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Review Article

Exosomes as Advanced Nanocarriers for Targeted Drug Delivery: Recent Progress, Engineering Strategies and Translational Challenges

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ABSTRACT

Exosomes are nanosized extracellular vesicles that have emerged as biologically derived nanocarriers for targeted drug delivery. Their lipid-bilayer architecture, endogenous membrane proteins, low intrinsic immunogenicity, ability to protect labile cargo, and capacity to interact with recipient cells provide a distinct platform for transporting small molecules, proteins, messenger RNA, microRNA, short interfering RNA, and genome-editing components. This review summarizes recent advances from 2020 to 2026, with particular emphasis on 2023–2026, in exosome biogenesis, isolation, characterization, cargo-loading strategies, surface engineering, targeting mechanisms, therapeutic applications, and clinical translation. Endogenous loading through donor-cell engineering and exogenous techniques such as incubation, electroporation, sonication, extrusion, freeze–thaw cycling, and microfluidic or acoustofluidic processing are compared. Surface-functionalization approaches—including ligand display, antibody or aptamer conjugation, peptide insertion, genetic fusion, click chemistry, and hybridization with synthetic nanomaterials—are discussed in relation to tumor, brain, liver, bone, inflammatory and infectious disease targeting. Recent evidence shows that engineered exosomes can improve cellular uptake, tissue penetration, controlled intracellular release and therapeutic index relative to free drugs, although performance remains highly dependent on donor-cell source, isolation process, loading method, cargo physicochemical properties and disease model. The major barriers to clinical translation are heterogeneity, incomplete product definition, limited loading reproducibility, low yield, scalability, storage stability, biodistribution, potency testing, safety evaluation and evolving regulatory classification. Standardized manufacturing under good manufacturing practice, orthogonal characterization, quantitative potency assays and well-designed clinical studies are therefore essential. Exosomes are best viewed as promising but not yet universally validated precision nanomedicines; their future success will depend on reproducible engineering and clinically meaningful quality-by-design strategies.

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INTRODUCTION

The therapeutic performance of a drug is determined not only by molecular potency but also by its solubility, stability, biodistribution, cellular uptake, release kinetics and exposure at the intended site of action. Conventional dosage forms and many synthetic nanocarriers can improve one or more of these properties, yet non-specific distribution, premature clearance, immune recognition, dose-limiting toxicity and poor penetration into difficult tissues remain important limitations. These problems are particularly relevant for nucleic acids, proteins, peptides and hydrophobic anticancer agents, whose activity may be reduced by enzymatic degradation, inadequate intracellular delivery or accumulation in healthy organs.

Exosomes are a subset of small extracellular vesicles released after fusion of multivesicular bodies with the plasma membrane. They are surrounded by a lipid bilayer and carry proteins, lipids, metabolites and nucleic acids. Their biological role in intercellular communication gives them an inherent capacity for membrane interaction and cell entry. In drug-delivery research, this natural interface has been exploited to protect therapeutic cargo, improve circulation or tissue access, and facilitate uptake by selected recipient cells [1–5].

The field has progressed from using unmodified vesicles to engineering producer cells, modifying isolated vesicles, constructing exosome–liposome hybrids and applying microfluidic manufacturing. Between 2023 and 2026, the literature has increasingly focused on precision surface modification, large-molecule and gene-editing cargo, scalable bioprocessing, single-vesicle characterization and clinical translation [6–12]. However, the term exosome is still used inconsistently in the literature, and many studies report mixed extracellular-vesicle populations. Accordingly, this review uses exosome when the source study identifies an endosomal small-EV product, while recognizing the broader extracellular-vesicle terminology recommended by current consensus guidance [13].

The objective of this review is to provide an M.Pharm-level pharmaceutics synthesis of exosomes as advanced nanocarriers for targeted drug delivery, emphasizing formulation-relevant principles, recent evidence, translational constraints and future development priorities.

