Journal of Regenerative Medicine and Molecular Innovation
Vol 1 No 2 Februari 2025
ISSN: XXXX-XXXX (Electronic)
Open Access: https://journals.ai-mrc.com/jrmmi

Current and Future Advancements in miRNA Therapeutics Delivery Systems for Regenerative Medicine

Silvan Saputra[1], Reza Yuridian Purwoko[2], Budi Wiweko [3], Ivan R. Sini [4], Nining Handayani [5]
[1] PT. Riseta Medica Inovasia, Jakarta, Indonesia
[2] Center for Preclinical and Clinical Medical Research, Health Research Organization, National Research and Innovation Agency, Cibinong, West Java, Indonesia
[3] Human Reproduction, Infertility, and Family Planning, IMERI, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[4] Faculty of Medicine, Bogor Agricultural Institute, Bogor, West Java, Indonesia
[5] IRSI Research and Training Centre, Jakarta, Indonesia
Faculty of Medicine and Pharmacy, Universitas Indonesia, Jakarta, Indonesia

Article Info

Article history:
Received 17-01-2025
Revised 08-02-2025
Accepted 16-02-2025

Keyword:
MicroRNA (miRNA) Therapeutics; Gene Expression Modulation; Regenerative Medicine; Delivery Systems; Lipid-based Nanoparticles.

ABSTRACT

MicroRNA (miRNA) therapeutics offer a promising approach to treating complex diseases by modulating gene expression. However, challenges such as instability, poor cellular uptake, off-target effects, and immune responses limit their clinical use. This review synthesizes recent advancements in delivery systems aimed at overcoming these challenges, with a focus on regenerative medicine. A systematic review of the past decade's literature highlights key delivery platforms, including lipid-based nanoparticles, polymeric carriers, and exosome-based systems. Lipid-based systems, such as liposomes and solid lipid nanoparticles, provide enhanced stability and targeted delivery, particularly in cancer and cardiovascular therapies. Polymeric carriers, like PLGA and chitosan nanoparticles, enable controlled release and improved biocompatibility for long-term applications. Exosome-based delivery systems mimic natural cellular communication, facilitating efficient miRNA transfer with reduced immunogenicity. The review underscores the importance of chemical modifications, endocytosis-enhancing strategies, and stimuli-responsive materials in optimizing therapeutic efficacy. Combining bioengineering advancements with artificial intelligence holds potential to refine delivery systems and expedite clinical translation. Despite these innovations, challenges like scalability, regulatory issues, and manufacturing costs remain barriers to widespread adoption. This study highlights key opportunities and outlines future research directions to establish miRNA therapeutics as a cornerstone in regenerative medicine.

INTRODUCTION

MicroRNA (miRNA) therapeutics represent a promising approach in molecular medicine, particularly for targeting gene expression in a range of diseases (Dasgupta & Chatterjee, 2021). These small non-coding RNA molecules regulate gene expression by binding to messenger RNA (mRNA), either promoting its degradation or inhibiting its translation. miRNAs have the unique ability to target multiple genes within complex molecular networks, making them valuable for treating diseases such as cancer, cardiovascular disorders, and neurological conditions, where various pathways are often disrupted (Moraes et al., 2021).

However, translating miRNA-based therapies from the laboratory to clinical settings faces several significant challenges. The first challenge is the inherent instability of miRNAs in the bloodstream, where they are rapidly degraded by enzymes (Moraes et al., 2021). Additionally, the

`

negative charge of miRNAs' phosphate backbone hinders their passive diffusion across cell membranes, making cellular uptake a major hurdle (Zhang et al., 2013). Another challenge is the risk of off-target effects, as miRNAs may bind to unintended genes due to sequence homology (Dasgupta & Chatterjee, 2021). Furthermore, miRNAs can induce immune responses (Zhao et al., 2021), and targeted delivery to specific tissues remains a significant obstacle (El Sayed et al., 2021).

