Research Article

Design And Optimization Of Nucleic Acid Delivery Systems For Clinical Applications: A Review

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ABSTRACT

Recent advances in nucleic acid science have significantly expanded the scope of precision medicine, enabling therapeutic strategies that extend beyond conventional small molecules and biologics. This review examines the development and current state of mRNA- and nucleic acid based delivery platforms, emphasizing their growing importance in next-generation therapeutics. We begin with a brief historical overview, describing early challenges related to molecular instability, inefficient targeting, and limited cellular uptake, and how progressive technological innovations have successfully addressed these limitations. The mechanisms underlying mRNA and nucleic acid drug delivery are then discussed, with particular focus on their ability to regulate gene expression and modulate immune responses with high specificity. Key delivery technologies are highlighted, including lipid nanoparticles, polymer- based carriers, and conjugate systems, along with recent formulation advances that have improved safety, efficacy, and translational potential. Ongoing challenges such as cargo degradation, unintended immune activation, and suboptimal delivery efficiency are critically evaluated, and practical strategies to overcome these barriers are presented. Basically, the review explores future directions in the field, underscoring the promise of nucleic acid therapeutics in personalized medicine and the importance of continued research to optimize delivery platforms. Overall, this article provides a comprehensive overview of the evolving landscape of nucleic acid-based therapeutics and aims to inform clinicians, researchers, and pharmaceutical scientists about their current applications and future potential in modern healthcare.

KEYWORDS mRNA, Lipid nanoparticles, Transcription, Bioinformatics, mRNA Vaccine.

INTRODUCTION

Messenger RNA (mRNA) nanotechnology has rapidly emerged as a transformative and widely acclaimed drug delivery system, catalysing a new era in therapeutic development. Its development was started since 1869 and till date it is been evolving. This system is useful in the management of various diseases like cancer, infectious, neurological, metabolic, genetic, autoimmune and inflammatory diseases. This review provides a comprehensive synthesis of historical foundation, mechanism of action of this drug delivery system, advancements, current formulations, major challenges and how to overcome them and lastly the future prospective. The discussion is informed by a meticulous collection and critical appraisal of the latest published scientific literature, offering clear insights and future perspectives on this cutting-edge technology over the past decade.

Messenger RNA (mRNA) and nucleic acid drug delivery systems have redefined modern therapeutics through their ability to precisely modulate gene expression, stimulate protein synthesis, and advance personalized medicine[1]. Nucleic acid drugs (NADs), encompassing mRNA, small interfering RNA (siRNA), microRNA (miRNA), antisense oligonucleotides (ASOs), and gene-editing systems like CRISPR/Cas9, exert their therapeutic functions by either silencing or activating specific genes, replacing faulty proteins, or correcting genetic mutations[2]. These agents provide a powerful platform for treating various diseases once deemed “undruggable”, including cancer, infectious diseases, and rare genetic disorders. However, their clinical translation faces challenges such as instability, immunogenicity, rapid degradation by nucleases, and inefficient cellular uptake, which have driven the innovation of effective delivery carriers[3].

Lipid nanoparticles (LNPs) have emerged as the gold standard for nucleic acid delivery, offering high encapsulation efficiency, protection against enzymatic degradation, and targeted cellular uptake[3-4]. Pioneered in the 1970s and perfected through decades of nanotechnology and molecular biology research, LNPs have demonstrated remarkable

success in the formulation of mRNA-based COVID-19 vaccines[5]. Their composition—typically involving ionizable or cationic lipids, helper phospholipids (such as DSPC), cholesterol for membrane integrity, and PEG-lipids for stealth properties ensures controlled biodistribution and efficient endosomal escape. Adjusting lipid ratios and compositions can fine-tune the tissue tropism of LNPs, while advanced designs such as selective organ targeting (SORT) strategies and modified cholesterol analogs allow organ-specific delivery, particularly to the liver, spleen, or lungs[6-7].

Despite these advances, efficient and safe delivery of mRNA and other nucleic acids remains a multidisciplinary challenge. Delivery systems must preserve the biological integrity of nucleic acids, ensure escape from endosomes, and minimize immune activation[8]. Recent innovations incorporate artificial intelligence (AI) and machine learning (ML) to optimize lipid formulations, predict nanoparticle behavior, and accelerate preclinical design. AI driven approaches have successfully identified key parameters influencing LNP size, charge, encapsulation efficiency, and tissue targeting, achieving formulation precision that surpasses traditional trial-and-error techniques[8-10].