2. SCOPE AND LITERATURE-REVIEW APPROACH

This narrative review was prepared using recent peer-reviewed literature published from January 2020 through September 2026, with emphasis on 2023–2026 publications. Sources included PubMed/PMC-indexed reviews, systematic reviews, original preclinical studies, clinical-trial analyses and methodological consensus papers. Search concepts included exosome, extracellular vesicle, targeted drug delivery, engineered exosome, cargo loading, surface modification, bioprocessing, clinical translation and nanocarrier. The present article is a structured narrative review rather than a PRISMA systematic review; therefore, quantitative meta-analysis was not attempted.

3. EXOSOMES: BIOLOGICAL BASIS AND PHARMACEUTICAL RELEVANCE

3.1 Biogenesis and composition

Exosome formation begins with endocytosis and inward budding of the endosomal membrane, followed by the formation of intraluminal vesicles within multivesicular bodies. These bodies either fuse with lysosomes for degradation or with the

plasma membrane for release of intraluminal vesicles into the extracellular space. ESCRT-dependent and ESCRT-independent pathways, tetraspanins, ceramide metabolism and Rab/SNARE-mediated trafficking contribute to vesicle formation and secretion [3,14,15].

The exosomal membrane commonly contains tetraspanins such as CD9, CD63 and CD81, adhesion proteins, integrins, heat-shock proteins, phosphatidylserine and glycosylated surface molecules. The lumen can contain mRNA, microRNA, siRNA, long non-coding RNA, circular RNA, proteins and small metabolites. This composition is not fixed: it depends on donor-cell identity, culture conditions, hypoxia, inflammation, disease state, passage number, serum source and isolation method [4,16].

From a pharmaceutics perspective, the lipid bilayer protects hydrophilic cargo from extracellular nucleases and proteases, while the membrane can accommodate hydrophobic molecules. The nanoscale size and biological surface can promote tissue penetration and cellular uptake. Nevertheless, the same biological complexity that gives exosomes their functionality also creates batch variability and complicates quality control.

3.2 Advantages and Limitations Versus Synthetic Nanocarriers

Table 1. Pharmaceutical Advantages and Limitations of Exosomes Compared with Synthetic Nanocarriers.

Feature	Potential Advantage of Exosomes	Important Limitation
Biocompatibility	Biological membrane and endogenous proteins may reduce acute material-associated toxicity.	Source- and disease-dependent cargo may cause unintended biological effects.
Cargo protection	Lipid bilayer protects RNA, proteins and some small molecules.	Loading capacity and encapsulation efficiency are variable.
Targeting	Native tropism and engineered ligands can support cell-specific delivery.	Natural targeting is often incomplete; liver, spleen and lung uptake remain common.
Biological barriers	Some preparations can cross or interact with the blood–brain barrier and mucus layers.	Barrier crossing is context-dependent and difficult to quantify.
Immunogenicity	Often lower than viral vectors and some cationic systems.	Repeated dosing, impurities or allogeneic components may activate immunity.
Manufacturing	Producer cells can generate complex biologic vesicles.	Low yield, heterogeneity and difficult GMP standardization.
Clinical translation	Multiple EV clinical studies demonstrate feasibility of administration and monitoring.	Few products have reached definitive regulatory approval as drug carriers.

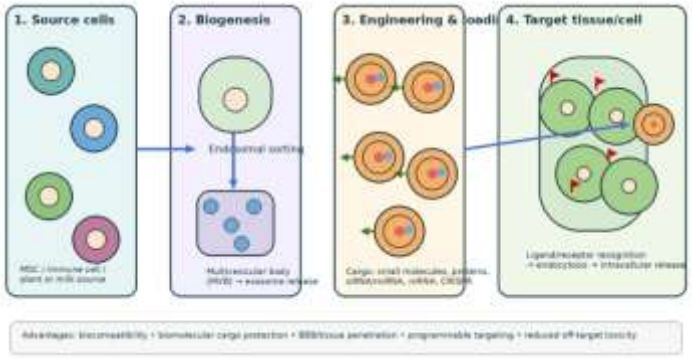

Figure 1. Schematic workflow of exosome generation, cargo loading, surface engineering and target-cell delivery. The figure is an original schematic prepared for this review.