To address these challenges, several innovative delivery systems have been developed, utilizing nanotechnology and biomaterials. Among these, lipid-based nanoparticles (LNPs) have gained prominence due to their ability to protect miRNAs from degradation while promoting efficient cellular uptake through endocytosis (Dasgupta & Chatterjee, 2021). Polymeric nanoparticles offer complementary advantages, such as the ability to regulate their properties and facilitate targeted delivery (Ban et al., 2019). Additionally, nature-inspired platforms, such as exosome-based delivery systems, have emerged due to their ability to mimic natural cellular signaling, which enhances tissue-specific targeting and reduces immunogenicity (Zhang et al., 2013). Other approaches, including aptamer-based systems (El Sayed et al., 2021) and inorganic nanoparticles (Zhao et al., 2021), provide additional solutions for targeting and multi-functional delivery.

These delivery systems are critical for advancing miRNA therapeutics toward clinical applications. Each platform addresses specific challenges—such as enhancing stability, improving cellular uptake, achieving targeted delivery, and minimizing off-target effects. As these delivery technologies continue to evolve and new methods are discovered, miRNA-based therapies are increasingly becoming viable clinical treatments. The continuous progress in delivery technologies, coupled with a deeper understanding of miRNA biology, will unlock the full therapeutic potential of miRNAs, particularly in the management of multifactorial diseases.

Research Aim

The aim of this work is to review the current approaches for delivering miRNA therapeutics in regenerative medicine, examining both the challenges and emerging solutions. This review focuses on identifying the most effective strategies to address key issues such as stability, targeting accuracy, and side effects, while also exploring the future development of miRNA-based therapies in regenerative applications

RESEARCH METHODS

This research adopts a literature review strategy to examine the development of miRNA therapeutics delivery systems in regenerative medicine. The scope of the review was defined from the outset to include only peer-reviewed articles that focus on miRNA delivery systems, their associated challenges, and applications in regenerative therapies. Special attention was given to studies that present new approaches to delivery systems, aiming to enhance stability, targeting ability, and therapeutic effect.

To identify relevant literature, systematic searches were conducted in several well-established databases, including PubMed, Scopus, and Web of Science. The following search terms were used: 'miRNA therapeutics', 'nanoparticles', 'regenerative medicine', and 'targeted delivery'. Only articles published within the last decade were considered to ensure the inclusion of the most up-to-date research (2013–2023). However, to provide essential background information and context, some older studies were also included.

Articles were selected based on the following inclusion criteria: (1) studies focusing on delivery systems for miRNA-based therapeutics, (2) research exploring challenges and solutions related to miRNA delivery in regenerative medicine, and (3) articles that contributed significantly to understanding the development of novel delivery technologies. Exclusion criteria included (1) studies unrelated to miRNA therapeutics or regenerative medicine, (2) non-peer-reviewed sources, and (3) articles that did not provide original research (e.g., reviews or meta-analyses).

.

After defining the relevant literature, critical data points—such as the types of delivery systems, the processes governing them, and their therapeutic uses—were extracted. The results were then summarized thematically, with a particular focus on advancements in key areas, including stability, cellular uptake, and targeting specificity. This narrative approach facilitated a coherent discussion of the current possibilities and challenges associated with different delivery systems, as well as identifying promising avenues for future research.

RESULTS AND DISCUSSION

Cellular Uptake Mechanisms

Successful miRNA delivery depends on efficient cellular internalization via endocytosis and direct membrane penetration. Endocytosis pathways, including clathrin-mediated (CME), caveolae-mediated (CavME), and macropinocytosis, play distinct roles in uptake and endosomal release. CME is the dominant pathway for nanoparticle-based miRNA delivery but often results in endosomal entrapment, requiring additional release strategies (Ma et al., 2018). CavME avoids lysosomal degradation, enhancing miRNA cytoplasmic availability, while macropinocytosis allows bulk-phase uptake, useful for high payloads (Han et al., 2023; Arafiles et al., 2020).

