International Journal of Research and Technology (IJRT)

International Open-Access, Peer-Reviewed, Refereed, Online Journal

ISSN (Print): 2321-7510 | ISSN (Online): 2321-7529

| An ISO 9001:2015 Certified Journal |

Next-Generation Delivery Systems for Biopharmaceuticals Recent Advances in Protein, Peptide, mRNA, and Gene Delivery

[1]Sumit Kumar

[1]Dept. of Pharmaceutical Sciences, Central University of Haryana, Jant-Pali, Mahendergarh

[1]drsumitkumar@cuh.ac.in

https://doi.org/10.64882/ijrt.v13.i4.1796

ABSTRACT

The development of next-generation delivery systems has become essential for unlocking the therapeutic potential of biopharmaceuticals, particularly proteins, peptides, messenger RNA (mRNA) and gene therapeutics. This review examines recent advances in nanotechnology-enabled and biomimetic delivery platforms designed to overcome major biological and formulation barriers, including enzymatic degradation, poor membrane permeability, instability, rapid clearance, inefficient cellular uptake and inadequate tissue targeting. Contemporary systems such as lipid nanoparticles, liposomes, polymeric nanoparticles, lipid-based carriers, extracellular vesicles, viral vectors and non-viral gene delivery platforms are evaluated according to their mechanisms, therapeutic applications, advantages and translational limitations. Particular emphasis is placed on lipid nanoparticles, which have demonstrated substantial clinical success in mRNA delivery and have subsequently stimulated research into vaccines, protein replacement, cancer therapy and gene-editing applications. Advanced protein and peptide delivery approaches are also considered, with emphasis on oral bioavailability, permeation enhancement, controlled release and protection from gastrointestinal degradation. The review further discusses targeted and intracellular delivery strategies, manufacturing challenges, safety considerations, tissue selectivity and regulatory barriers The evidence indicates a transition from conventional passive carriers towards multifunctional, precision-engineered systems capable of integrating cargo protection, targeting, cellular uptake and controlled intracellular release. Continued advances in biomaterials, molecular engineering and delivery optimisation are expected to improve the clinical translation of complex biopharmaceutical therapeutics.

Keywords: Biopharmaceuticals, Protein delivery, Peptide delivery, mRNA delivery, Gene delivery, Lipid nanoparticles, Nanocarriers, Targeted drug delivery

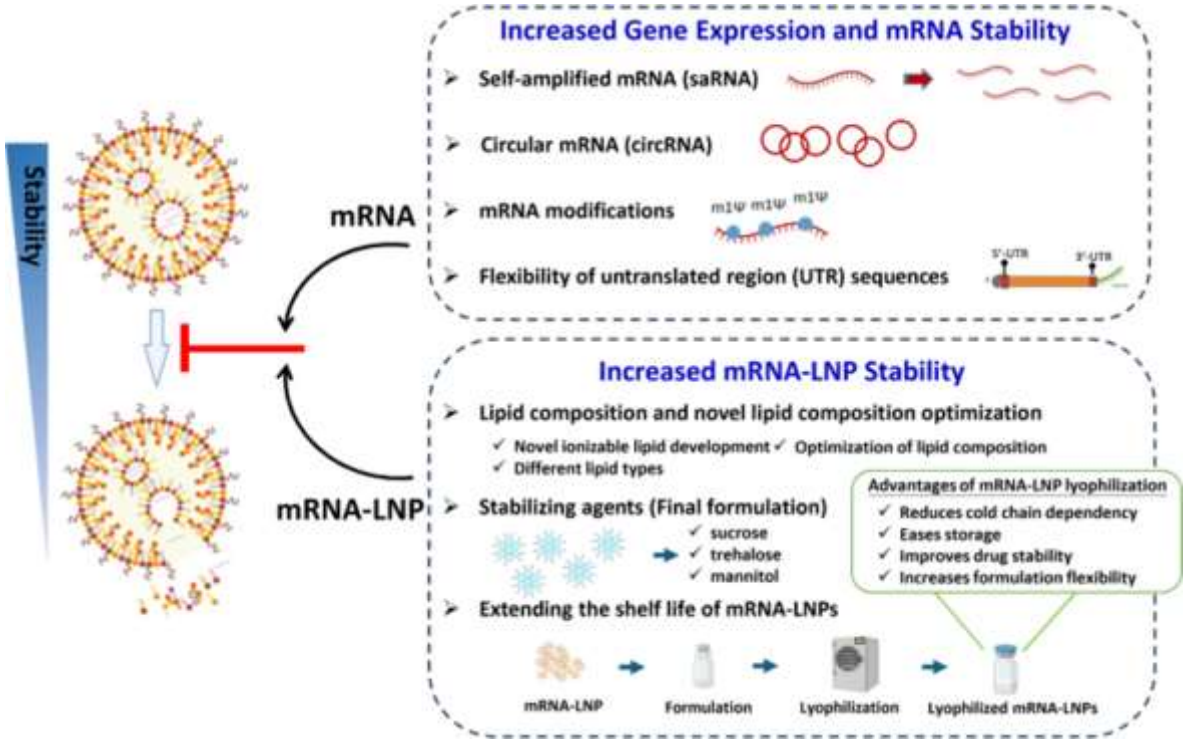
INTRODUCTION

Biopharmaceuticals, including proteins, peptides, messenger RNA (mRNA) and gene-based therapeutics, have transformed modern pharmacotherapy by enabling highly specific modulation of biological pathways that are often inaccessible to conventional small-molecule drugs. However, the clinical potential of these macromolecular therapeutics is strongly dependent on the development of delivery systems capable of protecting fragile cargos, overcoming biological barriers, achieving appropriate tissue and cellular localisation, and maintaining therapeutic activity. Unlike conventional drugs, proteins and peptides are

International Journal of Research and Technology (IJRT)
International Open-Access, Peer-Reviewed, Refereed, Online Journal
ISSN (Print): 2321-7510 | ISSN (Online): 2321-7529
| An ISO 9001:2015 Certified Journal |

susceptible to enzymatic degradation, aggregation and poor membrane permeability, whereas nucleic-acid therapeutics such as mRNA are highly vulnerable to extracellular and intracellular degradation and possess physicochemical characteristics that restrict passive cellular uptake (Mitchell et al., 2021). Consequently, delivery technology has increasingly become a central component of biopharmaceutical development rather than merely a formulation consideration.