4. ISOLATION, PURIFICATION AND CHARACTERIZATION

4.1 Isolation and purification

Exosome isolation is a critical formulation step because recovery, purity, membrane integrity and biological activity depend on the process. Differential ultracentrifugation remains widely used, but shear stress, aggregation, operator dependence and co-isolation of protein or lipoprotein contaminants limit reproducibility. Density-gradient ultracentrifugation can improve purity but is time-consuming. Ultrafiltration and tangential-flow filtration support larger volumes, while size-exclusion chromatography is relatively gentle and preserves vesicle structure but can dilute the product. Polymer precipitation is simple and scalable but frequently co-precipitates non-vesicular proteins. Immunoaffinity capture offers high specificity for selected markers but is costly and poorly suited to bulk manufacturing. Microfluidic and acoustofluidic systems are emerging for rapid, low-volume and potentially automated processing [17–22].

Table 2. Common Exosome Isolation Approaches and Their Pharmaceutical Implications.

METHOD	STRENGTHS	LIMITATIONS	FORMULATION RELEVANCE
Differential ultracentrifugation	Common, no specialized consumables	Low throughput; aggregation; possible damage	Useful for discovery; less suitable as a stand-alone GMP process
Density-gradient centrifugation	Improved purity and separation by density	Long processing time; limited scale	Good for mechanistic studies and reference batches
Ultrafiltration / TFF	Scalable concentration and buffer exchange	Membrane fouling; size-similar contaminants	Promising for process intensification
Size-exclusion chromatography	Gentle; good recovery of vesicle integrity	Sample dilution; limited loading capacity	Useful polishing step
Polymer precipitation	Simple and low equipment burden	Protein/lipoprotein contamination	Generally requires orthogonal polishing
Immunoaffinity	High marker specificity	Expensive; capture bias; not bulk scalable	Useful for analytical subpopulations
Microfluidics / acoustofluidics	Rapid, low-volume, potentially automated	Device cost and scale-up validation	Emerging platform for integrated isolation and loading

4.2 Characterization and Release Testing

A single analytical method cannot define an exosome product. A fit-for-purpose panel should include particle concentration and size distribution by nanoparticle-tracking analysis or an equivalent technique; morphology by transmission electron microscopy or cryo-electron microscopy; protein identity by immunoblotting, flow cytometry or high-sensitivity immunoassay; cargo profiling by qPCR, sequencing, proteomics or mass spectrometry; and impurity testing for host-cell proteins, DNA, albumin, lipoproteins, endotoxin, mycoplasma and residual process reagents. Recent consensus guidance emphasizes reporting the source, collection conditions, isolation method, storage, particle-to-protein ratio, markers and functional potency rather than relying on the word exosome alone [13,23].

Identity: positive EV-associated markers such as CD9, CD63, CD81 and source-specific markers; absence or reduction of non-EV contaminants.

Purity: particle/protein ratio, removal of serum proteins and lipoproteins, endotoxin and microbial testing.

Physical quality: particle size distribution, concentration, morphology, zeta potential where relevant and aggregation state.

Cargo quality: drug content, encapsulation efficiency, free-drug fraction, RNA/protein integrity and potency.

Functional potency: target-cell uptake, intracellular release, gene-silencing or protein activity, and disease-relevant bioassays.

Stability: particle recovery, size, cargo retention and potency after intended storage, freeze–thaw and administration conditions.

5. CARGO-LOADING STRATEGIES

Cargo loading can be classified as pre-loading (endogenous loading during vesicle biogenesis) or post-loading (direct incorporation into isolated vesicles). The optimal approach depends on molecular size, hydrophobicity, charge, membrane permeability, sensitivity to shear or electrical stress, and the desired release profile [24–27].

Table 3. Exosome cargo-loading strategies relevant to targeted drug delivery.

