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EXOSOME BASED DRUG DELIVERY SYSTEM

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ABSTRACT

Exosome-based drug delivery systems have emerged as a novel and promising platform in nanomedicine due to their natural origin, excellent biocompatibility, and intrinsic ability to mediate intercellular communication. Exosomes are extracellular vesicles (30–150 nm) secreted by nearly all cell types and found in various body fluids, including blood, saliva, and urine. They carry a complex cargo of proteins, lipids, and genetic materials such as mRNA transcript and miRNA, which play critical roles in regulating biological and disease associated processes. These biological vesicles possess unique advantages over synthetic nanoparticles, including high stability, low immunogenicity, efficient cellular uptake, and the ability to transport across protective biological membranes.[1] In recent years, exosomes have gained significant attention as natural carriers for delivering therapeutic molecules, including small drugs, nucleic acids, and proteins, for the treatment of diseases such as cancer, neurodegenerative disorders, and cardiovascular conditions. Advanced techniques in exosome isolation, purification, and engineering—such as surface modification and cargo loading—have enhanced their targeting efficiency and therapeutic potential. Despite these advantages, several challenges remain, including difficulties in large-scale production, lack of standardized isolation protocols, limited drug loading capacity, and concerns related to storage stability and biodistribution.[3] Ongoing research aims to overcome these limitations through bioengineering approaches and hybrid exosome systems that combine natural and synthetic components. Overall, exosome based drug delivery systems represent a cutting-edge, biocompatible, and versatile strategy for achieving precise, targeted, and personalized therapy in modern biomedical research.[14]

KEYWORDS: Exosomes, Extracellular vesicles, Drug delivery systems, Targeted therapy, Nanocarriers, Biocompatibility, Cargoloading, Regenerativemedicine, Nanomedicine.[1]

INTRODUCTION

Drug delivery is one of the most important fields in modern medicine. The aim of drug delivery systems is not only to transport drugs to the body but also to make sure that the drug reaches the correct site, in the correct amount, and with minimum side effects. Traditional drug delivery systems such as liposomes, polymeric nanoparticles, and micelles are useful, but they often face problems like toxicity, poor targeting, low stability, and inability to cross barriers such as the blood–brain barrier.[16]

Exosomes, which are natural extracellular vesicles secreted by cells, are now considered as a new and powerful option for drug delivery. Exosomes are very small in size (30–150 nm) and are found in blood, urine, saliva, breast milk, and many other body fluids.[3]

They naturally carry proteins, nucleic acids, and lipids from one cell to another, and thus play an important role in cell communication. Because of their biological origin, exosomes are more biocompatible, stable in circulation, and less immunogenic compared to artificial nanoparticles.

Moreover, they can be engineered to carry drugs, genes, and other therapeutic molecules, which makes them highly suitable for targeted therapy in diseases like cancer, neurodegenerative disorders, cardiovascular diseases, and inflammation.Although exosome based drug delivery shows great potential,challenges such as large scale isolation ,standardisation , loading efficacy and safety evalution still remain.This review will provide an overview of exosome biology, method of isolation and charecterisation strategies for drug loading and modification and application in various disease.[14]

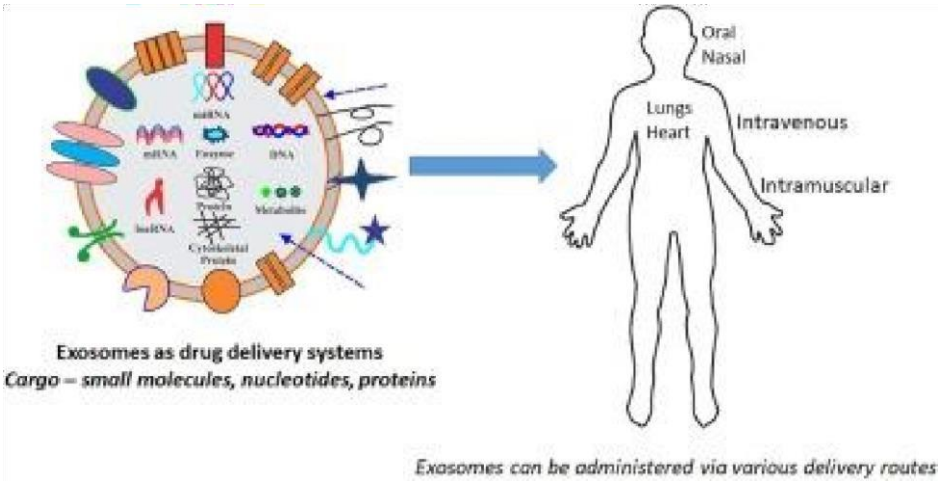

Fig. 1: Cargo delivery system.