Recent advances in nanotechnology, biomaterials, lipid engineering and molecular targeting have substantially expanded the range of platforms available for biopharmaceutical delivery. Nanoparticles, liposomes, polymeric carriers, lipid nanoparticles (LNPs), micelles, dendritic systems, extracellular vesicles and biomimetic carriers are being investigated to improve stability, bioavailability, intracellular trafficking and controlled release. Among these technologies, LNPs have achieved particularly important clinical validation through their application in mRNA vaccines, demonstrating that sophisticated non-viral delivery systems can successfully transport nucleic-acid therapeutics into human cells at large scale (Hou et al., 2021). The subsequent expansion of LNP research towards protein replacement, cancer therapy and genome editing has further established delivery engineering as a major determinant of the therapeutic scope of mRNA technologies (Wu et al., 2022).



At the same time, delivery strategies for proteins and peptides are moving beyond conventional parenteral administration towards long-acting injectable systems, permeation-enhancing formulations, nanocarriers and alternative administration routes. These approaches seek to address the traditionally poor oral bioavailability and limited stability of peptide and protein therapeutics while improving patient convenience and treatment adherence (Daugherty et al., 2021). Gene delivery has similarly progressed through both viral and non-

viral vectors, with increasing emphasis on tissue specificity, immunological safety, transient or durable expression and scalable manufacturing. The emergence of targeted and organ-selective delivery systems is particularly significant because therapeutic efficacy increasingly depends not only on the biological activity of the payload but also on its ability to reach the appropriate cellular compartment (Paunovska et al., 2022).

Against this background, this review examines recent advances in next-generation delivery systems for protein, peptide, mRNA and gene therapeutics, with particular emphasis on carrier design, biological barriers, targeting strategies, therapeutic performance, translational challenges and emerging opportunities.

NEXT-GENERATION DELIVERY PLATFORMS FOR BIOPHARMACEUTICAL THERAPEUTICS

The development of next-generation delivery platforms has become central to improving the therapeutic performance of biopharmaceuticals. Conventional administration, particularly parenteral injection, can limit patient convenience, dosing frequency and therapeutic accessibility, while biological instability and poor tissue penetration restrict the effectiveness of many macromolecular drugs. Advanced nanocarriers address these limitations by protecting therapeutic cargos from degradation, improving cellular uptake and facilitating controlled or targeted release. Polymeric nanoparticles, liposomes, lipid-based nanocarriers, micelles, solid lipid nanoparticles, nanostructured lipid carriers and hybrid systems have therefore attracted considerable attention for protein and peptide delivery. These systems can improve protection against gastrointestinal enzymes and enhance interaction with biological membranes, although achieving reproducible absorption remains challenging (Jash et al., 2021). For nucleic-acid therapeutics, lipid nanoparticles have emerged as particularly successful platforms because their composition can be engineered to facilitate encapsulation, cellular internalisation and endosomal escape. The clinical success of mRNA–lipid nanoparticle formulations has demonstrated the translational potential of this approach and stimulated broader investigation into therapeutic vaccines, protein replacement and genetic medicines (Hou et al., 2021). Polymeric and inorganic nanocarriers also provide opportunities for stimulus-responsive delivery, surface functionalisation and tissue-specific targeting. Increasingly, delivery platforms are being designed around the physicochemical characteristics of individual cargos rather than relying on a universal carrier architecture. This shift towards rational and multifunctional carrier engineering is important because proteins, peptides, mRNA and gene-editing components encounter different extracellular and intracellular barriers. Consequently, contemporary delivery research increasingly integrates nanotechnology, biomaterials science, molecular targeting and formulation engineering to improve therapeutic exposure and biological activity.

Delivery platform	Major biopharmaceutical application	Principal delivery advantage	Major limitation
Liposomes	Proteins, peptides,	Biocompatibility and	Stability and

	mRNA	versatile cargo encapsulation	manufacturing complexity
Lipid nanoparticles	mRNA and gene-related therapeutics	Efficient cellular delivery and endosomal escape	Tissue targeting and potential toxicity
Polymeric nanoparticles	Proteins, peptides and nucleic acids	Controlled release and surface modification	Possible polymer-related toxicity
Solid lipid nanoparticles/NLCs	Proteins and peptides	Protection from degradation and improved absorption	Limited loading of some macromolecules
Micelles and nanoemulsions	Peptides and proteins	Improved solubilisation and membrane interaction	Variable gastrointestinal performance
Hybrid nanocarriers	Multiple biopharmaceutical cargos	Combination of complementary delivery mechanisms	Scale-up and formulation complexity

RECENT ADVANCES IN PROTEIN, PEPTIDE, MRNA, AND GENE DELIVERY

Recent research demonstrates a diversification of delivery strategies according to the specific biological barriers associated with different biopharmaceutical classes. Protein and peptide delivery has increasingly focused on overcoming enzymatic degradation, poor epithelial permeability and limited gastrointestinal stability through permeation enhancers, lipid-based systems, polymeric nanoparticles, mucoadhesive formulations and specialised oral delivery technologies (Mehrotra et al., 2022). Lipid-based nanocarriers are particularly relevant because they can protect macromolecules while facilitating interactions with mucus and epithelial membranes. In parallel, mRNA delivery has progressed rapidly through ionisable lipid nanoparticles capable of protecting RNA and promoting intracellular release. Their clinical validation in mRNA vaccines has provided an important foundation for expanding mRNA applications towards cancer immunotherapy, infectious diseases and genetic disorders (Hou et al., 2021). Recent lipid-carrier research has also explored liposomes, lipid–polymer hybrids, nanoemulsions, exosomes and lipoprotein-based systems to address tissue targeting and intracellular trafficking requirements (Liu et al., 2022). Gene delivery similarly encompasses viral vectors and increasingly sophisticated non-viral systems designed to improve transfection while reducing immunogenicity and manufacturing constraints. For protein and peptide therapeutics, novel oral technologies seek to combine chemical protection, enzyme inhibition and absorption enhancement to increase systemic exposure (Verma et al., 2021). Collectively, these developments indicate a transition from simple cargo encapsulation towards multifunctional systems capable of coordinating protection, targeting, cellular uptake and controlled intracellular release.