Strategy	Typical Cargo	Advantages	Limitations
Passive incubation / co-incubation	Hydrophobic small molecules, some drugs	Simple; mild; preserves membrane structure	Often low loading for hydrophilic or macromolecular cargo
Donor-cell incubation or transfection	miRNA, siRNA, mRNA, proteins, small molecules	Uses natural biogenesis; good cargo bioactivity	Variable sorting; donor-cell stress and heterogeneous product
Electroporation	RNA, oligonucleotides, some proteins	Rapid; can improve loading of hydrophilic cargo	Aggregation, RNA precipitation and membrane damage possible
Sonication	Small molecules, siRNA and proteins	High loading potential; relatively fast	May alter membrane proteins and vesicle integrity
Extrusion	Small molecules, proteins, nucleic acids	Can generate uniform vesicles and facilitate loading	Mechanical stress; possible loss of native properties
Freeze–thaw cycling	Small molecules and some proteins	Low equipment burden	Low or variable efficiency; damage to labile cargo
Microfluidics / acoustofluidics	Complex and combination cargo	Controlled mixing, short processing time, improved reproducibility	Device design and scale-up remain developmental
Hybridization / membrane fusion	Drug-loaded liposomes, nanoparticles, polymers	Combines exosome biology with synthetic loading capacity	More complex characterization and regulatory pathway

5.1 Small-Molecule Drugs

Hydrophobic drugs such as doxorubicin, paclitaxel, docetaxel, curcumin, berberine, quercetin, luteolin, rapamycin and atovaquone have been incorporated into cell-, milk- or plant-derived vesicles. Recent studies report improved solubility, protection from premature metabolism, enhanced uptake and reduced exposure of healthy cells. Examples include docetaxel-loaded exosomes for non-small-cell lung cancer, curcumin-loaded plant or MSC-derived vesicles for inflammatory diseases, rapamycin-loaded vesicles for glioblastoma or uveitis, and drug-loaded vesicles for antimicrobial or antifungal therapy [28–37].

5.2 Nucleic Acids, Proteins And Genome-Editing Cargo

Exosomes are especially attractive for RNA delivery because the lipid bilayer can protect nucleic acids from nucleases and support cytosolic uptake. Engineered vesicles carrying siRNA against KRASG12D, BACE1, CTGF or other disease targets, as well as miRNA, mRNA and antisense oligonucleotides, have demonstrated gene-silencing or protein-replacement effects in preclinical models. Surface display of RVG, GPC3, ApoB100-derived peptides, integrin-binding ligands and other targeting elements has been used to direct RNA or protein cargo to neurons, hepatocytes, tumors or immune cells [38–45]. Delivery of CRISPR–Cas systems is an emerging area, but it requires careful control of cargo size, editing specificity, off-target activity and long-term safety.

6. TARGETING AND SURFACE-ENGINEERING STRATEGIES

Targeting may be passive, endogenous or actively engineered. Passive targeting results from circulation, vascular permeability, tissue retention and uptake by the mononuclear phagocyte system. Endogenous targeting is determined by donor-cell origin, membrane proteins, integrins, glycans and chemokine receptors. Active targeting introduces a ligand that recognizes a disease-associated receptor. Recent reviews distinguish pre-isolation engineering—genetic, metabolic or donor-cell membrane engineering—from post-isolation modification—chemical conjugation, lipid insertion, click chemistry, physical fusion or hybridization [8,46–50].

Table 4. Representative surface-engineering strategies for targeted delivery.

Engineering Approach	Representative Targeting Element	Potential Application	Key Concern
Genetic fusion to exosome membrane proteins	Lamp2b–RVG; Lamp2b–anti-GPC3 scFv; CD63 fusions	Brain, hepatocellular carcinoma and gene therapy	Expression level, orientation and immunogenicity
Peptide or aptamer display	RGD, RVG, AS1411, bone-targeting peptides	Tumor, brain, bone and inflammatory sites	Ligand density and receptor heterogeneity
Antibody or nanobody display	EGFR, HER2 or tumor-associated antigens	Precision oncology and theranostics	Cost, stability and Fc-related immune effects
Chemokine-receptor engineering	CXCR4 and related receptors	Inflammatory tissue and tumor microenvironment	Potentially altered biodistribution
Metabolic labeling / click chemistry	Azide–DBCO or other bioorthogonal pairs	Tracking and modular targeting	Reaction control and residual reagents
Lipid insertion / post-isolation conjugation	Hydrophobic peptide, PEG-lipid or ligand conjugate	Rapid surface functionalization	Membrane perturbation and ligand shedding
Hybrid exosome–liposome or nanoparticle system	Drug-loaded liposome, SPION or polymer component	Higher loading, magnetic guidance or combination therapy	Product complexity and regulatory classification