Types of Exosomes

1. Based on Cell Source

Exosomes are named according to the cell type from which they originate:

I. Immune cell-derived exosomes – Released by cells like macrophages, dendritic cells, or T-cells. They help in immune signaling and antigen presentation.

II. Tumor cell-derived exosomes – Secreted by cancer cells and often carry oncogenic molecules that help in tumor growth and metastasis.

III. Stem cell-derived exosomes – From mesenchymal or other stem cells; these are known for their regenerative and healing properties.
IV. Neuronal exosomes – Released from nerve cells and play roles in communication between brain cells.
V. Epithelial or endothelial exosomes – Help in maintaining tissue barriers and cellular communication.

2. Based on Size and Density

Exosomes are usually 30–150 nm in size, but they can slightly differ depending on isolation methods:

I. Small exosomes (Exo-S) – Around 30–90 nm
II. Large exosomes (Exo-L) – Around 90–150 nm

Both carry proteins, lipids, and RNA, but their composition may vary slightly.

3. Based on Function

Depending on their biological roles, exosomes can be:

I. Signaling exosomes – Transfer genetic and protein information between cells.
II. Diagnostic exosomes – Used as biomarkers for diseases such as cancer or neurological disorders.
III. Therapeutic exosomes – Engineered to deliver drugs, RNA, or bioactive molecules for treatment.[16]

Biology and Biogenesis of Exosomes

Exosomes are small, membrane-bound extracellular vesicles ranging from 30 to 150 nanometers in diameter, originating from the endosomal pathway of most eukaryotic cells. They play a crucial role in cell-to-cell communication by transferring bioactive molecules such as proteins, lipids, and nucleic acids. The biogenesis of exosomes involves a highly regulated, multi-step process that begins with endocytosis and culminates in their release into the extracellular environment.[2]

The formation of exosomes starts with the inward budding of the plasma membrane to form early endosomes. These early endosomes mature into late endosomes, also known as multivesicular bodies (MVBs), which contain numerous intraluminal vesicles (ILVs). The generation of ILVs within MVBs is mediated through two primary mechanisms: the endosomal sorting complex required for transport (ESCRT)-dependent and ESCRT-independent pathways. The ESCRT machinery, composed of several protein complexes (ESCRT-0, I, II, and III), facilitates cargo selection, membrane invagination, and vesicle scission. In contrast, the ESCRT-independent mechanism relies on lipid raft domains, ceramide, and tetraspanin proteins such as CD9, CD63, and CD81 for vesicle formation.[1]

Once formed, MVBs have two possible fates: fusion with lysosomes for degradation or fusion with the plasma membrane, leading to the release of ILVs as exosomes into the extracellular space. The secretion process is regulated by small GTPases (e.g., Rab27a, Rab11, and Rab35) and cytoskeletal elements. After release, exosomes interact with recipient cells through receptor-ligand binding, membrane fusion, or endocytosis, thereby influencing numerous physiological and pathological processes, including immune modulation, tumor progression, and tissue regeneration.[3] Overall, understanding the biology and biogenesis of exosomes provides fundamental insights into their role in cellular communication and therapeutic applications in drug delivery and regenerative medicine.[3]

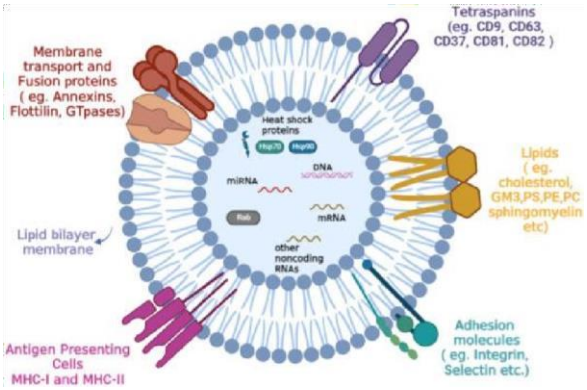

Fig. 2: Biogenesis of exosome.

