. **Non-viral**: Lower immunogenicity (if designed well); larger cargo capacity (some systems); safer, easier manufacture; flexibility in tuning.	**Viral**: Immunogenicity; risk of insertional mutagenesis (for integrating vectors); limited cargo size for many viral vectors; pre-existing immunity in host can reduce effectiveness; complicated regulatory / production concerns. **Non-viral**: Often lower expression levels; transient expression; may require higher doses; challenges with delivery to specific tissues and overcoming biological barriers; stability issues.	Viral vectors are used for permanent / long term gene therapy (genetic disorders etc.), ex vivo gene therapy; non-viral systems are attractive in vaccine RNA, transient gene editing, applications where repeat dosing is feasible, or where viral risks are undesirable.

formulation stability, and anatomical obstacles are important factors.[25]

Intravenous Administration

Nano formulations can be delivered into systemic circulation via intravenous (IV) injection, assuring immediate bioavailability. The IV route is especially effective for targeting organs with high perfusion such as the liver and spleen that are primary organs of mRNA uptake.[26] However, intravenous injection is linked to the mononuclear phagocyte system's quick clearance as well as possible systemic adverse effects, such as organ damage and immunological activation. To increase circulation time and decrease immunogenicity, formulation techniques including PEGylation and the addition of ionizable lipids are used.

Intramuscular Administration

Nano formulations are injected intramuscularly (IM) into muscle tissue, where they can be gradually absorbed into the bloodstream. mRNA vaccines are among the many vaccinations that are frequently delivered by this method. Many antigen-presenting cells are found in muscles, which makes it easier for the nano formulations to be efficiently absorbed. However, local inflammation and discomfort at the injection site may result with IM administration, and tissue composition and blood flow may have an impact on the rate of absorption.[27]

Subcutaneous Administration

Nano formulations are deposited into the subcutaneous tissue by subcutaneous (SC) injection, which creates a depot effect for prolonged release. For treatments that call for extended drug exposure, this approach is beneficial. However, because of variations in lymphatic drainage and blood flow, SC administration may produce varying absorption rates. Furthermore, the distribution and absorption of nano formulations may be impacted by the presence of subcutaneous fat.[28]

Safety, Immunogenicity, and Off-target Effects

Immune responses may be triggered by the injection of nano formulations, which might result in toxicity and inflammation. The innate immune system can be stimulated by lipid nanoparticles (LNPs), which are frequently used for mRNA delivery. This can lead to the release of cytokines and the activation of complement. Ionizable lipids, PEGylation, and the use of stabilizing excipients are methods to lessen these effects.[29] Furthermore, improving the size and surface charge of nanoparticles can improve targeted delivery and decrease off-target accumulation.

Technical Expansion: Mechanistic and Formulation Insights

Endosomal Escape Mechanisms

Endosomal escape is a pivotal step in successful intracellular delivery of mRNA and gene therapeutics. Once internalized by endocytosis, nanocarriers become entrapped in acidic endosomes.[30] Ionizable lipids play a crucial role here: they are neutral at physiological pH (reducing systemic toxicity) but protonate in acidic endosomal conditions, leading to membrane destabilization via the "proton sponge" or "ion-pair" mechanism. This disrupts the endosomal membrane, releasing nucleic acid cargo into the cytoplasm. Helper lipids such as DOPE assist this process by adopting an inverted hexagonal (HII) phase, further promoting endosomal rupture.

Role of Lipid Composition: Ionizable Lipids, Helper Lipids, Cholesterol, and PEG Alternatives

Ionizable lipids form the functional backbone of lipid nanoparticles (LNPs), governing encapsulation efficiency and endosomal escape. Helper lipids (such as DSPC or DOPE) stabilize bilayer structures and aid membrane fusion. Cholesterol enhances membrane rigidity and stability while modulating lipid packing density to improve biodistribution and endosomal release. PEGylated lipids, while extending circulation half-life and minimizing opsonization, are being critically re-evaluated due to immunogenic concerns and anti-PEG antibody formation. Alternatives such as zwitterionic phospholipids, polysarcosine, or glycolipids offer comparable "stealth" performance without triggering complement activation.[31]

Anti-PEG Immunity and Complement Activation-Related Pseudo Allergy (CARPA)

Repeated administration of PEGylated nanoparticles has been associated with anti-PEG antibody formation, leading to accelerated blood clearance (ABC) and hypersensitivity reactions. The CARPA phenomenon arises from complement activation by nanoparticle surfaces, triggering pseudo allergic responses. Strategies to counter this include (i) replacing PEG with zwitterionic or biomimetic coatings, (ii) optimizing nanoparticle surface charge and hydrophobicity, and (iii) using pre-medication or slow infusion protocols to minimize acute immune activation.

Microfluidic and Continuous Manufacturing of LNPs

Microfluidic mixing technologies have revolutionized scalable LNP manufacturing by enabling precise control over lipid–nucleic acid self-assembly. Techniques such as staggered herringbone micromixers and continuous flow reactors allow reproducible nanoparticle size distribution, high encapsulation efficiency, and consistent batch quality. Continuous manufacturing approaches integrate inline quality monitoring, sterility assurance, and automated process control, aligning with Quality by Design (QbD) and GMP frameworks. This transition from batch to continuous production minimizes variability and enhances scalability for clinical-grade mRNA therapeutics.[32]

Dosing Volume and Depot Effects for Intramuscular (IM) vs Subcutaneous (SC) Administration

According to the U.S. Centers for Disease Control and Prevention (CDC) General Best Practice Guidelines for Immunization (2023) and World Health Organization (WHO) Best Practices for Injections and Related

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Procedures Toolkit (2021), the intramuscular (IM) route typically accommodates 1–2 mL in the deltoid muscle and up to 5 mL in the gluteal region, depending on formulation viscosity and site tolerance. The subcutaneous (SC) route generally permits ≤2 mL per injection site, providing a slower, depot-type absorption profile suitable for sustained RNA or gene therapy dosing.