The synergistic integration of mRNA biotechnology, nanocarrier engineering, and AI-driven predictive modeling now defines the new era of nucleic acid therapeutic design. These developments promise to overcome persistent barriers in delivery efficiency, specificity, and safety paving the way for next-generation vaccines, gene therapies, and regenerative medicine applications with unprecedented speed and precision[3, 10].

HISTORICAL BACKGROUND

The historical context of mRNA and nucleic acid-based drug delivery systems highlights over fifty years of advancements in molecular biology and nanotechnology leading to therapeutic innovations. The roots of nucleic acid research can be traced back to 1869, when Friedrich Miescher identified "nuclein," which would later be recognized as DNA, from white blood cells[10]. By the middle of the 20th century, breakthroughs in molecular biology demonstrated that DNA and RNA serve as carriers of genetic information, setting the stage for nucleic acid-based therapies. The idea of utilizing nucleic acids for therapeutic purposes developed from the 1960s to the 1990s with the rise of gene therapy, antisense oligonucleotides, and aptamer technologies[10-11].

In 1987, Robert Malone developed a method for formulating mRNA with lipid droplets, marking a significant shift towards the Lipid Nanoparticle (LNP) delivery systems that are currently utilized in vaccines. The initial clinical trials for an mRNA-based antitumor vaccine began in 1999, utilizing mRNA-modified dendritic cells to target tumour-specific antigens[12]. In 2005, Katalin Karikó and Drew Weissman identified that modifications to nucleosides—like pseudouridine—could diminish the immune detection of mRNA, transforming its stability and safety. This breakthrough made it possible to administer mRNA systemically and repeatedly[13].

By 2008, the scope of clinical testing broadened to include prostate cancer with Provenge, which is a dendritic-cell-driven immunotherapy[13-14]. The early 2010 witnessed the emergence of preventive mRNA vaccines aimed at infectious diseases like MERS[14].

Throughout the COVID-19 pandemic (2020–2021), the significant progress made in the field led to the development of the Pfizer/BioNTech and Moderna vaccines, marking the first extensive medical use of mRNA drug delivery. These vaccines showed an effectiveness rate greater than 90% and confirmed that lipid-based delivery is a practical approach for clinical applications[15].

Nucleic acid-based drug delivery systems have developed alongside each other to tackle issues of stability, compatibility with biological systems, and targeted delivery. Three significant strategies have arisen which involves DNA/RNA nanotechnology demonstrating the creation of self-assembling nucleic acid structures, Multivalent nucleic acid nanostructures to enhance cellular uptake and Aptamer systems to facilitate highly precise targeting of cells similar to how antibodies operate[11]. Lipid nanoparticles (LNPs), polymeric carriers, and hybrid nanostructures have become the primary vehicles for delivery, allowing nucleic acids to penetrate cell membranes and achieve precise timing in drug release[16]. In the modern era from 2020 to 2025, leading pharmaceutical pipelines have integrated mRNA and nucleic acid therapies for the treatment of cancer, rare disorders, and infectious diseases. RNA interference (RNAi) and mRNA therapies now constitute the third generation of gene therapies, emphasizing targeted delivery, adaptable nanocarriers, and improved control over cell-specific translation[13, 17].

Significant developments include DNA origami and tetrahedral nanostructures designed for the delivery of anticancer medications such as doxorubicin, alongside aptamer-drug conjugates (ApDCs) that enable species-specific targeting and minimize systemic toxicity. Additionally, DNA amphiphiles and spherical nucleic acids (SNAs) facilitate the combined delivery of hydrophobic drugs and gene regulators without the need for traditional polymeric carriers. Current nucleic acid-based drug delivery systems focus on stimuli-responsive release mechanisms, including

temperature, pH, and molecular triggers, which allow for precise control of drug release in tissues or tumours. These constructs exemplify a carrier-free molecular engineering strategy, moving away from traditional vector-based methods to self-sufficient nucleic acid nanocarriers[11].