Biopharmaceutical	Principal delivery barrier	Recent delivery approaches	Desired therapeutic outcome
Proteins	Enzymatic degradation and poor permeability	Nanoparticles, liposomes, permeation enhancers	Improved stability and systemic exposure
Peptides	Gastrointestinal degradation and low absorption	Lipid carriers, oral nanocarriers, mucoadhesive systems	Enhanced oral bioavailability
mRNA	RNase degradation and inefficient cellular entry	Ionisable lipid nanoparticles, lipid hybrids, exosomes	Efficient intracellular protein expression
Gene therapeutics	Cellular barriers and vector-associated immunity	Viral vectors, polymeric nanoparticles, lipid systems	Targeted and sustained genetic modification
Gene-editing cargos	Intracellular delivery and tissue specificity	LNPs and targeted non-viral carriers	Precise genome modification

COMPARATIVE PERFORMANCE, TRANSLATIONAL CHALLENGES, AND FUTURE PERSPECTIVES OF ADVANCED BIOPHARMACEUTICAL DELIVERY SYSTEMS

The performance of next-generation delivery systems depends on more than encapsulation efficiency or particle size; biological distribution, intracellular trafficking, cargo integrity, release kinetics, immunological responses and manufacturability increasingly determine translational success. Protein and peptide systems face particularly demanding gastrointestinal barriers, including acidic conditions, proteolytic degradation, mucus entrapment and limited epithelial permeability. Consequently, advanced oral systems often combine several mechanisms rather than relying on a single delivery technology (He et al., 2021). Nanocarriers can improve protection and absorption, but variability in gastrointestinal physiology and difficulties in predicting human bioavailability remain important barriers. For mRNA and gene therapeutics, intracellular delivery presents a different challenge because carriers must protect nucleic acids extracellularly while enabling efficient endosomal escape after cellular uptake. LNPs have demonstrated strong performance in this regard, yet issues involving tissue selectivity, inflammatory responses, storage stability, batch reproducibility and large-scale manufacturing remain relevant to broader clinical applications (Hou et al., 2021). The future direction of the field is therefore moving towards precision-engineered and biologically responsive carriers capable of recognising specific tissues or cellular environments. Computational formulation design, combinatorial lipid screening, biomimetic nanoparticles and organ-selective delivery may further improve therapeutic indices. Integration of delivery engineering with molecular biology and personalised medicine could

ultimately enable biopharmaceuticals to be administered through more convenient routes while achieving precise spatial and temporal control of therapeutic activity.

Parameter	Protein/peptide delivery	mRNA delivery	Gene delivery	Future development priority
Cargo stability	Major concern	Extremely important	Important	Protective carrier design
Cellular uptake	Moderate–high importance	Essential	Essential	Targeted internalisation
Endosomal escape	Relevant for some systems	Critical	Critical	Ionisable and responsive materials
Tissue targeting	Increasing importance	Major challenge	Major challenge	Organ-selective carriers
Manufacturing	Scale-up can be difficult	LNP manufacturing is advanced but complex	Vector production remains demanding	Scalable GMP processes
Safety	Immunogenicity and excipients	Innate immune activation	Vector-associated immunity	Biocompatible materials
Clinical translation	Oral bioavailability remains challenging	Strong clinical validation for vaccines	Application-specific	Improved predictability and targeting

BACKGROUND TO THE STUDY

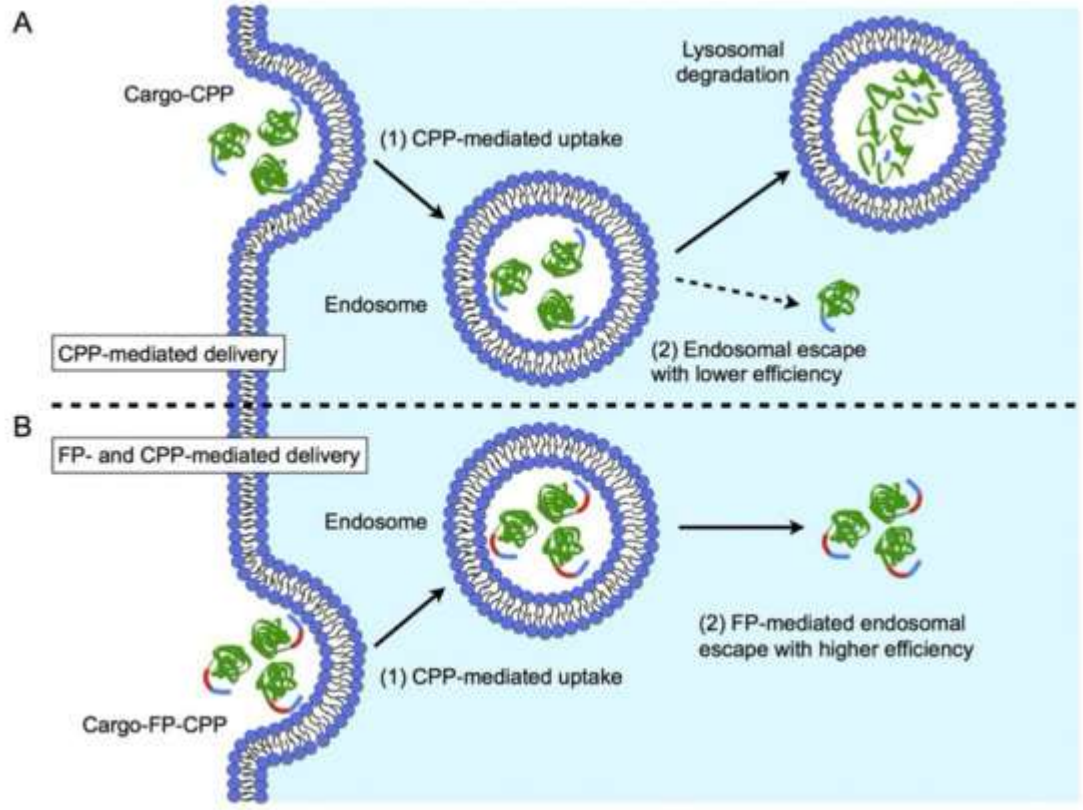
The rapid expansion of biopharmaceutical therapeutics has created a growing need for delivery technologies capable of transporting complex biological molecules safely and efficiently to their sites of action. Proteins and peptides offer high molecular specificity but are commonly associated with enzymatic degradation, instability and poor membrane permeability, which restrict their administration and bioavailability. Similarly, mRNA and gene therapeutics are highly sensitive to degradation and require specialised carriers to facilitate cellular uptake, intracellular trafficking and functional release. These limitations have encouraged the development of advanced delivery platforms based on nanotechnology, lipid systems, polymers and biomimetic materials. Lipid nanoparticles have emerged as an important breakthrough in nucleic-acid delivery, particularly following their successful application in mRNA vaccines, demonstrating the clinical feasibility of sophisticated carrier systems (Hou et al., 2021). Advances in nanocarrier engineering have also enabled improved protection and controlled delivery of protein and peptide therapeutics, while novel permeation-enhancing approaches are expanding possibilities for non-invasive administration