The issue of endosomal release is still critical for effective miRNA delivery because internalized miRNAs are often trapped within endosomes and thus cannot exert their therapeutic effects. Several innovative strategies have been developed to address this barrier: pH-sensitive materials take advantage of endosomal acidification to initiate a release of the cargo, with compounds such as nigericin, which cause osmotic swelling of endosomes to allow the release of miRNA into the cytosol (Orellana et al., 2019). Tat and NickFect CPPs have been proven to disrupt endosomal membranes and enhance cytosolic delivery of miRNA mimics and alleviating inflammation in dermatitis models (Carreras-Badosa et al., 2020). Further, photo chemical therapies based on light sensitive materials–indocyanine green have also shown potential in cancer treatments due to targeted capabilities of light (Wang et al., 2020). Direct membrane penetration adapt another transport route with respect to endocytic pathways wherein it entrails that cargo does not have to go through the vesicular structures at all rather it takes it directly to the cytosol. This mechanism is most useful for nanoparticles below 10 nm, and arginine functionalized nanoparticles have been shown to transfect proteins and nucleic acids through energy-independent direct penetration (Panja & Jana, 2020).

These different pathways and mechanisms have been integrated in different ways to bring about enhanced progress in miRNA therapeutics. For example, integrating caveolae-mediated endocytosis with redox-responsive release systems enhances the therapeutic efficacy of treatment for triple-negative breast cancer (Han et al., 2023). Likewise, other techniques of endosomal release such as CPP based delivery systems has opened up new avenues of miRNA usage in inflammatory and cancer models. The future development of miRNA delivery systems also require further improvement of endocytosis pathways and membrane penetrationmechanisms. By targeting specific cellular pathways for delivery and improving endosomal release mechanisms, the therapeutic application of miRNA-based therapies is further extended, thus providing hope for more successful clinical use. Due to the specific cellular delivery and the increase of endosomal escape, the application of miRNA-based therapies can be promoted.

Non-Viral Delivery Systems

A. Lipid-based Systems

Lipid-based delivery systems have emerged as crucial vehicles for miRNA therapeutics, with three main categories showing particular promise: lipoplexes, solid lipid nanoparticles, and liposomes. Both systems have their benefits for efficient miRNA delivery and overcome different limitations in the therapeutic application. Lipoplexes are a novel method of miRNA delivery, which are created by the electrostatic attraction between the positively charged lipid and the negatively charged miRNA. These complexes serve multiple crucial functions: these include improving stability of miRNAs against nucleases, improving uptake of the particles into cells, and improving escape of the particles

.

from endosomes. It has been most prominent in cancer treatments where using lipoplex-conveyed miRNAs, the cells are efficiently targeted and oncogenic gene expression minimized. A major advancement was made to cationic lipoplexes for the co-delivery of miR-34a with chemotherapeutic drugs, which showed better therapeutic efficacy and less side effects (Scheideler et al., 2019). Subsequent studies have also supported that lipoplex based miRNA delivery systems increase the cellular transfection efficiency with low toxicity (Campani et al., 2020).

Another complex strategy of miRNA delivery is solid lipid nanoparticles (SLNs) containing biocompatible and biodegradable lipids in their structure. Their distinctive solid-state structure at both room and body temperature confers several advantages: These include improved stability, controlled release properties, and low immunogenicity of the resultant nanoparticles. These properties have been successfully applied in different therapeutic uses. For example, SLNs have demonstrated great potential in the targeting of miRNA-21 inhibitors in reversing drug resistance in breast cancer models and improving therapeutic effects with reduced side effects (Silva-Cázares et al., 2020). Apart from cancer applications, SLNs have shown promising future in cardiac therapy; the miRNA mimics were successfully delivered to cardiac cells and improved tissue repair in myocardial infarction (Bejerano et al., 2018).