6.1 Cellular Uptake and Intracellular Trafficking

Following circulation and tissue distribution, exosomes interact with target cells through receptor–ligand binding, electrostatic interactions, phagocytosis, macropinocytosis, clathrin-mediated endocytosis, caveolae-mediated uptake or membrane fusion. The final therapeutic outcome depends not only on uptake but also on

endosomal escape and cytosolic release. Therefore, high fluorescence uptake does not necessarily prove functional cargo delivery; potency should be measured using a biological readout such as gene silencing, protein activity, apoptosis or disease-specific repair [51–54].

7. THERAPEUTIC APPLICATIONS

7.1 Oncology

Cancer is the most extensively studied application because exosomes can carry chemotherapeutics, gene-silencing agents, immunomodulators and photosensitizers. Preclinical studies have reported enhanced delivery of doxorubicin, paclitaxel, docetaxel, gemcitabine, cisplatin, bleomycin, berberine, curcumin and combination payloads. Examples include SDF1–CXCR4-mediated osteosarcoma targeting, RGD or antibody targeting of glioblastoma and colorectal cancer, macrophage-derived vesicles for breast cancer, and TRAIL-engineered exosomes carrying cisplatin for cervical cancer. Combination strategies, such as simultaneous delivery of a cytotoxic drug and miRNA or a photosensitizer and immunomodulator, are increasingly prominent [31,34,55–61].

7.2 Central Nervous System Delivery

The blood–brain barrier makes CNS delivery a major target for exosome engineering. RVG-functionalized vesicles, Angiopep-2-modified exosomes, neural-stem-cell-derived vesicles and exosome–drug combinations have been investigated for glioblastoma, Alzheimer's disease, Parkinson's disease, stroke and CNS infections. Reported cargos include siRNA, miRNA, rifampicin, donepezil, quercetin, rapamycin, cetuximab and doxorubicin. Although several studies demonstrate improved brain accumulation or therapeutic response in rodents, translation requires rigorous assessment of human BBB transport, dose scaling, off-target neural effects and repeated-administration safety [39,40,62–65].

7.3 Inflammatory, Autoimmune and Regenerative Disorders

MSC-, macrophage-, platelet-, plant- and milk-derived vesicles have been investigated for spinal cord injury, rheumatoid arthritis, osteoarthritis, periodontitis, alopecia areata, uveitis, diabetes, wound healing, corneal injury and inflammatory bowel disease. The therapeutic effect may arise from the delivered drug, endogenous vesicle cargo, immunomodulatory membrane components or a combination. Hydrogel–exosome systems and microneedle arrays are being developed to increase local retention and prolong release, which is particularly useful for skin, bone and wound applications [32,36,66–71].

7.4 Infectious Diseases

Macrophage-derived exosomes loaded with atovaquone, lysostaphin and vancomycin, iPSC-derived exosomes carrying amphotericin B, and plant or bacterial vesicles containing antibiotics illustrate the potential for intracellular antimicrobial delivery. These systems may exploit natural uptake by macrophages or infected cells and can increase drug concentration at intracellular pathogen reservoirs. However, source-cell safety, endotoxin control, antimicrobial resistance, immunological effects and scale-up require careful evaluation.

8. Clinical Translation and Regulatory Considerations

Clinical translation has accelerated, but the field remains early. A 2024 systematic review of EV clinical trials found substantial variability in

source, isolation, characterization and reporting, with only a minority of studies using defined EV subpopulations. A 2026 analysis of ClinicalTrials.gov identified 355 human-derived EV trials initiated through the end of 2025, including 148 interventional studies; MSC-derived EVs were common in interventional work, while oncology, inflammatory disorders, respiratory disease and regenerative medicine were recurrent areas [10,11]. These data demonstrate clinical interest but do not equate to regulatory approval of exosome drug-delivery products.