To summarize, the evolution from Miescher's "nuclein" in 1869 to the current modular lipid nanoparticle mRNA therapies illustrates how nucleic acid-based delivery systems have transitioned from being biological oddities to precise therapeutic tools, signifying a significant change in contemporary drug development.

MECHANISM OF ACTION OF mRNA AND NUCLEIC ACID DRUG DELIVERY SYSTEM

The intricate mechanism by which mRNA and nucleic acid drug delivery systems operate includes several complex stages that guarantee the therapeutic nucleic acids arrive at their target cells and produce the desired genetic effects. This delivery is essential since bare mRNA or nucleic acids are unstable and can be easily degraded by nucleases in biological settings.

1. Formulation and protection: mRNA molecules undergo chemical modifications and are enclosed in delivery systems, mainly lipid nanoparticles (LNPs), polymers, or inorganic nanostructures. These carriers safeguard mRNA from nuclease degradation, improve cellular internalization, and enable regulated release[18-19]. LNPs generally comprise ionizable lipids, structural lipids, cholesterol, and PEGylated lipids to maintain stability and facilitate endosomal escape[18].

2. Cellular Uptake: Endocytosis is the primary method by which the mRNA-loaded nanoparticles reach target cells, where they are taken up by endosomes[20-21]. By building complexes with mRNA, encouraging membrane contacts, and boosting absorption, cell-penetrating peptides (CPPs) like arginine-rich motifs can also aid in mRNA delivery[21].

3. Endosomal Escape: To prevent lysosomal degradation, delivery systems must allow the mRNA to leave the endosome and enter the cytoplasm. In the acidic endosomal environment, ionizable lipids acquire a positive charge, which destabilizes the endosomal membrane and promotes the release of mRNA into the cytoplasm[18, 21]. At endosomal pH, peptides such as Ras-related protein Ral-A (RALA) undergo conformational changes to create holes that aid in escape[22].

4. Translation in Cytoplasm: Unlike DNA-based therapeutics, mRNA does not necessitate entry into the nucleus; translation occurs directly within the cytoplasm where ribosomes produce the specified protein. This characteristic facilitates quicker and more temporary protein expression, thereby minimizing risks such as genome integration and offering improved safety profiles for vaccines and treatments[18, 20].

5.

Mechanism of Nucleic Acid (DNA, siRNA, miRNA) Delivery:

DNA Delivery requires nuclear entry following cytoplasmic release to initiate transcription and subsequent protein synthesis, presenting an additional intracellular obstacle[21]. siRNA and miRNA Delivery aims to influence gene expression by degrading target mRNA or inhibiting translation[23]. Their delivery methods are aim to those of mRNA, necessitating cytoplasmic delivery and endosomal escape[19, 22].

Advances and Targeting Strategies:

Nanoparticles are designed for tissue-specific targeting using ligands such as antibodies or peptides, which allow for delivery to particular cell types, such as dendritic cells for vaccines or liver cells for gene therapies[24, 25].Chemical modifications of nucleic acids enhance stability, decrease immune activation, and improve therapeutic effectiveness 26.

Fig. 1 depicts the process of delivering nucleic acids (DNA, siRNA, miRNA) via a nanoparticle vehicle that encapsulates mRNA. Initially, the mRNA enters the target cell and is internalized

into an endosome. Following endosomal escape, the mRNA is liberated into the cytoplasm, where it facilitates ribosomal protein synthesis, leading to the generation of the intended intracellular, transmembrane, or secreted protein. Subsequently, the delivery vehicle undergoes degradation, thereby concluding the efficient delivery of nucleic acid-based therapeutics.