Isolation of Exosomes

Exosomes are tiny vesicles released by cells, so they need special techniques to separate them from blood, urine, or cell culture fluids. Several methods are used to isolate exosomes, each with advantages and disadvantages.[2]

1. Ultracentrifugation

Ultracentrifugation is the most common method. The sample is spun at very high speeds in steps:

- Low-speed spin: Removes cells and large debris.
- Medium-speed spin: Removes bigger vesicles.
- High-speed spin (100,000 × g): Pellets exosomes at the bottom.

The pellet is washed to remove impurities. This method is widely used but takes a long time and requires expensive machines.

2. Ultrafiltration

Ultrafiltration uses special filters with tiny pores. The sample is passed through these filters so that only small particles like exosomes pass through, while larger ones are blocked. This method is faster and simpler than ultracentrifugation but may slightly damage exosomes if pressure is too high.

3. Precipitation

Precipitation uses chemicals or polymers to make exosomes clump together and settle at the bottom when centrifuged. This method is easy, quick, and does not need special machines. However, other unwanted particles may also be collected, reducing purity.

4. Size-Exclusion Chromatography (SEC)

SEC separates particles based on size using a column filled with a gel-like material. Large particles pass through quickly, while smaller ones like exosomes take longer to come out. This method gives high-purity exosomes and keeps them intact, making it suitable for research and clinical use.

5. Microfluidic Techniques

Microfluidics is a modern method using small lab-on-a-chip devices. Exosomes are separated using electric or magnetic fields or size-based channels. This technique is fast, precise, and requires very small sample volumes. It is promising for clinical applications but still expensive.

Characterization of Exosomes

After isolating exosomes, it is important to check their size, shape, and composition to confirm that they are pure and suitable for research or drug delivery. Several methods are commonly used:[6]

1. Transmission Electron Microscopy (TEM)

TEM uses a powerful microscope to take detailed images of exosomes. It shows their round or cup-shaped structure and confirms their size, which is usually 30–150 nanometers.

2. Nanoparticle Tracking Analysis (NTA)

NTA measures both the size and concentration of exosomes in a sample. It tracks the movement of individual particles in liquid using light scattering.

3. Dynamic Light Scattering (DLS)

DLS is another technique that measures particle size based on how exosomes scatter light in a solution. It helps confirm uniformity in size distribution.

4. Protein Marker Analysis

Exosomes carry specific proteins on their surface, such as CD9, CD63, CD81, and Alix. Techniques like Western Blotting or Flow Cytometry are used to detect these markers, ensuring the particles are true exosomes.

5. Zeta Potential Measurement

This measures the surface charge of exosomes, which helps determine their stability in solution. Stable exosomes are less likely to clump together and are better for drug delivery.[5]

Drug Loading into Exosomes

Drug loading is the process of putting medicine or therapeutic molecules inside exosomes so they can safely reach the target cells in the body. There are two main ways to do this: passive loading and active loading.[15,19]

1. Passive Loading

- Exosomes are simply mixed with the drug.
- Small or fat-soluble drugs naturally enter the exosomes over time.
- Simple method but usually less efficient, meaning not much drug gets inside.

2. Active Loading

Uses special techniques to improve drug entry into exosomes:

- Electroporation: A small electric pulse makes tiny pores in the exosome membrane so drugs or RNA can enter.
- Sonication: Sound waves temporarily open the membrane for drug entry.
- Extrusion: Exosomes and drugs are forced through tiny filters to mix together.
- Freeze–thaw cycles: Repeated freezing and thawing opens and closes the membrane, allowing drug entry.

3. Cell-Based Loading

Drugs or genetic materials are first introduced into the donor cells. These cells naturally package the drugs into exosomes during secretion. Useful for RNA or gene delivery.