Liposomes complete the list of the lipid based systems, which consist of phospholipid bilayers containing the miRNA molecules. This structure offers basic shielding from nucleasedegradation, as well as the opportunity for efficient cellular uptake. This can be seen most clearly in their ability to deliver simultaneously miRNA mimics and chemotherapeutic agents. The use of liposomes has been expanded by modifying their surface, for example, by conjugating targeting moieties such as folic acid to increase their selectivity toward cancer cells and decrease off-target effects. They have been recently used to load miR-34a together with doxorubicin to improve the anticancer efficacy in mice (He et al., 2020). The field remains active with recent enhancements in liposomal engineering especially through the fabrication of pH sensitive liposomes that enhance delivery efficacy and release at tumor site (Boloix et al., 2021).

B. Polymer-based Systems

Polyethylenimine (PEI) is a synthetic polymer with a high density of amine groups, enabling strong electrostatic interactions with miRNAs. Its "proton sponge effect" facilitates endosomal escape, making it a highly efficient carrier. However, its cytotoxicity remains a limitation. To address this, researchers have developed PEGylated PEI systems to reduce toxicity and improve biocompatibility while retaining delivery efficiency. For example, PEI-based nanoparticles were used to deliver miR-155 inhibitors in glioblastoma models, resulting in significant tumor regression (Hussein et al., 2019). Additionally, novel formulations incorporating targeting ligands have improved PEI's tumor-specific uptake (Manikkath et al., 2022).

Poly(lactic-co-glycolic acid) (PLGA) is a biodegradable polymer approved by the FDA for drug delivery. PLGA nanoparticles provide sustained and controlled release of miRNAs, allowing for prolonged therapeutic effects. Surface modifications, such as the addition of targeting ligands, improve tissue specificity. For example, PLGA nanoparticles delivering miR-122 mimics to hepatocellular carcinoma cells demonstrated significant downregulation of oncogenes and increased apoptosis (Saw et al., 2019). Recent advances in encapsulation methods have further improved the bioavailability and targeting of PLGA-based miRNA carriers (Malik et al., 2020).

Chitosan, a natural polysaccharide, has been extensively studied for miRNA delivery due to its biodegradability, biocompatibility, and mucoadhesive properties. Chitosan nanoparticles (chNPs) efficiently encapsulate miRNAs and protect them from enzymatic degradation. In cardiovascular research, chNPs delivering miR-33a have been shown to reduce cholesterol levels by targeting ABCA1 gene expression in macrophages (Nguyen et al., 2019). Enhanced chitosan formulations incorporating stabilizers like tripolyphosphate (TPP) have demonstrated improved stability and delivery efficiency (Bejerano et al., 2018).

C. Inorganic Nanoparticles

`

Gold nanoparticles (AuNPs) are known for their stability, biocompatibility and the ability to modify their surface chemistry which makes them suitable for miRNA delivery. The AuNPs conjugated with miR-145 mimics have demonstrated a remarkable efficacy in suppressing the growth of breast cancer tumor due to up-regulation of tumor-suppressor genes. In addition, modifications of monolayer-coated AuNPs have enhanced their transfection efficiency with minimal cytotoxicity and off-target effects. This has made them popular in cancer treatment since their efficiency and safety can be easily achieved (Bai et al., 2019). Additional functionalization techniques like ligand conjugation also enhance the ability of AuNPs to home specifically to the tumor microenvironment, thus improving the efficacy of the treatment (Hoang et al., 2023).

Magnetic nanoparticles (MNPs) have some advantages over other delivery systems, particularly in neurotherapeutic applications. These particles can pass through the blood-brain barrier when carrying miR-124 mimics which are important in treating neurological disorders. The combination of external magnetic guidance systems with MNPs improves their targeting ability, thus allowing the therapeutic payload to be delivered effectively to the target site. Research has established that such systems have enhanced the treatment of ailments such as Parkinson and Alzheimer by enhancing the quality of the treatment (Roy et al., 2021). Moreover, magnetic control methods allow for external regulation of MNP activity, thus minimizing interactions with other tissues and organs, and, consequently, side effects (Kimura et al., 2021).