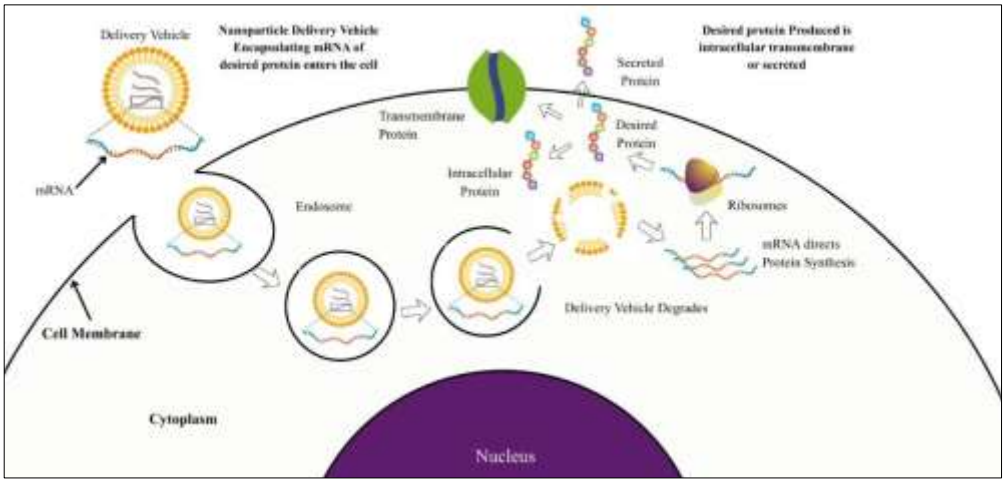


Figure 1. Mechanism of Nucleic Acid (DNA, siRNA, miRNA) Delivery

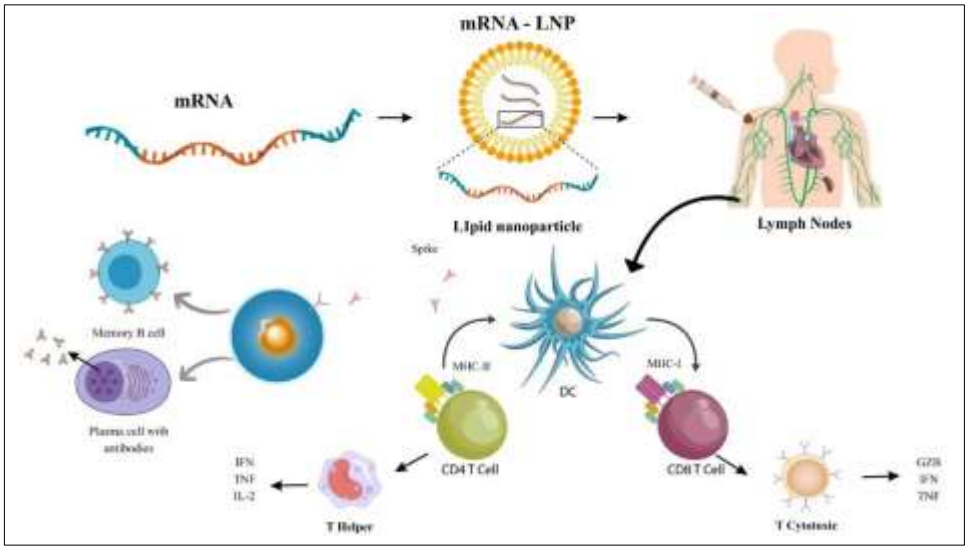
ADVANCEMENTS IN mRNA DRUG DELIVERY SYSTEMS

The given information provides a broad overview of the numerous delivery systems used for mRNA-based therapeutics. It contains information on lipid-based carriers, like LNPs, frequently used for their effectiveness in protecting and delivering mRNA into cells; Viral and non-viral vectors which include a variety of natural and synthetic materials intended to facilitate mRNA delivery, protein-mRNA complexes, in which proteins are used to stabilize and transport mRNA and polymer-based carriers uses synthetic polymers to protect and encapsulate mRNA. These many strategies are essential for maximizing the targeting, stability, and effectiveness of mRNA-based treatments.

LNPs:

Lipid-based carriers, such as lipoplexes and LNPs, are widely employed for the delivery of nucleic acids. Effective and modified engineering enables the successful encapsulating of mRNA within LNPs and lipoplexes, safeguarding it from internal degradation while promoting cellular uptake and endosomal escape[27]. Key components, including phospholipids, polyethylene glycol lipid, cholesterol, and cationic or ionizable lipids, plays crucial role in the encapsulation and stability of mRNA. The precise molar ratios of these components yield LNPs with the required functionalities for mRNA delivery[28]. Optimization research has concentrated on the variables like identity of phospholipids, the lipid-to-mRNA weight ratio, and the molar ratios of lipid components to improve transfection capacity[29]. Innovative ionizable or cationic lipids with modified head or tail groups have been investigated to enhance delivery effectiveness[30]. Furthermore, various elements, including vitamins, aminoglycosides and proteins have been employed to create efficient LNPs for mRNA delivery[31]. Zwitterionic phospholipids have also attracted interest due to their role in facilitating endosomal escape through membrane fusion. pH-switchable ionizable phospholipids with multiple tails have demonstrated potential in mRNA delivery, showing organ selectivity in vivo[32]. Nonetheless, concerns about their toxicity, particularly those made of polycationic and PEGylated lipids, have been highlighted in various studies. Polycationic lipids, recognized for their capacity to effectively encapsulate nucleic acids, may also provoke cytotoxic effects due to their positive charge, which can disrupt cellular membranes and result in cell death. This issue is especially pertinent in therapeutic contexts, where achieving a balance between effective delivery and cellular safety is essential[33]. While PEGylated lipids enhance the stability and circulation duration of LNPs in the bloodstream, they may also trigger immune responses that could lead to adverse effects. Research indicates that PEGylation may modify the pharmacokinetics of nanoparticles, which could lead to unforeseen toxicity[34]. For example, the development of anti-Polyethylene glycol antibodies has been recorded, potentially resulting in the expedited clearance of pegylated nanoparticles and diminished therapeutic effectiveness[35]. Additionally, the buildup

of these nanoparticles in different tissues can trigger inflammatory reactions, underscoring the necessity for meticulous design and enhancement of lipid formulations[34]. For instance, the mechanism of action of mRNA-LNP vaccines is illustrated in figure 2 where mRNA-LNP vaccines enclose mRNA within lipid nanoparticles that transport it into host cells, where it is converted into protein antigens. These antigens are displayed on the surface of the cells, which activate dendritic cells that stimulate CD4+ helper T cells, CD8+ cytotoxic T cells, and B cells, resulting in the production of antibodies and the formation of memory cells for enduring immunity.



Vaccines Viral Vectors and non-viral Delivery methods

mRNA delivery can be achieved with both viral and non-viral vectors. Viral vectors, such as adeno-associated viruses and engineered viruses, provide benefits like local replication and cytoplasmic expression. Nonetheless, cytotoxic effects and possible host rejection present difficulties for viral vectors[36]. Non-viral vectors consist of naked mRNA, which can be delivered intramuscularly, subcutaneously, or intradermally, overcoming barriers linked to systemic administration. Naked mRNA has shown effective translation and stimulation of immune responses, especially with subcutaneous delivery[37]. Different physical and active techniques have been utilized to improve skin absorption and mRNA transfer including microporation, electroporation, and microneedle delivery. These methods provide benefits like lower costs and decreased risks, but unprotected mRNA encounters issues like a brief plasma half-life and vulnerability to breakdown[38].

Protein- mRNA complex

Cationic proteins can create complexes with anionic charged mRNA through electrostatic interactions, which promotes the self-assembly of protein-mRNA complexes[39]. Protamine, a protein rich in arginine and positively charged, is been employed in forming complexes with mRNA vaccines, boosting immune response by activating the TLR7 receptor[40]. Research has shown that mRNA encoding tumour-associated antigens complexed with protamine can trigger a robust antitumor immune response in mice and in patients with metastatic melanoma, all with minimal toxicity[41]. Furthermore, the mammalian retrovirus-like protein PEG10 has emerged as a viable option for mRNA delivery, known for its ability to bind, stabilize, and efficiently deliver mRNA in human cells, including both single-guide RNA and Streptococcus pyogenes Cas9 (SpCas9)[42].

Polymer-based delivery systems

Polymeric nanoparticles is a promising delivery mechanism for mRNA-based therapeutics (Figure 4). Cationic polymers can interact with mRNA creating nanoparticles known as mRNA polyplexes[43]. Although initial materials like PEI and poly(l-lysine) exhibited limited in vivo effectiveness and toxicity, current focus has shifted towards biodegradable and functional polymers to achieve improved results[44]. Charge-altering releasable transport (CART) systems, changes charge characteristics in varying pH conditions, facilitate mRNA release within the cytoplasm,