The IM route offers rich vascularization and abundant antigen-presenting cells, supporting rapid uptake and immune priming — ideal for vaccines. SC injections, conversely, produce prolonged release and are preferred for long-acting formulations or repeated therapeutic dosing. These CDC/WHO guidelines provide an evidence-based foundation for dose volume, site selection, and injection technique optimization in translational mRNA and gene therapy studies.

Centers for Disease Control and Prevention (CDC)

General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). Updated March 2023.[75]

World Health Organization (WHO)

WHO Best Practices for Injections and Related Procedures Toolkit. Geneva: WHO Press; 2021.[76]

Quantitative and Translational Considerations for Parenteral Nano Formulations

The physicochemical parameters of nanocarriers critically influence their in vivo performance. Typical lipid nanoparticles (LNPs) used for mRNA delivery exhibit mean hydrodynamic diameters of 60–100 nm, polydispersity index (PDI) values below 0.2, and zeta potentials near neutral (−10 to +10 mV) at physiological pH 7.4, which minimize aggregation and complement activation while supporting efficient endosomal escape.[33] Optimal LNP formulations usually maintain encapsulation efficiency above 90%, ensuring stability and high payload delivery efficiency. According to WHO and CDC injection guidelines, the intramuscular (IM) route accommodates 1–2 mL in the deltoid muscle and up to 5 mL in the gluteal region, depending on formulation viscosity and site tolerance. The subcutaneous (SC) route generally permits ≤2 mL per injection site, producing a slower, depot-type absorption profile suitable for long-acting RNA or gene therapy regimens. Biodistribution is governed by particle size, surface charge, and protein corona composition. Nanoparticles between 50–150 nm preferentially accumulate in the liver and spleen, facilitated by Apolipoprotein E (ApoE) adsorption, which mediates receptor-mediated hepatic uptake via the LDL receptor. Smaller particles (<50 nm) often display enhanced lymphatic transport and rapid renal clearance, whereas larger aggregates (>200 nm) may show limited systemic mobility and faster clearance by the mononuclear phagocyte system (MPS). Re-dosing considerations remain pivotal for mRNA therapeutics. PEGylated lipids, while extending circulation half-life, can trigger anti-PEG antibody formation, leading to accelerated blood clearance (ABC) phenomenon upon repeat administration. Emerging strategies include using zwitterionic or polysarcosine coatings, biodegradable lipid conjugates, or pre-dose immune modulation to mitigate anti-PEG immune memory.

Together, these quantitative insights and dosing norms strengthen the translational understanding of parenteral nanocarrier behaviour, bridging physicochemical design with clinical applicability.

Stability and Sterility Challenges

To guarantee therapeutic effectiveness, mRNA stability inside nano formulations must be maintained. Nucleases and environmental elements like pH and temperature can break down mRNA. Although encapsulation in lipid nanoparticles provide protection, handling and storage issues are introduced. Cryoprotectants and lyophilization are two popular methods for improving stability. Furthermore, maintaining sterility throughout the production process is crucial to avoiding contamination and guaranteeing patient safety.[34]

Scope Delimitation Between mRNA and Gene Therapy

Scope Clarification:

While both mRNA and gene therapies share parenteral nanocarrier platforms, the subsequent sections are treated distinctly to prevent conceptual overlap. Section 4 focuses exclusively on cytoplasmic, transient-acting mRNA therapeutics (e.g., vaccines and protein replacement). Section 5 addresses nuclear or genomic-level gene therapies, including viral and non-viral systems for durable correction. Comparisons appear only where mechanistic or carrier advantages intersect.

While both mRNA and gene therapy rely on parenteral nanocarriers for nucleic acid delivery, their therapeutic intent and biological mechanisms differ fundamentally. mRNA formulations act in the cytoplasm to direct transient protein expression without genomic integration, making them ideal for vaccines and temporary protein replacement. In contrast, gene therapy delivers DNA or gene-editing components (e.g., CRISPR–Cas systems) that operate at the nuclear or genomic level, enabling long-term or permanent effects.[35] To translate these mechanistic and formulation insights into practical guidance, the following section introduces a structured framework that aligns therapeutic goals with delivery routes and carrier classes.

Proposed Route–Carrier Decision Framework for Nucleic Acid Therapeutics

The design of an optimal nucleic acid delivery system depends on aligning the therapeutic objective with the administration route and nanocarrier class. Figure 2 presents a conceptual framework that integrates these parameters to guide formulation and translation choices. For instance, mRNA vaccines, which require transient expression and localized immune activation, are best delivered via intramuscular (IM) lipid nanoparticles (LNPs). In contrast, systemic protein replacement therapies Favor intravenous (IV) delivery with LNPs or polymeric systems to achieve broad biodistribution, while long-term gene correction relies on viral