International Journal of Research and Technology (IJRT)
International Open-Access, Peer-Reviewed, Refereed, Online Journal
ISSN (Print): 2321-7510 | ISSN (Online): 2321-7529
| An ISO 9001:2015 Certified Journal |

(Daugherty et al., 2021). In gene delivery, both viral and non-viral vectors continue to evolve towards improved targeting, reduced immunogenicity and enhanced therapeutic precision. Consequently, current research is increasingly focused on designing delivery systems according to the physicochemical properties of the therapeutic cargo and the biological barriers encountered during transport. A comprehensive evaluation of these developments is therefore necessary to understand the technological progress, therapeutic potential and translational challenges associated with next-generation biopharmaceutical delivery systems.

SCOPE OF THE RESEARCH

This review focuses on recent advances in next-generation delivery systems developed for biopharmaceutical therapeutics, with particular emphasis on proteins, peptides, messenger RNA (mRNA) and gene-based medicines. The research examines the major delivery platforms, including lipid nanoparticles, liposomes, polymeric nanoparticles, lipid-based carriers, biomimetic systems and viral and non-viral vectors, in relation to their ability to protect therapeutic cargos, improve stability, facilitate cellular uptake and enhance therapeutic efficacy. Particular attention is given to the biological barriers that influence biopharmaceutical delivery, including enzymatic degradation, poor membrane permeability, gastrointestinal instability, endosomal entrapment and tissue-specific delivery requirements.



The review also considers emerging approaches for targeted, controlled and organ-selective delivery, alongside developments in formulation engineering and nanotechnology. Recent clinical and translational progress in mRNA and gene delivery is considered to identify how advances in carrier design are moving from experimental research towards therapeutic

application. For protein and peptide therapeutics, the scope includes strategies intended to improve bioavailability and enable alternative administration routes. The research further compares the advantages and limitations of different delivery technologies in terms of efficacy, safety, stability, targeting potential, manufacturing complexity and scalability.

LITERATURE REVIEW

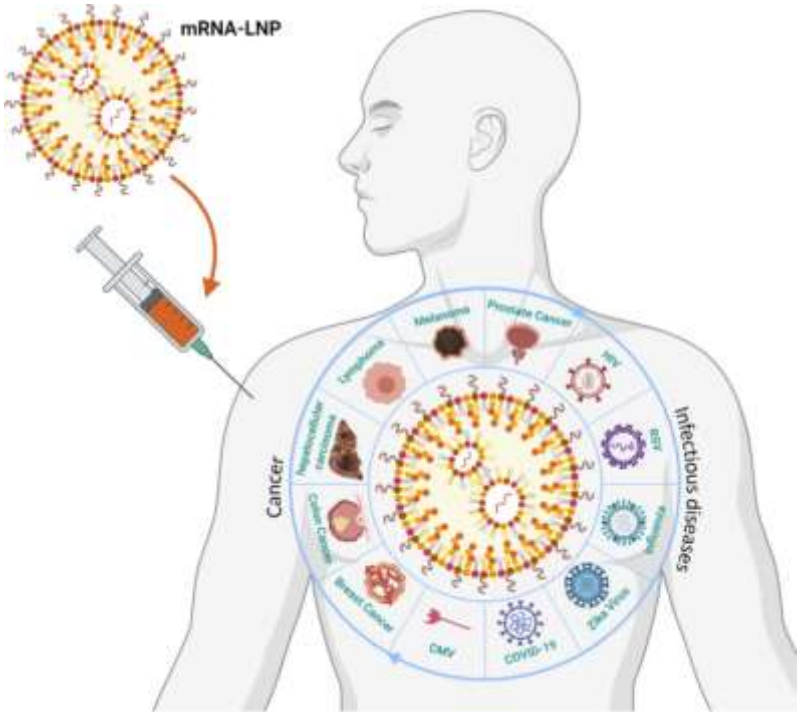
Hou et al. (2021) established that the emergence of mRNA therapeutics has substantially changed the requirements for biopharmaceutical delivery systems because naked mRNA is highly susceptible to extracellular degradation and cannot efficiently cross cellular membranes. Their review highlighted lipid nanoparticles (LNPs) as one of the most successful platforms for overcoming these barriers through encapsulation, cellular uptake and intracellular release. LNPs generally incorporate ionisable lipids, helper phospholipids, cholesterol and polyethylene glycol (PEG)-lipids, with each component influencing particle stability, biodistribution, cellular internalisation and endosomal escape. The clinical success of LNP-based mRNA vaccines represented an important validation of this technology and demonstrated that nucleic-acid delivery platforms can progress from experimental formulations to large-scale therapeutic applications. The authors also identified manufacturing, storage stability, safety, tissue targeting and administration route as important considerations for future translation.