thereby increasing transfection efficiency. Numerous chemical structures of CARTs have been successfully investigated[45]. Furthermore, poly β-amino esters (PBAEs) and their derivatives, including polycaprolactone-based PBAEs and oligopeptide end-modified PBAEs, have shown potential in mRNA delivery by promoting complex formation and improving endosomal escape. Hyperbranched PBAEs, is produced using a trifunctional amine, which has exhibited greater transfection efficiency and stability compared to linear PBAEs, especially in the context of delivering mRNA to the lung epithelium[46]. Collections of biodegradable polymers such as poly(amine-co-ester) have been created to measure endosomal escape, with high encapsulation efficiency recognized as a vital factor in mRNA transfection[47]. Ionizable amphiphilic Janus dendrimers (IAJDs) have emerged as a straightforward yet effective one-component system for mRNA delivery. Various IAJDs have been synthesized and assessed, with some demonstrating high transfection efficacy, while the cation-π interaction has been recognized as a promising direction for further design enhancement[48]. Figure 3 illustrates the polymer-mRNA delivery system, in which mRNA is associated with a cationic polymer to create nanoparticles that are absorbed by the cell. Following cellular absorption, the polymer-mRNA complex exits the endosome and enters the cytoplasm. The liberated mRNA is subsequently translated by ribosomes to effectively produce the target protein within the cell.

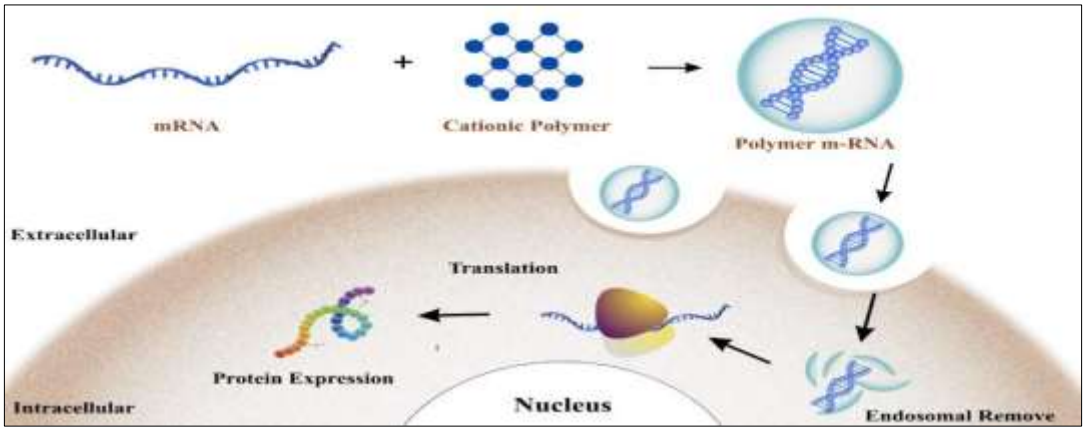


Figure 3. Polymer-mRNA delivery system for protein expression

CURRENT AND NOVEL FORMULATIONS IN mRNA AND NUCLEIC ACID DRUG DELIVERY SYSTEMS

Following table summarizes overview of current and novel formulations in mRNA and nucleic acid drug delivery systems.

Table no.1. Overview of current and novel formulations in mRNA and nucleic acid drug delivery systems:

Formulation / Delivery System	Key Features and Description	Reference
Lipid Nanoparticles (LNPs)	LNPs remain the most advanced platform for mRNA and nucleic acid delivery. Recent 2025 studies have used AI-based design to improve tumor targeting, cellular uptake, and reduced toxicity. These systems are widely applied in cancer immunotherapy and restoration of tumor suppressor genes.	[49]
Hybrid Polymeric / Peptide- Based Systems	Polymeric nanoparticles, dendrimers, polysaccharide carriers, and peptide-derived hybrids enhance mRNA stability, control release, and modulate immune response, improving therapeutic outcomes.	[50]
Stereochemically Tuned LNPs	Ionizable lipids with controlled stereochemistry influence delivery efficiency and safety. Stereo pure lipid structures improve bioavailability and minimize toxicity.	[51]