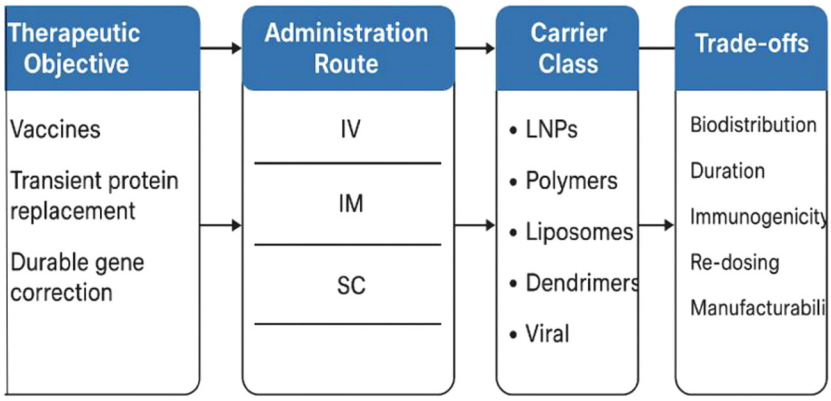

Fig 2 | Serves as the conceptual core of this review, unifying the preceding mechanistic discussion with translational strategy

or hybrid vectors offering durable expression despite higher immunogenic and manufacturing challenges. This integrative approach links therapeutic intent → route of delivery → carrier platform → trade-offs such as biodistribution, duration, immunogenicity, re-dosing feasibility, and manufacturability. Such a unified decision framework supports rational development of next-generation parenteral formulations for mRNA and gene therapy. "The alignment between therapeutic objectives, delivery route, and carrier class is mapped in Table 2".

Central Route–Carrier Decision Framework for Nucleic-Acid Therapeutics

This schematic integrates therapeutic objectives (vaccines, protein replacement, gene correction) with optimal administration routes (IV, IM, SC) and carrier classes (LNPs, polymers, liposomes, dendrimers, viral), outlining explicit trade-offs in biodistribution, expression duration, immunogenicity, re-dosing feasibility, and manufacturability. In this unified route–carrier decision framework (Figure 2).

This section is limited to mRNA nano-formulations that act through cytoplasmic translation, highlighting advances where non-viral carriers—particularly LNPs—are most competitive in transient, repeat-dose applications.

Illustrative Case Studies: Applying the Framework

Case Study 1 — Intramuscular (IM) LNPs for mRNA Vaccines:

The COVID-19 mRNA vaccines (Pfizer–BioNTech and Moderna) provide a benchmark example of the framework's IM–LNP alignment. These lipid nanoparticle formulations deliver nucleoside-modified mRNA encoding viral antigens directly to muscle tissue, achieving localized uptake by antigen-presenting cells and robust systemic immune activation. Clinical data demonstrated >90% efficacy with transient expression lasting several days and strong antibody titers within two doses. Re-dosing feasibility was confirmed through seasonal boosters, although mild anti-PEG responses were reported. These outcomes validate IM–LNP pairing for transient, immune-stimulating objectives with manageable re-dosing intervals.

Case Study 2 — Intravenous (IV) LNPs for Systemic Protein Replacement:

In preclinical and early clinical models (e.g., transthyretin amyloidosis, factor IX deficiency), IV-administered LNPs encapsulating mRNA encoding therapeutic proteins achieved broad hepatic transfection, resulting in detectable serum protein levels within 6–12 hours. Expression persisted for several days, supporting periodic dosing cycles. However, repeated administration induced accelerated blood clearance (ABC) due to anti-PEG antibodies, highlighting the need for biodegradable or zwitterionic lipid alternatives for chronic indications. This example illustrates IV–LNP suitability for systemic but transient protein replacement, with immune memory as a limiting factor.

Case Study 3 — AAV Vectors for Durable Gene Correction:

Adeno-associated virus (AAV)-based therapies (e.g., Luxturna for RPE65 retinal dystrophy; Zolgensma for spinal muscular atrophy) exemplify IV-delivered, long-term gene correction. AAV vectors provide stable

Table 2 | Proposed mapping of therapeutic objectives to route and carrier class for nucleic acid therapeutics

Therapeutic Objective	Typical Duration of Expression	Preferred Route	Representative Carrier	Key Advantages	Key Trade-offs
Vaccines (e.g., COVID-19, cancer immunotherapy)[36]	Short-term (days–weeks)	IM / SC	LNPs, Liposomes	Strong immune activation; scalable manufacture	Local inflammation; cold-chain sensitivity
Transient Protein Replacement (enzyme/hormone therapy)[37]	Medium (days–months)	IV	LNPs, Polymers	Systemic distribution; non-integrating	Hepatic accumulation; re-dosing immune response
Durable Gene Correction (e.g., CRISPR, AAV gene therapy)	Long-term or permanent	IV	Viral, Dendrimers, Hybrid	Sustained expression; high efficiency	Immunogenicity; insertional mutagenesis; complex production
Cancer Immunotherapy / Personalized[38] RNA therapeutics	Medium-term	IM / IV	LNPs, Polymeric NPs	Targeted Immune Modulation	Tumour microenvironment barriers
Long-acting saRNA or circRNA therapies	Medium-term	SC	LNPs, Polymers	Depot effect; sustained expression	Variable absorption; depot irritation

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Table 3 | Approved and ongoing clinical trials of mRNA nano formulations

S.no	mRNA Therapeutic	Indication	Delivery System	Trial Status
1.	Comirnaty (Pfizer-BioNTech)[40]	COVID-19	LNP	Approved
2.	Spikevax (Moderna)	COVID-19	LNP	Approved
3.	CVnCoV (CureVac)[41]	COVID-19	LNP	Phase II/III
4.	mRNA-4157 (Moderna)	Cancer vaccine	LNP	Phase II
5.	SYS6020 (CSPC Pharma)[42]	Cancer cell therapy	LNP	Clinical trials approved in China
6.	GSK mRNA Influenza vaccine[43]	Influenza	LNP	Phase II/III

nuclear episomes enabling sustained protein expression for years from a single administration. However, host immune memory restricts re-dosing potential, and pre-existing neutralizing antibodies exclude certain patients from treatment. This demonstrates how durable gene correction favors viral vectors, while the trade-off lies in limited repeat administration feasibility and complex manufacturing control.