Varanko et al. (2020) examined the growing contribution of protein- and peptide-based biomaterials to advanced drug delivery and demonstrated a movement towards biomaterials that are themselves biologically functional. Protein and peptide materials offer advantages including biocompatibility, structural tunability, molecular recognition and the capacity for self-assembly. Their application has expanded beyond conventional carriers towards injectable particles, drug depots, protein–drug conjugates and systems capable of transporting nucleic acids. Such approaches are particularly relevant to biopharmaceutical delivery because the carrier can be designed around biological interactions rather than solely around physicochemical encapsulation. The review further indicated that recombinant proteins, naturally derived biomolecules and synthetic peptides can be engineered to modify degradation, release behaviour and tissue interactions, providing opportunities for developing delivery systems with greater biological precision (Varanko et al., 2020).

Dubey et al. (2021) emphasised that oral administration remains one of the most important unmet objectives in protein and peptide delivery because most biopharmaceuticals continue to depend on parenteral administration. The gastrointestinal tract presents multiple barriers, including acidic conditions, proteolytic enzymes, mucus, epithelial permeability restrictions and first-pass metabolism. These barriers are particularly problematic for large, hydrophilic and structurally complex molecules. The literature has consequently explored nanocarriers, permeation enhancers, enzyme inhibitors, site-specific delivery and stimuli-responsive systems to improve intestinal absorption. Nanotechnology is particularly attractive because carriers can simultaneously protect the therapeutic molecule and facilitate its interaction with epithelial surfaces. However, the considerable variability of gastrointestinal physiology makes consistent systemic exposure difficult to achieve, indicating that improvements in

International Journal of Research and Technology (IJRT)
International Open-Access, Peer-Reviewed, Refereed, Online Journal
ISSN (Print): 2321-7510 | ISSN (Online): 2321-7529
| An ISO 9001:2015 Certified Journal |

formulation design must be accompanied by better understanding of absorption mechanisms (Dubey et al., 2021).



Zizzari et al. (2021) further demonstrated that advances in oral peptide delivery have increasingly incorporated nanotechnology and molecular engineering. Nanoparticles and micelles can protect peptides from enzymatic degradation while facilitating interaction with intestinal membranes, whereas permeation-enhancing approaches attempt to temporarily increase epithelial transport. Chemical strategies such as peptide cyclisation and conjugation can additionally modify stability and pharmacokinetic properties. The authors noted that the development of orally active peptide medicines represents an important transition because improved bioavailability could reduce dependence on injections and increase treatment acceptability. Nevertheless, the translation of promising laboratory systems into clinically reliable formulations remains challenging because improvements in intestinal permeability must be balanced against safety, reproducibility and preservation of biological activity (Zizzari et al., 2021).

Samarasinghe et al. (2021) highlighted lipid-based nanocarriers as particularly promising for oral protein and peptide delivery because their composition can be adapted to address several gastrointestinal barriers simultaneously. Self-emulsifying drug delivery systems, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers, liposomes and micelles can enhance the apparent lipophilicity of macromolecules, protect them from gastrointestinal degradation and facilitate interactions with mucus and epithelial membranes. Muco-inert systems may improve movement through the mucus layer, while lipid-mediated uptake can involve endocytosis, transcytosis or membrane interaction. The combination of lipid carriers with permeation enhancers has therefore created multifunctional systems capable of addressing both stability and absorption. However, differences in loading capacity,

formulation stability and absorption mechanisms continue to influence their translational performance (Samarasinghe et al., 2021).

Verma et al. (2021) similarly identified poor stability, enzymatic degradation and inadequate membrane permeability as major determinants of the limited oral bioavailability of proteins and peptides. Their analysis indicated that molecular size, charge, hydrophilicity and structural characteristics strongly influence gastrointestinal absorption. Advanced delivery approaches therefore aim to protect macromolecules while increasing their interaction with epithelial membranes. Nanoparticles, liposomes, polymeric systems, permeation enhancers and enzyme-protective formulations have demonstrated potential in experimental models. However, increased permeability alone does not necessarily guarantee clinically meaningful systemic exposure, as intestinal degradation, intracellular trafficking and hepatic first-pass effects can remain significant. The literature consequently supports a multifunctional design philosophy in which protection, transport and release are addressed simultaneously rather than independently (Verma et al., 2021).

Hou et al. (2021) also demonstrated that the development of mRNA delivery systems involves a sequence of biological barriers extending from administration to cytoplasmic translation. Following administration, mRNA must remain protected from nucleases, avoid premature clearance and reach the appropriate tissue. After cellular uptake, the carrier must facilitate endosomal escape so that mRNA can reach the cytoplasm and undergo translation. This makes intracellular trafficking a critical determinant of therapeutic performance. Ionisable lipids are particularly important because they can remain relatively neutral under physiological conditions while becoming protonated in acidic endosomal environments, promoting interactions with endosomal membranes. Consequently, the optimisation of lipid composition, particle structure and physicochemical properties has become a major research focus in mRNA formulation development (Hou et al., 2021).

Wang et al. (2022) reviewed emerging mRNA technologies and demonstrated that delivery development has expanded beyond conventional liposomes towards sophisticated LNPs and lipoplexes. The different lipid components perform complementary functions: ionisable lipids interact with nucleic acids and facilitate endosomal escape, cholesterol contributes to structural stability and membrane interactions, phospholipids influence particle organisation, and PEG-lipids regulate aggregation and circulation behaviour. Precise control of lipid composition is therefore central to achieving efficient mRNA encapsulation and intracellular release. The review also highlighted the broader therapeutic possibilities of mRNA beyond vaccination, including protein replacement, immunotherapy and treatment of genetic disorders. These applications require delivery systems capable of achieving appropriate tissue distribution and controlled intracellular expression, making formulation optimisation a key determinant of future therapeutic expansion (Wang et al., 2022).

Mitchell et al. (2022) demonstrated that LNP development is increasingly moving towards selective intracellular and organ-specific delivery. Conventional LNPs have shown strong activity in hepatic tissues, but many therapeutic applications require delivery to extrahepatic organs such as the lungs, spleen, lymph nodes, bone marrow and central nervous system.