Rolling Circle Replication (RCR)-Based Nanostructures	RCR-based DNA/RNA nanostructures enable programmable, size-controlled assembly, longer circulation time, adjustable drug loading, and enhanced endosomal escape—suitable for extended-release therapeutics.	[52]
RNA-Based Cancer Vaccines	Clinical mRNA cancer vaccines (2024–2025) show high efficacy in melanoma, glioblastoma, and pancreatic cancer using AI-optimized mRNA and layered nanoparticles for precision oncology.	[53]
Extracellular Vesicle (EV)-Mediated Delivery Systems	EVs and exosome-based formulations show promise for low-immunogenic nucleic acid delivery, prolonging in vivo half-life and enhancing tissue targeting.	[54]
Multimodal Nanoparticle Platforms	Multi-layered nanoparticles integrating CRISPR tools, peptides, and AI-tuned nucleic acid sequences provide precise, programmable release and enhanced immune modulation for oncology and gene therapy.	[50, 55]

KEY CHALLENGES AND THEIR SOLUTIONS IN mRNA AND NUCLEIC ACID DRUG DELIVERY SYSTEMS

The following table summarizes the major challenges in mRNA and nucleic acid drug delivery systems, their brief explanations, and the representative strategies to overcome them.

Table no.2. Challenges and solutions in mRNA and Nucleic acid drug delivery system:

Challenge	Brief Explanation	How to Overcome	Reference
Stability and Protection of Cargo	mRNA is highly unstable and rapidly degraded by nucleases, reducing therapeutic effect.	Use of lipid or polymeric carriers and chemical modifications (e.g., nucleoside modification) is beneficial to stabilize and protect mRNA from enzymatic degradation.	[16, 56]
Cellular Uptake and Intracellular Trafficking	Negatively charged nucleic acids cannot easily penetrate cell membranes, leads to poor uptake.	Optimize lipid nanoparticles (LNPs) and polymeric systems to improve cellular uptake and cytosolic transfection efficiency.	[29, 57]
Endosomal Escape and Intracellular Release	After entering cells, mRNA often remains trapped in endosomes, limiting its availability in the cytosol.	Incorporating pH-responsive materials or membrane- disruptive peptides in delivery systems is useful for facilitating efficient endosomal escape.	[32, 36]
Immunogenicity and Safety	Unmodified nucleic acids can activate immune responses and cause inflammation or toxicity.	Use of modified nucleoside (e.g., pseudouridine) and biocompatible materials minimizes immune activation while retaining therapeutic efficacy.	[36, 58]
Specificity, Targeting, and Biodistribution	Achieving tissue-specific delivery is difficult; off-target accumulation may occur. This off-target accumulation reduces the effective dose at the target site, increasing the required dosage and potentially leading to side effects in non- target tissues due to unintended mRNA expression.	Employing targeting ligands or receptor-binding motifs can optimize LNP formulations to ensure selective delivery.	[59]

Manufactu ring, Scalability, and Quality Control	Consistent large-scale production and maintaining formulation stability remain challenging because companies have limited expertise in scaling up production processes which involve multiple critical steps from plasmid DNA template production to formulation.	Development of standardized manufacturing protocols and scalable technologies can ensure batch consistency and product stability.	[60,61]
Regulatory and Translation al Hurdles	Limited regulatory guidance and incomplete understanding of biological barriers slow clinical translation.	Establishment of clear regulatory frameworks, standardized evaluation assays, and translational models for novel delivery systems.	[62]

FUTURE PROSPECTIVES

The future outlook for mRNA and nucleic acid drug delivery systems presents transformative opportunities for healthcare by offering safer, more effective, and versatile therapeutic alternatives across a wide range of diseases. mRNA and nucleic acid-based vaccines and therapies can replicate traditional live organism vaccines while providing enhanced safety and efficacy benefits. They are capable of inducing robust cell-mediated immunity and simultaneously activating both B and T cell responses, which allows for precise targeting and a diminished risk of genomic integration compared to DNA vaccines. The transient expression of mRNA and its cytoplasmic delivery further enhance safety by mitigating risks such as insertional mutagenesis.

The advancement of sophisticated delivery technologies, particularly lipid nanoparticles (LNPs), has been crucial in stabilizing mRNA for effective intracellular delivery, as evidenced by the swift and successful deployment of COVID- 19 vaccines. These delivery systems safeguard the nucleic acid from enzymatic degradation, facilitate efficient cellular uptake, and can be tailored for targeted delivery methods such as aerosol inhalation, eye drops, or intravitreal injections based on clinical requirements.