Together, these case studies contextualize the proposed framework — mapping therapeutic intent to route, carrier, and re-dosing feasibility — and demonstrate its translational utility across transient, systemic, and durable genetic interventions.

Current Advances in mRNA nano formulations

Recent breakthroughs in mRNA formulations and nano-carriers have greatly improved the effectiveness, targeting, and scalability of mRNA therapeutics. In summary, several key advances can be highlighted:

Clinical Trials and Approved Products

mRNA therapies utilizing lipid nanoparticles (LNPs) have become increasingly involved and many products are in clinical development: Approved products - In several regions, the Pfizer-BioNTech and Moderna COVID-19 vaccines employing LNPs for mRNA delivery have received full approval and emergency use authorization. Current clinical trials - Two mRNA therapeutics from CSPC Pharmaceutical Group, SYS6020 (anti-cancer cell therapeutic) and SYS6016 (RSV vaccine), have recently been approved for human clinical trials by Chinese regulators; this is a significant milestone in mRNA therapeutics.[39] "Key approved and ongoing clinical trials of mRNA nano formulations are listed in Table 3".

LNP Composition Optimization

It is important to optimize LNP formulations for successful mRNA distribution: Lipid Composition: Studies have determined that ionizable lipids, phospholipids, cholesterol, and PEGylated lipids. Helper lipids such as DSPC or DOPE contribute to membrane stability and fusogenicity, enhancing endosomal escape efficiency to membrane stability and fusogenicity." are important for enhancing mRNA loading and distribution efficiencies. Formulation Methodologies: LNP formulations have been extensively optimized with design of experiment (DOE) strategies to enhance stability and to improve delivery outcomes.

Targeting Ligands and Adjuvants

The therapeutic efficacy of LNPs can be enhanced by adding adjuvants and targeted ligands: Ligand Targeting: Conjugating LNPs to ligands such as mannose, anti-langerin, and anti-CLEC9A has been examined as a means to target the delivery of mRNA to specific immune cells like dendritic cells. Adjuvants: The addition of adjuvant lipids to LNPs enhances innate immune responses, enhancing the efficacy of mRNA vaccines.[44]

Figure 3 shows the intracellular trafficking process including endocytosis, endosomal escape, mRNA release, and translation within the cytoplasm.

This section addresses gene therapy formulations involving nuclear delivery and potential genomic integration, distinguishing viral vectors from emerging non-viral carriers that compete by offering safer, modular, and scalable alternatives.

Current Advances in Gene Therapy Nano Formulations

The use of nanotechnology in gene therapy has led to notable breakthroughs that have improved the

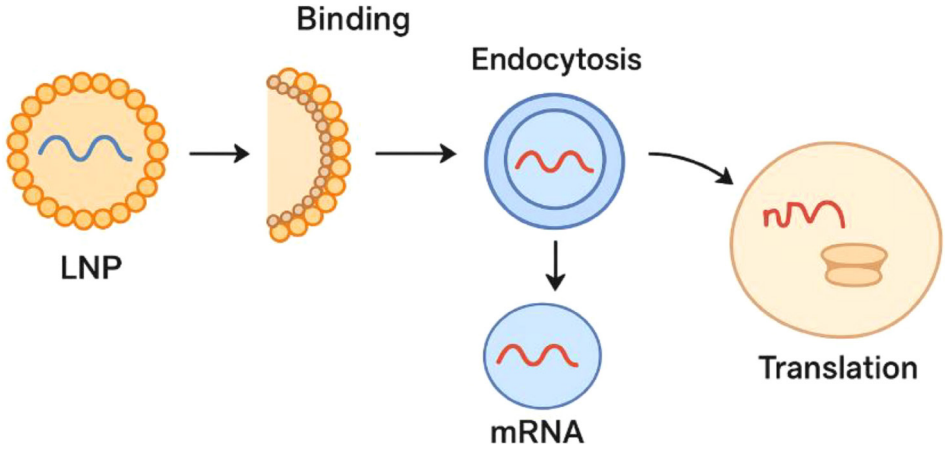

Fig 3 | Mechanism of lipid nanoparticle (LNP)-mediated mRNA delivery inside cells.

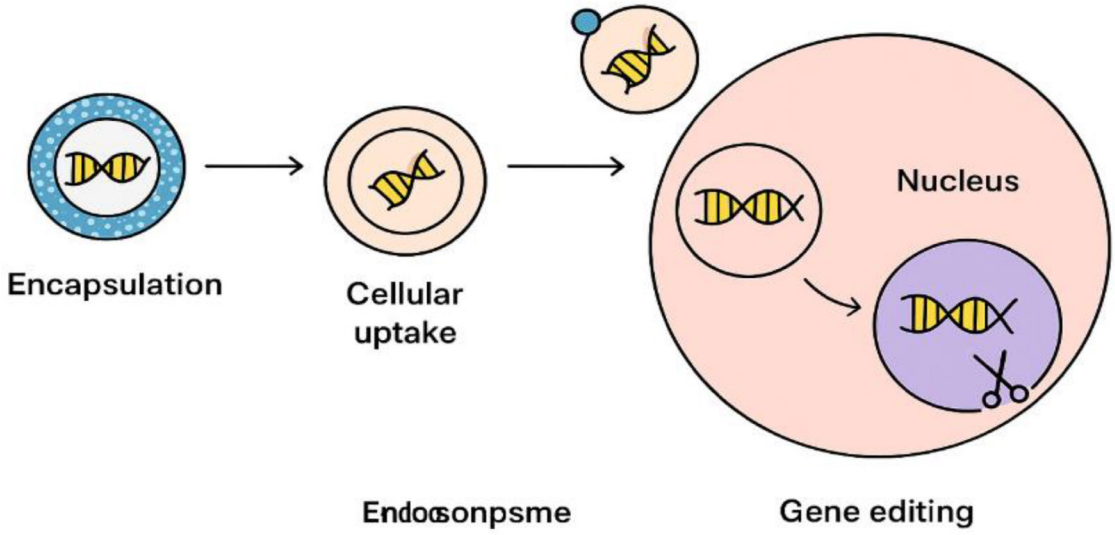

Fig 4 | Nanocarrier-based gene therapy and CRISPR-Cas delivery mechanisms

effectiveness and delivery of therapeutic medicines. This chapter explores the most recent advancements in gene therapy employing nanotechnology, with an emphasis on delivery vectors, non-viral system advances, and methods for overcoming immune reactions.[45]