Rational modification of ionisable lipids and other formulation components can alter biodistribution, cellular uptake and endosomal escape. This has encouraged the development of structure–activity relationships linking lipid chemistry with biological performance. The ability to control organ distribution is particularly important for mRNA therapeutics because transient protein expression is only therapeutically useful when the encoded protein is produced at the desired anatomical site. Therefore, next-generation LNP research increasingly prioritises tissue selectivity alongside conventional measures such as encapsulation efficiency and particle size (Mitchell et al., 2022).

Cheng and Hill (2022) identified extracellular vesicles (EVs) as an emerging biomimetic alternative to synthetic nanocarriers for therapeutic delivery. EVs possess naturally derived lipid membranes and participate in intercellular communication, giving them intrinsic capabilities for transferring proteins, lipids and nucleic acids between cells. Their biological origin may provide advantages in terms of biocompatibility and cellular interaction, while surface engineering can potentially improve tissue targeting. EVs have therefore been investigated for the delivery of therapeutic RNAs, proteins and other bioactive molecules. Nevertheless, challenges involving source-cell selection, isolation, purification, loading efficiency, characterisation, storage and manufacturing remain significant. The heterogeneity of EV populations also complicates standardisation and regulatory development. Thus, although EVs provide an attractive biomimetic strategy, their clinical translation requires greater control over composition and biological function (Cheng & Hill, 2022).

Li et al. (2022) specifically examined exosome-mediated nucleic-acid delivery and reported growing interest in these naturally occurring vesicles as carriers for RNA and gene-based therapeutics. Their favourable biocompatibility, relatively low immunogenicity and capacity for interaction with recipient cells make exosomes attractive for transporting fragile nucleic-acid cargos. Engineering strategies can modify their surface properties or loading characteristics to improve targeting and therapeutic activity. Such systems may be particularly useful for cancer and other diseases requiring delivery of genetic material to specific cell populations. However, variability in exosome production, purification and cargo loading remains a major obstacle. Compared with established synthetic nanoparticles, exosome systems currently face greater challenges in manufacturing consistency and regulatory characterisation, limiting immediate clinical scalability despite substantial preclinical potential

Li et al. (2022) also described biopharmaceutical nanoclusters as an emerging approach for protein and peptide delivery in which the therapeutic molecule itself forms the major structural component of the nanocarrier. This strategy seeks to address the low loading efficiency and possible toxicity associated with additional carrier materials. By organising therapeutic proteins or peptides into nanoscale assemblies, these systems may improve stability, absorption and biological activity while reducing the proportion of inactive excipients. However, protein and peptide nanoclusters are inherently complex because their assembly depends on molecular interactions, structural stability and environmental conditions. Controlling particle size, aggregation, release behaviour and reproducibility

remains necessary before these systems can achieve broad translational application. The approach nevertheless represents a shift towards self-delivering biopharmaceutical formulations in which carrier and therapeutic functions are integrated into a single architecture (Li et al., 2022).

Wang et al. (2022) reported that non-viral gene delivery has progressed considerably through the development of lipid nanoparticles, polymeric materials, dendrimers and other nanostructured vectors. Non-viral systems offer several potential advantages over viral vectors, including lower immunogenicity, greater flexibility in cargo size and the possibility of repeated administration. LNPs are particularly significant because their established capacity for nucleic-acid delivery can be adapted for DNA, RNA and genome-editing components. Polymeric vectors also provide opportunities for controlled release and chemical modification. Nevertheless, efficient gene delivery requires coordinated management of extracellular stability, cellular uptake, endosomal escape, intracellular trafficking and nuclear or cytoplasmic localisation, depending on the therapeutic modality. Consequently, non-viral vectors continue to require optimisation of both material properties and biological specificity before their full clinical potential can be realised (Wang et al., 2022).

Dogbey et al. (2022) compared viral and non-viral approaches and emphasised that vector selection is closely related to the biological objective of gene therapy. Viral vectors can provide highly efficient cellular transduction and, depending on vector type, sustained expression, but their application can be limited by immunogenicity, manufacturing complexity, cargo restrictions and concerns associated with repeated administration. Non-viral systems provide greater chemical flexibility and can accommodate emerging nucleic-acid modalities, although their transfection efficiency and tissue targeting may remain lower in some contexts. Recent technological developments are therefore focused on combining the efficiency of biological delivery mechanisms with the tunability of synthetic materials. This has encouraged the development of hybrid, biomimetic and targeted vectors designed to improve therapeutic selectivity while reducing systemic toxicity (Dogbey et al., 2022).

Lundstrom (2022) noted that viral vectors remain an important component of modern gene therapy because of their capacity for efficient gene transfer and their extensive development across inherited diseases, cancer and other therapeutic areas. Adeno-associated virus, adenoviral and lentiviral systems each possess distinct biological characteristics that influence their suitability for particular applications. However, immune responses against vector components, limitations in manufacturing and restrictions on repeat dosing remain important considerations. The continuing development of viral vectors therefore reflects an attempt to improve tissue specificity, reduce immunogenicity and increase therapeutic safety. In parallel, non-viral technologies are increasingly competitive for applications involving transient expression, mRNA delivery and genome editing, suggesting that future gene delivery will likely involve complementary rather than universally superior vector classes (Lundstrom, 2022).

Qin et al. (2022) highlighted the increasing role of LNPs in CRISPR/Cas9 genome-editing delivery, demonstrating how advances originally developed for RNA therapeutics can be

extended towards gene editing. CRISPR components require coordinated delivery of guide RNA and nuclease-related molecules while limiting unwanted systemic exposure. LNPs offer an attractive non-viral platform because their composition can be modified to control cargo encapsulation, cellular uptake and intracellular release. Their transient delivery characteristics may also be advantageous where temporary expression of genome-editing machinery is preferred. Nevertheless, tissue specificity, off-target effects, endosomal escape and efficient delivery to relevant cell populations remain significant challenges. Continued development of targeted LNPs may therefore be important for translating CRISPR-based therapeutics from proof-of-concept studies towards broader clinical applications (Qin et al., 2022).