Among all the nanoparticles, silica nanoparticles (SiNPs) have a particularly porous structure which allows them to carry a large number of miRNA molecules and release them at a desired rate. SiNPs have been used to transfect miR-34a into drug-resistant cancer cells and improve chemosensitivity and the inhibition of tumor growth. This is because SiNPs can avoid conventional drug-resistance strategies while at the same time being highly biocompatible. Moreover, it has been postulated that SiNPs have the potentials for theranostic application since it can deliver the imaging agents and the therapeutic miRNAs at the same time to diagnose and treat diseases (Wang et al., 2019). Recent developments in surface engineering, including enzyme-responsive coatings, improve their specificity to target and kill certain cancer types with reduced side effects (Liu et al., 2022).

Biological Delivery Systems

A. Extracellular Vesicles

Exosomes are small membrane-bound vesicles (30-150 nm) secreted by most of the cells. They, therefore, sequester bioactive molecules such as miRNAs from enzymatic degradation in the extracellular milieu. Exosomes have an inherent targeting ability owing to the presence of specific cell surface markers. These vesicles have been demonstrated to possess a great promise in the delivery of therapeutic miRNAs to tissues of interest. For example, tumor derived exosomes can be designed to deliver tumor suppressive miRNAs like miR-145 that induced breast cancer cell apoptosis and suppressed cell proliferation with high efficiency in models of breast cancer (Ramesh et al., 2023). The current developments in exosome engineering have enhanced the techniques of delivering miRNAs. Electroporation methods for the loading of antitumor miRNAs, including miR-31 and miR-451a, into exosomes increase the therapeutic efficacy in treating hepatocellular carcinoma. These engineered exosomes further promote apoptosis in cancer cells through the suppression of major anti-apoptotic signaling (Pomatto et al., 2019). Also, ligand-functionalized exosomes enhance the targeting of tissues, thus enhancing the delivery of the miRNA payload to specific tumor microenvironments.

Microvesicles, larger extracellular vesicles (100–1000 nm) are formed through outward budding of the plasma membrane. Like exosomes, they contain proteins, lipids, and miRNAs; they also function as signaling molecules. The microvesicles have been shown to overcome some barriers such as the blood-brain barrier hence ideal for brain cancer treatment. Microvesicles containing neural stem cells and miR-100 have been reported to have potential in glioblastoma treatment; they inhibit tumor growth and improve the treatment's efficacy (Wang et al., 2021). The size and uniformity of therapeutic microvesicles have been enhanced in terms of scalability and size using microfluidic production methods. It also allows for the proper control of vesicle size and the loading of benefit miRNAs in therapeutic application to improve the reliability and effectiveness of treatment (Matsuzaka & Yashiro, 2022).

`

B. Cell-based Delivery

Among stem cells, MSCs are ideal for miRNA delivery because of their inherent capacity to secrete EVs containing therapeutic miRNAs. These vesicles are anti-inflammatory and regenerative, and therefore ideal for use in degenerative conditions. For instance, MSC-derived EVs contain miR-101 that inhibits metastasis in the models of osteosarcoma by down regulating the oncogenic signaling pathways (Zhang et al., 2020). In neurological applications, MSC derived exosomes containing miRNAs have been shown to have potential in treating radiation induced brain injuries. They cross the blood-brain barrier and decrease neuroinflammation, promote neuronal outgrowth and functional recovery. This approach avoids the general issues that come with stem cell transplantation for instance immune rejection or even tumor formation (Leavitt et al., 2018).

The engineered cell systems offer a versatile system for miRNA delivery. Cells are engineered to secrete therapeutic miRNAs at higher levels and these miRNAs are encapsulated in EVs. For example, when HEK293T cells producing vesicles containing miR-199a, it was observed that the overall therapeutic efficacy of vesicles was significantly improved in liver cancer models, as it inhibited the tumour growth besides inducing apoptosis (Sutaria et al., 2017). Improvements in aptamer-functionalized vesicles have also been made in the aspect of target specificity. Aptamer-modified nucleolin-targeted extracellular vesicles have been employed to transfect miRNAs into breast cancer cells. This strategy enhances the specificity of drug delivery, and the therapeutic impact while reducing side effects on other targets (Wang et al., 2017).