CRISPR / Cas Delivery Vectors

Although CRISPR/Cas technologies have transformed gene editing, delivery issues are impeding its clinical use. Lipid nanoparticles (LNPs), dendrimers, and exosome-like vesicles are examples of nanoparticle-based carriers that have been designed to contain CRISPR components, enabling effective and precise delivery to cells. By enhancing cellular absorption and shielding the genetic material from deterioration, these nanocarriers increase editing efficiency and lessen off-target consequences.[46]

This diagram (Figure 4) demonstrates a process of gene therapy using nano formulations. The therapeutic gene/CRISPR components are encapsulated in nanoparticles, and are taken up into the cell via endocytosis, escape the endosome, and deliver into the nucleus for gene editing. This diagram also demonstrates how the presence of viral (AAV, lentiviral) and non-viral (LNPs, polymers) vectors may improve the efficiency of gene delivery).

Table 4 | Comparison of Viral vs. Non-Viral Vectors for Gene Therapy[50]

S.No.	Feature	Viral Vectors (AAV, Lentivirus)	Non-Viral Vectors (LNPs, Polymers)
1.	Transfection Efficiency	High	Moderate to High
2.	Immune Response	Integration Risk	Generally Low
3.	Payload Capacity	Limited	High
4.	Integration Risk	Present (Lentivirus)	Minimal
5.	Integration Risk	Challenging	Feasible
6.	Manufacturing Scalability	Complex and Expensive	Easier and Cost-Effective

AAV and Lentiviral Vectors

Two common viral delivery methods in gene therapy are lentiviral vectors and adeno-associated viruses (AAV). Lentiviral vectors are used because of their capacity to integrate into the host genome, guaranteeing steady gene expression, whereas AAV vectors are preferred for their low immunogenicity and long-term expression. Recent developments concentrate on designing these vectors to improve transduction efficiency, decrease immunological reactions, and improve tissue selectivity.[47]

Innovations in Non-Viral Systems

Safer substitutes for viral vectors are non-viral ones, such as lipid-based nanoparticles, polymeric nanoparticles, and hybrid nano systems. These systems have a lower risk of insertional mutagenesis, can carry bigger genetic payloads, and are more tolerant of repeated doses. In order to increase efficiency, recent developments have focused on co-delivery of gene-editing components, targeted ligands, and stimuli-responsive nanoparticles.[48]

Overcoming Immune Response

The effectiveness of gene therapy vectors may be restricted by the immune system's reaction to them. Co-administration of immunosuppressive drugs, surface modification of nanoparticles to avoid immune detection, and the use of biomimetic vectors—which imitate natural particles—to lower immunogenicity are all methods to lessen immune responses. These strategies seek to improve therapeutic medicines' distribution to target cells and extend their circulation duration.[49] "A structured comparison of viral versus non-viral vectors for gene therapy is provided in Table 4."

Sections 4 and 5 were delineated by biological mechanism and vector class. This comparative analysis now integrates both, identifying domains where non-viral carriers match or surpass viral vectors in clinical practicality (e.g., safety, scalability, repeat dosing).

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Table 5 | Comparative overview of mRNA vs gene therapy formulations

Feature	mRNA Nano Formulations	Gene Therapy Nano Formulations
Mechanism of Action	Cytoplasmic translation of delivered mRNA→ transient protein synthesis	Nuclear delivery of DNA or gene-editing components → long-term or permanent expression[53]
Expression Duration	Short-lived (hours–days)	Sustained or permanent (weeks–lifetime if integrated)
Genome Integration	None (non-integrating, transient)	Possible (especially with viral vectors like lentivirus)[54]
Repeat Dosing Feasibility	High – suitable for vaccines or periodic therapies	Limited – constrained by immune response to viral vectors[55]
Immunogenicity[56]	Moderate (can be mitigated via ionizable lipids or PEG alternatives)	High, especially for viral carriers
Typical Carriers	LNPs, liposomes, polymeric nanoparticles	Viral vectors (AAV, lentivirus); non-viral LNPs, dendrimers, hybrids
Manufacturing Complexity	Relatively simple, cell-free, scalable (microfluidic processes)	Complex, cell-based production requiring advanced QC
Clinical Use Cases	Vaccines, cancer immunotherapy, enzyme or hormone replacement	Inherited disorders, durable gene correction, enzyme deficiencies
Regulatory Complexity	Moderate – focus on lipid/mRNA stability and sterility	High – focus on integration risk, vector shedding, long-term safety

Comparative Analysis: mRNA vs. Gene Therapy Formulations

Two different but complimentary approaches in contemporary medicine are the therapeutic use of mRNA and gene therapy formulations. Although they both use nano formulations for delivery, their length, immunological response, repeat dose, expression effectiveness, and manufacturing viability vary.