Hou et al. (2021) indicated that the future of biopharmaceutical delivery will depend increasingly on overcoming the limitations of current carrier systems rather than simply increasing drug-loading capacity. For mRNA, the major challenges include tissue targeting, endosomal escape, formulation stability, storage, safety and scalable manufacturing. Comparable challenges occur in protein and peptide delivery, where gastrointestinal barriers and variable absorption continue to restrict non-invasive administration. In gene therapy, the need for precise tissue localisation and controlled expression adds further complexity. Across these modalities, next-generation systems are consequently moving towards multifunctionality, combining protection, targeting, controlled release and intracellular trafficking within a single delivery platform. The increasing convergence of nanotechnology, biomaterials engineering, molecular biology and computational formulation design is likely to accelerate the development of delivery systems capable of matching specific carriers to specific therapeutic cargos and biological targets.

Biopharmaceutical	**Major delivery challenge**	**Prominent next-generation systems**	**Key mechanisms**	**Major advantages**	**Persistent limitations**	**Overall research direction**
Proteins	Enzymatic degradation, instability and poor membrane permeability	Polymeric nanoparticles, liposomes, lipid-based carriers, protein-based materials	Encapsulation, protection, controlled release and membrane interaction	Improved stability and potential for sustained delivery	Low loading efficiency, structural instability and scale-up challenges	Development of stable, targeted and non-invasive delivery systems
Peptides	Gastrointestinal degradatio	Nanoemulsions, lipid nanopartic	Protection from enzymes	Potential improvement in oral	Variable absorption and	Multifunctional oral and

	n and poor oral absorption	les, micelles, permeation-enhancing systems	and enhancement of epithelial transport	bioavailability and patient compliance	concerns regarding permeation-enhancer safety	mucosal delivery platforms
mRNA	RNase degradation, poor cellular uptake and endosomal entrapment	Ionisable lipid nanoparticles, lipoplexes, polymeric nanoparticles and extracellular vesicles	Encapsulation, cellular internalisation and endosomal escape	High intracellular delivery efficiency and transient protein expression	Tissue targeting, inflammatory responses, stability and manufacturing complexity	Organ-selective and clinically scalable LNPs
Gene therapeutics	Extracellular degradation, cellular barriers and tissue specificity	Viral vectors, LNPs, polymeric nanoparticles and hybrid vectors	Transduction, endocytosis, intracellular trafficking and genetic expression	Efficient gene transfer and potential long-term therapeutic effects	Immunogenicity, vector capacity, manufacturing and repeat-dosing limitations	Safer, targeted and more controllable gene delivery
CRISPR/gene editing	Co-delivery and precise intracellular localisation of editing components	LNPs, polymeric systems and biomimetic carriers	Cytoplasmic delivery, endosomal escape and transient expression	Potential for precise genetic modification without permanent vector persistence	Off-target effects, tissue targeting and delivery efficiency	Targeted non-viral genome-editing delivery
Extracellular vesicles	Production,	Exosomes and	Natural intercellul	Biocompatibility and	Heterogeneity,	Engineered and

	purification and cargo-loading variability	engineered extracellular vesicles	ar transport and membrane-mediated uptake	biomimetic delivery characteristics	standardisation and manufacturing difficulties	scalable biomimetic carriers
Overall advanced systems	Multiple biological barriers occurring sequentially	Multifunctional, targeted and stimuli-responsive nanocarriers	Protection, targeting, uptake, trafficking and controlled release	Integrated management of several delivery barriers	Regulatory complexity, reproducibility and translation from laboratory to clinic	Precision-engineered, organ-selective and clinically scalable platforms

NEXT-GENERATION DELIVERY SYSTEMS FOR BIOPHARMACEUTICALS

Hou et al. (2021) demonstrated that lipid nanoparticles have achieved the strongest translational progress among emerging biopharmaceutical delivery technologies, particularly for mRNA therapeutics. Their ability to encapsulate fragile nucleic acids, facilitate cellular uptake and promote endosomal escape provides advantages over conventional delivery approaches. Protein and peptide delivery systems, including polymeric nanoparticles, liposomes, lipid-based carriers and permeation-enhancing formulations, primarily address enzymatic degradation and poor epithelial permeability (Verma et al., 2021). Viral vectors remain highly effective for gene transfer, although immunogenicity, manufacturing complexity and repeat-administration constraints influence their broader application (Lundstrom, 2022). Non-viral systems provide greater chemical flexibility and are increasingly relevant to mRNA and genome-editing applications. Extracellular vesicles additionally offer biomimetic characteristics, although their manufacturing and standardisation remain less mature (Cheng & Hill, 2022). Overall, comparative evidence indicates that delivery performance depends strongly on cargo characteristics and the biological barriers associated with the intended route and target tissue.

Delivery system	**Main cargo**	**Key performance characteristic**	**Major limitation**
Lipid nanoparticles	mRNA, gene-editing components	Efficient intracellular delivery	Targeting and long-term stability
Liposomes	Proteins, peptides, nucleic acids	Versatile encapsulation	Leakage and stability
Polymeric	Proteins, peptides,	Controlled release	Material-related

nanoparticles	nucleic acids		toxicity
Viral vectors	Gene therapeutics	High transduction efficiency	Immunogenicity
Extracellular vesicles	RNA, proteins	Biomimetic cellular delivery	Manufacturing variability

ADVANCES IN TARGETED AND INTRACELLULAR DELIVERY OF PROTEIN, PEPTIDE, MRNA, AND GENE THERAPEUTICS

Mitchell et al. (2022) showed that contemporary delivery research is increasingly focused on tissue selectivity rather than simply improving systemic exposure. This is particularly important for mRNA and gene therapeutics, where therapeutic activity depends on reaching specific cell populations and intracellular compartments. Ionisable lipid systems can facilitate endosomal escape, while surface modification and lipid composition can influence biodistribution. For proteins and peptides, advanced oral delivery technologies seek to protect molecules from gastrointestinal degradation and increase epithelial transport (Dubey et al., 2021). Permeation enhancers, nanocarriers and lipid-based formulations have consequently become important strategies for improving absorption (Samarasinghe et al., 2021). In gene editing, LNPs provide a non-viral approach for transient intracellular delivery of editing components, potentially reducing some limitations associated with persistent viral expression (Qin et al., 2022). Biomimetic carriers such as exosomes may provide additional opportunities for targeted transport because of their natural cellular communication functions (Li et al., 2022). These developments indicate that next-generation delivery is increasingly based on coordinated control of protection, targeting, cellular uptake and intracellular release.