Targeted Delivery Strategies

A. Surface Modification

Targeting ligands essentially form the backbone of drug delivery systems that offer enhanced precision. Such ligands target receptors that are present in excess quantities on diseased cells and help deliver drugs precisely to these cells. Galactose-modified micelles, for example, have been extremely effective in targeting a tumor-cell line in liver cancer via galactose receptors. The micelles increased drug accumulation in tumors and resulted in superior cellular uptake and significant tumor suppression (Yan et al., 2017). These perfectly coincide with reports on gluco-glycosylated dendrimers that were also down silicated from erfolgreichen hinsichtlich glioblastomazialmatrixen and improved levels of the selectivity and infiltration of tumor-associated macrophages (TAMs) into brain tumors (Sharma et al., 2021). Folic acid is another experimentally investigated ligand for targeting cancer cells in general but is being used the most in tumors with an overexpressed folate receptor. It improved the intake of a folate-functionalized drug delivery vehicle in hepatocellular carcinoma models, giving better efficacy via specific binding to its receptor (Koirala et al., 2019).

Antibody-based delivery systems comprise targeted therapies. Such generation of antibodies and antibody fragments are directed towards drug delivery to a specific cell type or tissue, their element being the extreme affinity of these above molecules to a target antigen. These advancements, additionally in site-specific conjugation methods, increased the efficiency of using antibody-drug conjugates (ADCs) Nm. CD11b-targeting nanoparticles conjugated with antibodies were able to deliver drugs deep into tumor interiors, creating better therapeuticoutcomes but also reduced off-target effects (Lee et al., 2019). Another example is ADCs that target the fibroblast growth factor receptor 1 (FGFR1) and were able to achieve a very precise cytotoxicity against tumor cells overexpressing the FGFR1 due to the high efficiency with which the complex was formed with its cognate receptor at the cell surface.

B. Tissue-specific Targeting

The systems for targeted delivery to specific organs have been developed to a great extent in the therapeutic field. Nanoparticles with targeting ability are used in liver therapy to enhance the specificity of the drug by binding to asialoglycoprotein receptors present on the surface of hepatocytes. Ligand functionalized polysaccharide nanocarriers have been reported to exhibit improved liver targeting, thus improving drug therapeutic efficiency and minimizing hepatotoxicity (Maiti, 2017). In a similar manner, ligand-functionalized liposomes targeting PECAM-1 and ICAM-1 receptors were demonstrated to selectively enrich in pulmonary tissues and provide potential for

`

vascular-targeted therapies (Hood et al., 2018). In liver cancer models, micelles with grafted galactose showed stepwise targeting through the changes in extracellular and intracellular pH. This dual-stimuli-responsive system improved the drug loading, capture, and delivery inside liver tumours (Yan et al., 2017).

Tissue specificity is essential in the new model of medicine called precision medicine, especially in the treatment of diseases such as cancer and autoimmune diseases. Recent improvements in the functionalization of the antibody-functionalized nanocarrier system have made it possible to target dendritic cell subtypes selectively. For example, anti-CD11c antibody-functionalized nanocarriers improved the targeting of specific subsets of dendritic cells and improved their effectiveness in cancer immunotherapy (Simon et al., 2021). Furthermore, the

peptide-functionalized hydrogel particles have been used to target the hepsin-overexpressing cancer cells. These particles showed higher uptake in hepsin-positive cells than in

hepsin-negative cells, which makes them selective and efficient in drug delivery (Xue et al., 2018).With surface modification and tissue targeting, delivery strategies are changing therapeutic landscapes. These approaches include ligand decoration and antibody conjugation that allows for the selective targeting of cancer cells with little or no effect on the rest of the body. These methods will probably become even more important in the further course of research to develop an efficient, individualized treatment.