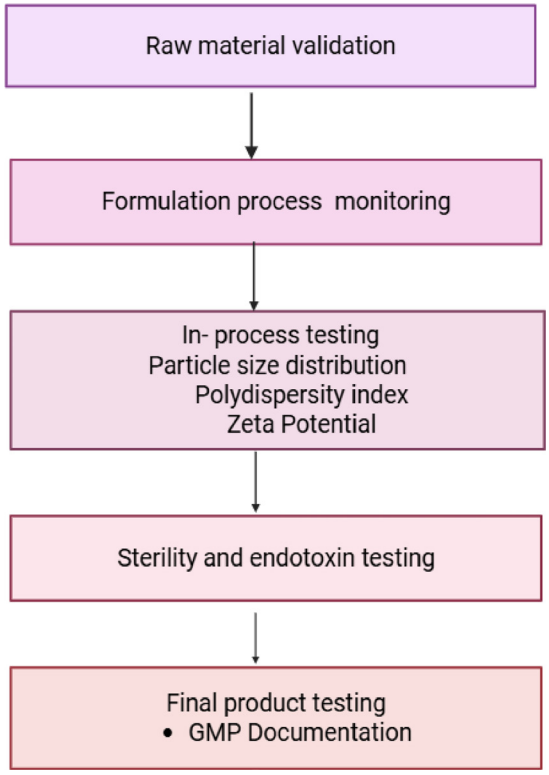

Fig 5 | Quality control workflow for parenteral nano formulations

Expression Efficacy and Duration

mRNA nano formulations are appropriate for vaccinations and short-term protein replacement treatments because they enable quick but fleeting protein production, typically lasting a few hours to several days. Gene therapy nano formulations, on the other hand, transmit DNA or gene-editing tools (like CRISPR), which, depending on whether integration into the host genome takes place, can offer long-term or even permanent expression.[51]

Repeat Dosing and Immune Tolerance

Since mRNA formulations do not integrate into the genome, they are often amenable to recurrent administration. Toll-like receptors (TLRs) and innate immune activation, however, can occasionally restrict tolerance and lower the effectiveness of treatment. However, while long-term expression is conceivable, gene therapy formulations frequently aim for a single-dose treatment. However, powerful neutralizing immune responses restrict repeat dose, particularly with viral vectors like AAV.[52]

Manufacturing and Cost Considerations

mRNA nano formulations have been produced quickly for vaccines like COVID-19 because they are scalable, affordable, and very easy to make. Gene therapy vectors are more costly and challenging to scale because they need intricate bioprocessing and quality control, especially for viral-based formulations. "Table 5 contrasts mRNA nanoformulations with gene therapy nanoformulations in terms of mechanism, duration, and repeat dosing."

Regulatory, Quality Control, and Manufacturing Challenges

There are significant regulatory, quality, and manufacturing challenges in the clinical translation of parenteral nano formulations, such as mRNA–lipid nanoparticles (LNPs) and nano formulated gene therapy vectors. Compliance with Good Manufacturing Practice (GMP) is crucial, necessitating verified and recorded procedures at each stage, from sourcing raw materials to the final sterile filling.[57] Regulatory bodies like the FDA and EMA require robust process knowledge, in-process controls, and repeatable results since nanomedicines are intrinsically more variable than traditional medications. Particle size characterisation, sterility assurance, and endotoxin detection are all included in quality control tests. Although surface adsorption of nanoparticles can make measurements more difficult, endotoxin testing with recombinant Factor C or Limulus Amoebocyte Lysate (LAL) tests is especially crucial for parenteral formulations.[58] While particle size, shape, and polydispersity are frequently evaluated using Transmission Electron Microscopy (TEM), Dynamic Light Scattering (DLS), or Nanoparticle Tracking Analysis (NTA), sterility is typically verified by membrane filtering or fast microbiological techniques. Beyond quality control, scaling up Nano formulation procedures is still very difficult since it necessitates

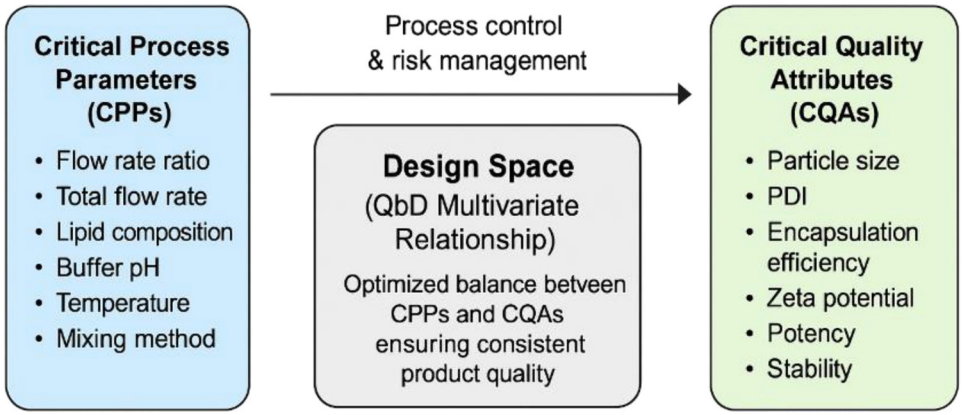

Fig 6 | Quality by Design (QbD) Design Space Linking CPPs to CQAs

exact control over mixing, flow rates, and self-assembly processes in order to maintain batch-to-batch consistency, encapsulation efficiency, and stability. Staggered herringbone mixers and microfluidic mixers are being used more and more to produce LNP in a scalable and repeatable manner. Furthermore, regulatory bodies expect thorough explanation of any process adjustments made during scale-up, and GMP-grade facilities with sterile filling lines, single-use modular systems, and stringent environmental controls necessitate considerable expenditure. In general, the regulatory road for parenteral nano formulations is defined by crucial obstacles such as guaranteeing GMP compliance, thorough quality testing, and scalable but reproducible manufacturing (Figure 5).