Therapeutic class	**Targeting requirement**	**Advanced approach**	**Desired outcome**
Protein	Tissue/cellular localisation	Functionalised nanoparticles	Improved therapeutic exposure
Peptide	Intestinal epithelium	Permeation-enhancing nanocarriers	Increased oral bioavailability
mRNA	Specific tissue and cytoplasm	Organ-selective LNPs	Efficient protein expression
Gene therapy	Target cells	Viral and non-viral vectors	Effective gene transfer
Gene editing	Target cells and intracellular compartment	Targeted LNPs	Precise transient editing

CONCLUSION

The review demonstrates that next-generation delivery systems are increasingly determining the therapeutic potential of biopharmaceuticals by addressing the fundamental limitations associated with proteins, peptides, mRNA and gene-based therapeutics. Conventional

delivery approaches remain constrained by enzymatic degradation, poor membrane permeability, instability, rapid clearance and inadequate tissue distribution, whereas advanced nanocarriers provide mechanisms for cargo protection, controlled release, cellular uptake and intracellular trafficking. Among the technologies examined, lipid nanoparticles have demonstrated particularly strong translational potential, with their successful application in mRNA vaccines providing clinical validation of sophisticated non-viral delivery platforms (Hou et al., 2021). Protein and peptide delivery has similarly progressed through lipid-based systems, polymeric nanoparticles, permeation enhancers and biomimetic approaches aimed at improving stability and bioavailability (Verma et al., 2021). Gene delivery continues to benefit from both viral and non-viral technologies, with increasing interest in safer, targeted and repeat-administration-compatible systems (Lundstrom, 2022).

Despite these advances, significant challenges remain concerning tissue-specific targeting, endosomal escape, immunogenicity, formulation stability, manufacturing scalability, reproducibility and regulatory requirements. Extracellular vesicles and other biomimetic platforms offer promising alternatives but require further standardisation before widespread clinical translation (Cheng & Hill, 2022). Future development is therefore expected to move towards multifunctional and precision-engineered delivery systems capable of integrating protection, targeting and controlled intracellular release within a single platform. Greater understanding of structure–activity relationships, organ-selective delivery and biological interactions will be essential for converting promising experimental technologies into reliable clinical therapies.

REFERENCES

1. Cheng, L., & Hill, A. F. (2022). Therapeutically harnessing extracellular vesicles. Nature Reviews Drug Discovery, 21(5), 379–399. https://doi.org/10.1038/s41573-022-00410-w
2. Dogbey, D. M., Torres, V. E. S., Fajemisin, E., Mpondo, L., Ngwenya, T., Akinrinmade, O. A., Perriman, A. W., & Barth, S. (2022). Technological advances in the use of viral and non-viral vectors for delivering genetic and non-genetic cargos for cancer therapy. Drug Delivery and Translational Research, 13(11), 2719–2738. https://doi.org/10.1007/s13346-023-01362-3
3. Hou, X., Zaks, T., Langer, R., & Dong, Y. (2021). Lipid nanoparticles for mRNA delivery. Nature Reviews Materials, 6(12), 1078–1094.
4. Lundstrom, K. (2022). Viral vectors in gene therapy: Where do we stand in 2022? Viruses, 15(3), 698. https://doi.org/10.3390/v15030698
5. Mitchell, M. J., Billingsley, M. M., Haley, R. M., Wechsler, M. E., Peppas, N. A., & Langer, R. (2021). Engineering precision nanoparticles for drug delivery. Nature Reviews Drug Discovery, 20(2), 101–124.
6. Qin, J., Xue, L., Gong, N., Zhang, H., Shepherd, S. J., Haley, R. M., Swingle, K. L., & Mitchell, M. J. (2022). RGD peptide-based lipids for targeted mRNA delivery and gene editing applications. RSC Advances, 12, 25397–25404. https://doi.org/10.1039/D2RA02771B

7. Samaridou, E., Heyes, J., & Lutwyche, P. (2020). Lipid nanoparticles for nucleic acid delivery: Current perspectives. Advanced Drug Delivery Reviews, 154–155, 37–63. https://doi.org/10.1016/j.addr.2020.06.002
8. Verma, S., Goand, U. K., Husain, A., Katekar, R. A., Garg, R., & Gayen, J. R. (2021). Challenges of peptide and protein drug delivery by oral route: Current strategies to improve the bioavailability. Drug Development Research, 82(7), 927–944. https://doi.org/10.1002/ddr.21832
9. Wang, C., Pan, C., Yong, H., Wang, F., Cong, W., & other authors. (2022). Emerging non-viral vectors for gene delivery. Journal of Nanobiotechnology, 21, 272. https://doi.org/10.1186/s12951-023-02044-5
10. Wang, H.-L., Wang, Z.-G., & Liu, S.-L. (2022). Lipid nanoparticles for mRNA delivery to enhance cancer immunotherapy. Molecules, 27(17), 5607. https://doi.org/10.3390/molecules27175607
11. Varanko, A., Saha, S., & Chilkoti, A. (2020). Recent trends in protein and peptide-based biomaterials for advanced drug delivery. Advanced Drug Delivery Reviews, 156, 133–187.
12. Yang, L., Gong, L., Wang, P., Zhao, X., Zhao, F., Zhang, Z., Li, Y., & Huang, W. (2022). Recent advances in lipid nanoparticles for delivery of mRNA. Pharmaceutics, 14(12), 2682. https://doi.org/10.3390/pharmaceutics14122682
13. Zhang, Y., Liu, Q., Zhang, X., Huang, H., Tang, S., Chai, Y., Xu, Z., Li, M., Chen, X., Liu, J., & Yang, C. (2022). Recent advances in exosome-mediated nucleic acid delivery for cancer therapy. Journal of Nanobiotechnology, 20, 279. https://doi.org/10.1186/s12951-022-01472-z
14. Zizzari, A. T., Pliatsika, D., Gall, F. M., Fischer, T., & Riedl, R. (2021). New perspectives in oral peptide delivery. Drug Discovery Today, 26(4), 1097–1105.