Future Perspectives

The advancement in technology in drug delivery is posing a new face to the pharmaceutical industry through improved targeted, effective and patient acceptable therapies. These innovations, however, are accompanied by issues that require resolution in order to fully realize their commercial value. These are the technical constraints, regulatory constraints, biological constraints, and issues of commensurate commercialization. The creation of modern drug delivery systems has a number of technical problems, such as the scale, stability, and manufacturability of the systems. For example, although 3D printed drug delivery system has been used to construct customized dosage forms, major barriers including high fabrication cost, policy restrictions and poor adaptability for mass production hinder its advancement (Wang et al., 2021). Likewise, biologic-based delivery systems face challenges in maintaining the stability and storage of the system because they are sensitive to the environmental factors (Badkar et al., 2021). Such challenges call for improved methods of manufacturing and better storage systems to make these innovative technologies available and reliable in a wider range of applications.

Nanopharmaceuticals and smart delivery systems including nanomedicines go through long regulatory approval procedures. For instance, nanoscale drug delivery systems are under much regulatory oversight because of their environmental and biological impacts (Vega-Vásquez et al., 2020). These technologies are still relatively dynamic and this poses a challenge to the regulatory bodies to allow these technologies to enter the market as fast as they are developing, which is a big challenge. Efficient procedures and the new regulations are crucial to the promotion of these sophisticated systems. However, there are still limitations, including the BBB and tumor microenvironments that are still difficult to overcome effectively. Current nanocarrier systems and stimuli-responsive materials have demonstrated certain degree of ability to overcome these barriers but the efficiency and safety of these systems still require optimization. There are natural biomolecules in protein-based drug delivery systems, which have demonstrated potential for biocompatibility and controlled release, although there are still issues. Protein-based drug delivery systems, which leverage natural biomolecules, have shown promise due to their biocompatibility and controlled release capabilities, yet challenges remain in achieving optimal targeting and bioavailability (Ferraro et al., 2024).

One of the main drawbacks of the new drug delivery systems is their high production cost and poor reproducibility. For example, the synthesis of protein-based drug delivery systems is a complicated and costly process, and therefore not suitable for the large market (Zhong et al.,2018).

.

Such scalability problems limit innovative technologies to specific areas of use and fail to allow their use in the broader market.

Among all the developments, the most commercially viable are the systems of targeted drug delivery. Some of the technologies include 3D printing that enable development of medication that suits the patient. Individualized treatments have shown better treatment results and fewer side effects, which gives a compelling argument for investment (Wang et al., 2021). In the same way, smart pens and wearable devices, IoT-enabled drug delivery systems are popular in the market because of the enhanced patient compliance and therapeutic efficiency (Raikar et al., 2023). These devices are also helping in making new standards in patient centered care by allowing real time monitoring and accurate dosing of drugs.

Biologics and gene therapies are highly specific and potent, and thus, their delivery has significant commercial potential. Recent developments in nanotechnology have enabled the delivery of these therapies to be targeted, this is due to the small size and stability issues of the therapies (Prajapati et al., 2024). These are particularly so in the case of genetic disorders, cancer and autoimmune diseases where accuracy is of paramount importance. The use of environmentally friendly systems for drug delivery is becoming a priority in the pharmaceutical industry. Sustainable materials and environmentally conscious production methods are being created to conform to the global sustainability agenda, which is a competitive bonus (Paul et al., 2017). These methods do not only have the effect of decreasing the environmental effects but also have the positive effects of improving the corporate image of the pharmaceutical companies among the public which will make the products of these companies more appealing to the consumers and investors.

New systems of drug delivery are promising to revolutionize medicine by increasing the effectiveness of therapeutic agents, decreasing toxicity, and increasing patient compliance. Despite such issues as scalability, regulatory constraints, and biological limitations, the commercial potential of these innovations is bright, especially in the field of personalized medicine, IoT devices, and biologic drugs. The current limitations will have to be addressed if these technologies are to be taken to the next level.