Quality control workflow for parenteral nano formulations. The quality control workflow for parenteral nano formulations is summarised in Figure 5. Workflow depicts raw material qualification, in-process particle assessment, sterility and endotoxin testing, and GMP documentation before batch release.

Quality by Design (QbD) Elements for Nanocarriers

Critical Quality Attributes (CQAs): particle size (mean and distribution), polydispersity index (PDI), zeta potential, encapsulation efficiency (EE), payload integrity (e.g., % intact mRNA), residual solvents, free (unencapsulated) nucleic acid, pH/osmolality, sterility/bioburden, endotoxin, appearance, and stability/potency over shelf-life. Critical Process Parameters (CPPs): flow rate ratio (FRR) and total flow rate (TFR) in microfluidic mixing, mixer geometry/temperature, lipid: mRNA N/P ratio, lipid composition (ionizable lipid %, helper lipid, cholesterol, PEG-lipid %), buffer pH/ionic strength, post-processing (diafiltration/ultrafiltration), and hold times. Use DoE to link CPPs→ CQAs and define a robust design space.[59]

The schematic (Figure 6) depicts how variations in critical process parameters influence critical quality attributes through an optimized QbD design space, aligning with ICH Q8 (R2) principles.

Release Testing and Example Specifications

Representative release tests and typical acceptance criteria for parenteral LNP/polymer nanocarriers (justify final limits with process capability, clinical phase, and stability data). "Representative release tests and typical acceptance criteria for parenteral nanocarriers are summarized in Table 6."

Table 6 | Representative release tests and acceptance criteria for parenteral nanocarrier formulations[60–64]

CQA (Attribute)	Method	Typical Acceptance Criterion
Size/PDI	DLS (Z-Avg), PDI	60–100 nm; PDI ≤ 0.20
Zeta potential	Electrophoretic mobility	−10 to +10 mV at pH 7.4
Encapsulation efficiency	Ribo Green or SEC-HPLC	≥ 90% EE
Identity/Integrity	mRNA integrity (CE-IVD/gel), lipid ID (FTIR/LC-MS)	≥ 80–90% intact mRNA; correct lipid profile
pH/Osmolality	pH meter / Osmometer	pH 6.8–7.6; 260–340 mOsm/kg
Endotoxin (BET)	Kinetic chromogenic LAL or rFC	≤ 0.5 EU/mL or ≤ 5 EU/kg per dose
Sterility	USP ‹71›/RMM	No growth
Appearance/Particulates	Visual; USP ‹788›	Meets requirements
Residual solvents/impurities	GC/LC	Below ICH limits

Comparability and Change Control (Scale-Up, Lipid/Supplier Changes)

For scale-up, mixer changes, or lipid/supplier switches, implement a comparability protocol:

(i) risk assessment mapping CPP→CQA impact[65]
(ii) side-by-side batches at pilot vs. commercial scale
(iii) equivalence testing of CQAs (size, PDI, EE, zeta, potency, impurity profile)
(iv) stability-indicating studies on retains
(v) raw-material controls (CoA verification; identity/impurity tests; peroxide/oxidation limits; PEG-lipid MW distribution)
(vi) predefined acceptance criteria and regulatory notification strategy. For PEG- and ionizable lipids, trend lot-to-lot degradation (e.g., aldehydes, peroxides) due to re-dosing safety and potency impact.

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Endotoxin Testing Caveats for Nanoparticles and Recommended Practices

Nanoparticles can interfere with BET. Cationic lipids/polymers, residual solvents, and surfactants may cause inhibition/enhancement in LAL. Recommended practicesValidate BET with product-specific inhibition/enhancement across multiple dilutions; set MVD to reduce matrix effects. Consider recombinant Factor C (rFC) to minimize β-glucan cross-reactivity; use β-glucan blockers with LAL where needed. Target spike recoveries 50–200%; document method suitability. Use endotoxin-free consumables; dehydrogenate vials (e.g., dry heat). Verify container-closure and hold-time do not add endotoxin. Where interference persists, justify alternate approaches (e.g., dilution/filtration, rFC) with formal validation and trending.[66]

Future Prospects and Emerging Trends

The field of parenteral nano formulations for mRNA and gene therapy is rapidly evolving, with several emerging technologies and translational approaches likely to shape its future.

Next-Generation Delivery

self-amplifying RNA (saRNA) and circular RNA (circRNA)- The ability of self-amplifying RNA (saRNA) to reproduce inside cells allows for robust and sustained protein production at a fraction of the dosage needed for traditional mRNA. For vaccinations and therapeutic protein replacement, this makes saRNA a desirable option. As an alternative to linear mRNA, circular RNA (circRNA) exhibits increased stability, less immunogenicity, and extended expression.[67]

Smart and Responsive Nanocarriers

Future nanocarriers are being developed to be stimuli-responsive, meaning that they will release their payload in reaction to changes in the body's pH, temperature, enzymes, or redox conditions. These technologies offer improved intracellular delivery, less side effects, and increased targeted selectivity.