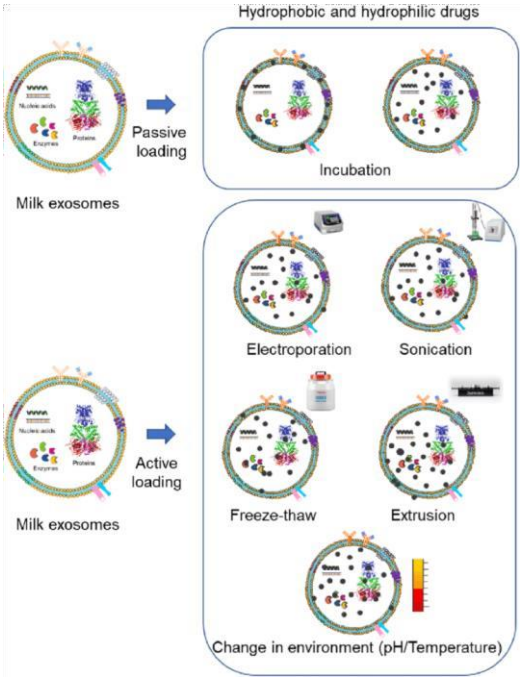

Fig. 3: Drug loading of exosome[5]

Applications of Exosomes in Drug Delivery

Exosomes are natural carriers that can deliver drugs, genes, and proteins safely and effectively. Their small size, natural origin, and ability to target specific cells make them very useful in medicine.[5]

1. Cancer Treatment

Exosomes can deliver anticancer drugs or genetic materials (like siRNA) directly to tumor cells. This targeted delivery reduces side effects on healthy tissues. For example, exosomes loaded with doxorubicin have been studied for effective cancer therapy.

2. Neurological Disorders

Exosomes can cross the blood–brain barrier, which most drugs cannot pass. They can carry drugs or RNA molecules for Alzheimer's, Parkinson's disease, or stroke, helping protect and repair brain cells.

3. Regenerative Medicine

Exosomes from stem cells can help repair tissues and promote healing. They are used in skin, heart, and nerve tissue repair by transferring growth factors and proteins that stimulate cell regeneration.

4. Immune System Modulation

Exosomes can carry antigens or immune regulators to stimulate or modulate the immune system. They are being explored for vaccine development and for treating autoimmune diseases.

5. Gene Therapy

Exosomes can deliver mRNA, siRNA, or other genetic materials into target cells. They protect these molecules from degradation, allowing efficient gene therapy.

6. Infectious Diseases

Exosomes can carry antiviral or antibacterial drugs directly to infected cells, improving treatment effectiveness and reducing side effects.[19,6]

Challenges and Future Scope of Exosome-Based Drug Delivery

Challenges

Even though exosomes are promising for drug delivery, several challenges still need to be addressed:

1. Low Yield and Difficult Isolation

Producing enough pure exosomes is difficult. Methods like ultracentrifugation are slow, require expensive equipment, and often give low amounts of exosomes.

2. Low Drug Loading Efficiency

It can be hard to load enough drug or genetic material into exosomes, and some methods may damage the exosomes.

3. Storage and Stability

Exosomes may lose their activity or clump together if not stored under the right conditions.

4. Lack of Standardization

Different labs use different isolation and testing methods, making it hard to compare results. Standard procedures are needed for consistency.

5. Safety and Regulatory Issues

Since exosomes come from living cells, it is important to ensure they are safe, pure, and free from harmful materials before use in humans. Regulatory approval is still limited.[11]

Future Scope

Despite these challenges, The use of exosomes in drug delivery provides new opportunities for developing safe and targeted treatments with high therapeutic efficiency.". Scientists are developing engineered exosomes that can target specific organs or cells more effectively.[9]

New technologies such as microfluidics, 3D cell culture, and genetic engineering are being used to improve production and quality. In the future, synthetic exosomes that mimic natural ones may also be used for large-scale drug delivery.[9] Exosomes may play an important role in personalized medicine, delivering treatments specifically designed for each patient based on their disease profile.[5]

CONCLUSION

Exosome-based drug delivery systems have emerged as one of the most promising and biocompatible nanoplatforms for targeted therapy. These naturally derived vesicles possess unique properties such as nanoscale size, low immunogenicity, and the ability to cross biological barriers, making them ideal candidates for transporting therapeutic

agents like nucleic acids, proteins, and small-molecule drugs. Their potential in cancer therapy, neurodegenerative diseases, and regenerative medicine highlights their broad biomedical significance.[1]

However, certain challenges—such as limited yield during isolation, difficulties in large-scale manufacturing, and a lack of standardized characterization protocols—still restrict their clinical translation. Addressing these limitations through advancements in exosome engineering, purification technologies, and regulatory frameworks will enhance their therapeutic applicability.[2]

In conclusion, continued interdisciplinary research and technological innovation will pave the way for exosomes to evolve into efficient, safe, and clinically viable drug delivery systems, ultimately contributing to the future of personalized and precision medicine.

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