CONCLUSION

The development of novel miRNA delivery systems has played a crucial role in overcoming key challenges, including stability, targeted delivery, and immune response mitigation. Lipid-based carriers such as liposomes and solid lipid nanoparticles offer enhanced stability and precision targeting, while polymeric nanoparticles, exosome-mediated systems, and inorganic nanocarriers provide additional advantages, including controlled release and reduced immunogenicity. Despite these advances, several critical barriers remain, particularly in large-scale production, regulatory approval, and precise tissue-specific targeting.

Future research should focus on optimizing these delivery platforms through advanced bioengineering approaches. This includes the integration of stimuli-responsive polymers that enable environment-triggered miRNA release, thereby enhancing therapeutic efficiency while minimizing off-target effects. Additionally, hybrid delivery platforms that combine lipid-based, polymeric, and exosome-mediated approaches could provide synergistic benefits by improving stability and cellular uptake while reducing cytotoxicity.

One of the most promising frontiers in miRNA therapeutics is the incorporation of artificial intelligence (AI) into delivery system design. AI-driven computational models can predict nanoparticle behavior, optimize formulation parameters, and identify the most effective delivery routes based on disease-specific factors. Machine learning algorithms can be leveraged to analyze vast datasets on miRNA interactions, helping to refine targeting strategies and improve precision medicine approaches. Furthermore, AI can assist in overcoming translational barriers by accelerating in silico screening of nanoparticle formulations, reducing reliance on time-consuming experimental trials, and increasing the likelihood of regulatory approval.

.

Clinical translation of miRNA therapeutics also requires addressing scalability and standardization challenges. Developing reproducible, cost-effective manufacturing processes will be essential for ensuring that miRNA-based therapies are viable for widespread clinical application. Collaboration between researchers, pharmaceutical companies, and regulatory agencies is necessary to establish guidelines for safety, efficacy, and large-scale production of nanocarrier-based delivery systems.

By advancing bioengineered delivery technologies and leveraging AI for precision formulation and predictive modeling, miRNA therapeutics can move closer to clinical reality. These innovations will be instrumental in overcoming current translational hurdles, ultimately enabling miRNA-based treatments to be successfully integrated into regenerative medicine and other clinical applications.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Arafiles, J. V. V., Hirose, H., Akishiba, M., Tsuji, S., Imanishi, M., & Futaki, S. (2020). Stimulating Macropinocytosis for Intracellular Nucleic Acid and Protein Delivery: A Combined Strategy with Membrane-Lytic Peptides To Facilitate Endosomal Escape. Bioconjugate Chemistry, 31(3), 547–553. https://doi.org/10.1021/acs.bioconjchem.0c00064

Badkar, A. V., Gandhi, R. B., Davis, S. P., & LaBarre, M. J. (2021). Subcutaneous Delivery of High-Dose/Volume Biologics: Current Status and Prospect for Future Advancements. Drug Design Development and Therapy, Volume 15, 159–170. https://doi.org/10.2147/dddt.s287323

Bai, Z., Wei, J., Yu, C., Han, X., Qin, X., Zhang, C., Liao, W., Li, L., & Huang, W. (2019).

Non-viral nanocarriers for intracellular delivery of microRNA therapeutics. Journal of Materials Chemistry B, 7(8), 1209–1225. https://doi.org/10.1039/c8tb02946f

Ban, E., Kwon, T., & Kim, A. (2019). Delivery of therapeutic miRNA using polymer-based formulation. Drug Delivery and Translational Research, 9(6), 1043–1056. https://doi.org/10.1007/s13346-019-00645-y

Bejerano, T., Etzion, S., Elyagon, S., Etzion, Y., & Cohen, S. (2018). Nanoparticle Delivery of miRNA-21 Mimic to Cardiac Macrophages Improves Myocardial Remodeling after Myocardial Infarction. Nano Letters, 18(9), 5885–5891. https://doi.org/10.1021/acs.nanolett.8b02578

Carreras-Badosa, G., Maslovskaja, J., Periyasamy, K., Urgard, E., Padari, K., Vaher, H., Tserel, L., Gestin, M., Kisand, K., Arukuusk, P., Lou, C., Langel, Ü., Wengel, J., Pooga, M., & Rebane,