Combination Therapies

In combination medicines, nano formulations will be utilized more often to co-deliver small-molecule medications, gene editing tools (like CRISPR), and mRNA. These multimodal strategies can target many pathways at once, providing novel therapeutic options for complicated illnesses including cancer, autoimmune diseases, and neurodegeneration.[68]

Precision Medicine Applications

The development of individualized nanomedicine, biomarkers, and genetic profiling will enable the customization of nano formulations to meet the specific requirements of each patient. This might support the larger objectives of precision medicine by enabling patient-specific dosage, fewer side effects, and better therapeutic results.[69]

Global Access and Sustainability

Ensuring fair access to these cutting-edge treatments globally is a significant future problem. Due of their high cost and technological requirements, current Nano formulation systems are only accessible in high-income nations. Future developments must concentrate on sustainable cold-chain solutions and low-cost, scalable production to guarantee accessibility and affordability worldwide.[70]

Challenges and Limitations

A number of obstacles prevent the clinical use of nano formulated parenteral delivery methods for mRNA and gene therapy, despite their encouraging promise. Nanocarrier stability poses a critical problem in that they may lose, agglomerate, or degrade therapeutic payloads both during storage and circulation, which decreases to efficacy. Moreover, immunogenicity (and off-target effects), which may cause fast clearance or undesirable responses when, recognized by the immune system, would also be an important consideration. Poor delivery to the intended site may result from limited tissue, or cell targeting, and cytotoxic or inflammatory reactions may be caused by the toxicity of some types of nanomaterial such as synthetic polymers or

Table 7 | Major limitations and possible solutions for nano formulated Parenteral Delivery[73]

S.No.	Challenge / Limitation	Description	Possible Solutions/ Studies
1.	Poor Stability of Nano formulations	Nanocarriers may aggregate, degrade, or lose payload activity during storage or circulation.	Optimization of excipients, lyophilization, PEGylation, and use of stabilizing agents.
2.	Immunogenicity and Off-target Effects	Immune recognition may result in negative responses or quick clearance.	Dosage optimization, targeted ligands, and surface modification (PEGylation, zwitterionic coatings).
3.	Limited Tissue/Cell Targeting	Delivery to targeted tissues may be less than ideal when passive dispersion is used.	Stimulus-responsive nanocarriers, aptamers, peptides, and antibodies are used for active targeting.
4.	Scale-up and Manufacturing Challenges	Scalability and reproducibility are challenging for clinical-grade manufacturing.	Continuous flow synthesis, microfluidics, and manufacturing process standardization.
5.	Toxicity of Nanocarriers	Certain nanomaterials, such as polymers and cationic lipids, have the potential to be cytotoxic.	Dosage titration, preclinical safety assessments, and biodegradable and biocompatible materials.
6.	Regulatory and Quality Control Hurdles	Unclear regulations pertaining to sophisticated nanomedicines.	Standardized assays, thorough characterisation, and early interaction by regulatory bodies.
7.	Short Circulation Time	Efficacy is decreased by the mononuclear phagocyte system's quick elimination.	Size optimization, stealth coatings, and surface PEGylation.

cationic lipids.[71] Additional and common limitations are short circulation times, which often relates to renal excretion or rapid clearance through the mononuclear phagocyte system. In addition, deficient manufacturing and scale-up processes also present setbacks, which make the consistent production of clinical-grade nano formulations mutually exclusive with clinical application, along with a lack of defined process in regulatory and quality control processes. There are various potential approaches, which are currently under investigation into surface modifications (PEGylation), biodegradable and biocompatible carriers, ligands for active targeting, stimuli-responsive systems, and standardized manufacture protocols in scaling into clinical applications safely and more efficiently.[72] "Major challenges in nanoformulated parenteral delivery and potential solutions are outlined in Table 7".

Ethical and Safety Considerations

Ethical and safety concerns are central to the clinical translation of gene therapy and advanced nanocarrier systems. Key risks include insertional mutagenesis, where integrating viral vectors (e.g., lentivirus) may disrupt host genomic integrity and potentially activate oncogenic pathways. Rigorous vector design, integration site mapping, and non-integrating vector alternatives are therefore emphasized by regulatory agencies. Immunogenicity and re-dosing constraints represent additional safety challenges, as both viral and PEGylated non-viral systems can elicit neutralizing antibodies that limit subsequent administrations.[74] Ethical frameworks demand transparent disclosure of these risks, long-term patient monitoring, and informed consent that reflects possible delayed adverse effects. Post-marketing surveillance and pharmacovigilance are vital for detecting rare or long-latency events, such as immune-related toxicities, inflammatory responses, or vector shedding. Sponsors are encouraged to establish gene therapy registries and long-term follow-up protocols (≥ 15 years) as recommended by the FDA and EMA. Furthermore, the ethical responsibility extends to ensuring equitable access, affordability, and diversity in clinical trial enrolment, preventing disparities in the availability of these transformative therapies. Collectively, ethical governance and safety monitoring underpin the responsible advancement of gene therapy and nanocarrier-based medicines.

Conclusion

The proposed Route–Carrier Decision Framework provides a cohesive lens for interpreting the evolving field of parenteral nano formulations, connecting therapeutic purpose with delivery design. This integrative perspective highlights how rational alignment of objective → route → carrier can accelerate safe and scalable translation. This narrative review concludes that nano-formulated parenteral delivery systems have transformed the therapeutic landscape for mRNA and gene therapy. Despite challenges in stability, immunogenicity, and large-scale production, these systems hold immense promise for precision medicine. Collaborative research efforts and harmonized regulatory pathways will be critical to ensure safe and scalable translation of these technologies into clinical use.

Abbreviations

AAV – Adeno-associated Virus
CARPA – Complement Activation–Related Pseudo allergy
CRISPR – Clustered Regularly Interspaced Short Palindromic Repeats
DLS – Dynamic Light Scattering
EMA – European Medicines Agency
FDA – Food and Drug Administration
GMP – Good Manufacturing Practice
IM – Intramuscular
IV – Intravenous
LAL – Limulus Amoebocyte Lysate
LNP – Lipid Nanoparticle
mRNA – Messenger RNA
NTA – Nanoparticle Tracking Analysis
PEG – Polyethylene Glycol
PEI – Polyethyleneimine
PLGA – Poly(lactic-co-glycolic acid)
RNA – Ribonucleic Acid
saRNA – Self-amplifying RNA
SC – Subcutaneous
TLR – Toll-like Receptor

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