Looking ahead, mRNA therapeutics show promise beyond infectious diseases, extending into personalized medicine, including cancer immunotherapy, treatment of genetic disorders, and autoimmunity. Ongoing advancements in nanoparticle carriers, including polymers, lipid-polymer hybrids, and virus-like particles, aim to enhance stability, transfection efficiency, and minimize side effects. Clinical trials are advancing for applications that encompass pandemic preparedness, cancer vaccines, and gene editing therapies, highlighting significant societal benefits through the reduction of disease burden and the facilitation of rapid responses to emerging health threats.

However, additional challenges persist, such as enhancing thermal stability for more straightforward distribution, scaling manufacturing in a cost-effective manner, and improving long-term immune memory responses. Ongoing advancements in mRNA sequence design, optimization of untranslated regions, and the development of delivery platforms will significantly improve the efficacy, longevity, and safety of these therapies.

CONCLUSION

mRNA and nucleic acid drug delivery systems signify a ground-breaking advancement in pharmaceutical science, facilitating safe, efficient, and highly targeted therapies for a diverse array of diseases. The creation of sophisticated delivery platforms such as lipid nanoparticles, polymers, and hybrid nanocarriers has successfully addressed significant challenges related to cellular uptake, stability, and tissue targeting, thereby unlocking the complete therapeutic potential of these molecules.

The integration of rational design, chemical modification, and nanotechnology has elevated mRNA and nucleic acid delivery systems to a prominent position in contemporary medicine, as evidenced by recent achievements with mRNA vaccines and emerging therapies for cancer and genetic disorders. These systems outperform traditional methods by their capacity to elicit precise cellular responses, enable rapid adaptation for new targets, and reduce risks such as genomic integration, inherently providing both safety and controlled pharmacokinetics.

Ongoing advancements in vector design especially lipid-based particles and customized biopolymers are yielding higher transfection efficiencies and wider applicability, while also addressing inherent biological challenges such as degradation and immune activation. Ultimately, the continuous enhancement of mRNA and nucleic acid drug delivery systems is laying a versatile groundwork for the next generation of targeted therapies, vaccine platforms, and personalized medicines that meet unmet clinical needs with outstanding safety, specificity, and scalability. This progress is set to redefine the limits of disease prevention and treatment, heralding a new era for pharmaceutical development and global health innovation.

ABBREVIATIONS

AI: Artificial Intelligence, ApDCs: Aptamer-drug conjugates, AsOs: Antisense Oligonucleotides, BSCs: Biological Safety Cabinets, CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats, CAS 9: CRISPR-associated protein, COVID-19: Coronavirus Disease 2019, CPPs: Cell Penetrating Peptides, CART: Chimeric Antigen Receptor T cells, CD4+: Cluster of Differentiation 4 Positive, CD8+: Cluster of Differentiation 8 Positive, DLS: - Dynamic Light Scattering, DNA: Deoxy Ribonucleic Acid, DSPC: - Distearoylphosphatidylcholine, EV: - Extracellular Vesicle, GMP: Good Manufacturing Practices, HPLC: High Performance Liquid Chromatography, IVT: In Vivo Transcription
, IAJDs: Ionizable Amphiphilic Janus Dendrimer, LNPs: Lipid Nanoparticles , mRNA: Messenger Ribonucleic Acid, miRNA: Micro Ribonucleic Acid, ML- Machine Learning, mRNA- LNPs: Messenger Ribonucleic Acid- Lipid Nanoparticles, NADs:Neutralizing Antibodies, PBAEs: - Poly (β-amino esters), PEI: -Polyethyleneimine: Polyethylene glycol, PCR: Polymerase Chain Reaction, RNA: Ribonucleic Acid, RNAi: Ribonucleic Acid interference
, RALA: Arginine-Alanine-Leucine-Alanine, RCR: Reverse Complementary RNA , SiRNA: Small interfering Ribonucleic Acid , SORT: Selective Organ Targeting , SNAs: - Spherical Nucleic Acids , TLR 7: Toll-Like Receptor 7,UFDF: Ultrafiltration and Diafiltration

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