Table 5. Key translational risks and quality-by-design responses.

Translation Domain	Current Issue	Recommended Pharmaceutical Response
Source material	Donor-cell and culture-condition variability	Define a qualified master cell bank, passage limits and culture medium.
Isolation and purification	Different methods yield different particle populations	Use a validated, scalable and orthogonal purification train.
Product identity	"Exosome" may include heterogeneous small EVs	Report MISEV-aligned source, markers, size, purity and function.
Cargo loading	Variable encapsulation and free-drug contamination	Quantify total, encapsulated and free cargo with validated assays.
Potency	No universal release assay	Use mechanism-linked cell-based potency assays.
Sterility and safety	Endotoxin, mycoplasma, residual DNA and immunogenicity concerns	Establish release specifications and repeat-dose toxicology.
Stability	Loss of membrane integrity or activity during storage	Develop cryoprotectant, lyophilization or controlled-temperature strategies.
Regulatory classification	Biologic, advanced therapy, drug or combination-product status may vary	Engage regulators early and prepare a complete CMC package.

9. MAJOR CHALLENGES AND FUTURE DIRECTIONS

Heterogeneity: donor-cell source, disease state and culture conditions change membrane composition and cargo.

Scalability: ultracentrifugation and affinity capture are difficult to translate directly to high-volume GMP production.

Loading reproducibility: encapsulation efficiency and cargo localization differ between methods and laboratories.

Targeting specificity: ligand-receptor heterogeneity, protein corona formation and reticuloendothelial uptake can reduce precision.

Endosomal escape: internalization does not guarantee cytosolic delivery or functional release.

Storage stability: freezing, thawing, agitation, concentration and container interactions can alter size and potency.

Analytical standardization: single-particle measurements, orthogonal methods and potency assays are required.

Safety and immunology: allogeneic source components, oncogenic cargo, residual DNA, thrombogenicity and repeat-dose effects need evaluation.

Regulatory science: product definition, comparability after process changes and clinical endpoints remain incompletely harmonized.

9.1 Promising development directions

Quality-by-design manufacturing using stirred-tank or perfusion bioreactors, tangential-flow filtration and in-line analytics.

Precision producer-cell engineering to control cargo sorting and membrane ligand display.

Microfluidic and acoustofluidic systems that integrate isolation, loading and surface modification.

Hybrid exosome–liposome or exosome–polymer systems to increase drug loading while retaining biological uptake.

Lyophilized or spray-dried formulations for improved storage and distribution, provided membrane functionality is preserved.

Single-vesicle multi-omics and machine-learning models to link composition with potency and biodistribution.

Clinically relevant large-animal studies and dose-ranging trials with validated pharmacokinetic and pharmacodynamic biomarkers.

10. CONCLUSION

Exosomes have evolved from biological messengers into highly adaptable nanocarriers capable of transporting small molecules, proteins and nucleic acids to selected tissues and cells. Their major pharmaceutical advantages are biocompatibility, endogenous membrane functionality, cargo protection, potential barrier penetration and the possibility of genetic or chemical surface engineering. Recent work from 2023–2026 has expanded the field toward ligand-displayed vesicles, gene-editing cargo, hybrid nanocarriers, continuous manufacturing and clinical-trial analysis. Nevertheless, exosome delivery is not yet a universally standardized technology. Heterogeneity, limited yield, inconsistent loading, incomplete potency assays, biodistribution uncertainty, storage instability and regulatory ambiguity continue to restrict clinical translation. For M.Pharm pharmaceutics, the most important development principle is that exosomes should be treated as complex biological drug products requiring a defined source, controlled process, validated characterization, mechanism-based potency and rigorous safety evaluation. With these controls, exosome-based targeted delivery may become a practical component of precision nanomedicine rather than remaining only a promising preclinical concept.

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