



EXOSOMES AS NEXT-GENERATION DRUG DELIVERY SYSTEMS: CURRENT ADVANCES AND FUTURE PROSPECTS

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Abstract:

Exosomes are nanoscale extracellular vesicles (approximately 30–150 nm) that naturally transport proteins, lipids and nucleic acids between cells. Their biological membrane, intrinsic cellular uptake and potential biocompatibility have made them attractive candidates for therapeutic delivery, offering a biological alternative to synthetic nanocarriers such as liposomes and polymeric nanoparticles, which can be limited by poor solubility, instability, rapid clearance and nonspecific toxicity. Since 2020, research has increasingly focused on loading small-molecule drugs, proteins and nucleic acids into exosomes and engineering their surfaces to improve targeting, stability and circulation time. Reported applications span cancer, neurological, cardiovascular and inflammatory disease, with hybrid exosome–nanoparticle systems emerging as a further engineering strategy. Despite strong preclinical promise, clinical translation remains constrained by vesicle heterogeneity, purification and characterization difficulties, variable loading efficiency, rapid clearance, storage instability, scalability and unresolved regulatory standardization. This review critically synthesizes the biological basis of exosome-mediated delivery, drug-loading and engineering strategies, therapeutic applications, isolation and characterization methods, current research advances (2020–2025), major challenges, clinical translation, and a comparative appraisal against synthetic nanocarriers, concluding with priorities for future research.

Keywords: Exosomes, Extracellular Vesicles, Drug Delivery, Exosome Engineering, Targeted Therapy, Nanomedicine.

1. Introduction

Effective drug delivery aims to achieve therapeutic concentrations at a target site while minimizing exposure of healthy tissue. Conventional small-molecule and biologic formulations are frequently constrained by poor aqueous solubility, chemical or enzymatic instability, unfavourable pharmacokinetics, and nonspecific tissue distribution that drives systemic toxicity. Nanotechnology-based carriers - liposomes, polymeric nanoparticles

and lipid nanoparticles - were developed to address these limitations, and each has achieved clinical use. Exosomes represent a biologically derived alternative to these synthetic platforms, arising from an intrinsic, evolutionarily conserved role in intercellular communication rather than from de novo chemical design (1,2,3,4). Exosomes are commonly described as small extracellular vesicles (sEVs), typically 30–150 nm in diameter, although the reported size range varies with cellular source, isolation method and analytical technique. They possess a lipid bilayer that encloses and partially protects a molecular cargo of proteins, lipids and nucleic acids. This natural capacity to package and transport biological material - combined with reported biocompatibility, low immunogenicity, and an ability to traverse some physiological barriers - has motivated their investigation as therapeutic carriers (1,3,5).

The field has progressed from the characterization of natural, unmodified vesicles toward drug-loaded, surface-engineered and hybrid exosome systems designed for defined therapeutic purposes. This trajectory mirrors, in compressed form, the maturation of earlier nanocarrier platforms: an initial phase establishing proof of concept, followed by a phase of engineering refinement, and finally a phase in which biodistribution, pharmacokinetics, manufacturing and quality control become the rate-limiting considerations for clinical translation. Current research increasingly emphasizes these translational variables rather than further proof-of-concept demonstrations (6,7,8,9).

This review critically synthesizes the biological basis of exosome-mediated delivery, cargo-loading and engineering strategies, therapeutic applications, isolation and characterization approaches, research advances between 2020 and 2025, major challenges and research gaps, clinical translation and regulatory considerations, and a comparative appraisal of exosomes against synthetic nanocarriers, concluding with priorities for future work. Throughout, findings are presented according to their level of evidence - in vitro, preclinical/animal, or clinical - so that biological plausibility is not conflated with demonstrated therapeutic benefit.

2. Biological basis and characteristics of exosomes

2.1 Exosome biogenesis

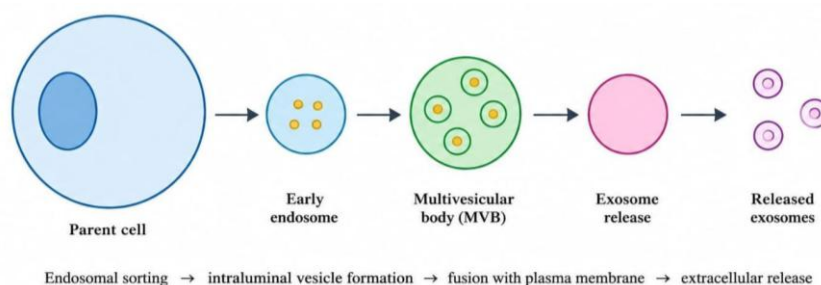


Figure 1: Simplified schematic of exosome biogenesis via the endosomal pathway

Exosome formation is associated with the endosomal pathway. Inward budding of the plasma membrane generates early endosomes, which mature into late endosomes containing intraluminal vesicles (ILVs) formed by a second round of inward budding of the limiting endosomal membrane; the resulting compartment is termed a multivesicular body (MVB). Cargo sorting into ILVs can proceed through an ESCRT (endosomal sorting complex required for transport)-dependent mechanism, or through ESCRT-independent routes involving ceramide and tetraspanin-enriched membrane microdomains; both mechanisms are thought to operate, to varying degrees, in different cell types and physiological states. Fusion of the MVB with the plasma membrane, a step associated with

specific Rab GTPases, releases the ILVs into the extracellular space as exosomes, while MVBs that instead fuse with lysosomes direct their contents toward degradation rather than secretion (3,8).

This biogenesis pathway distinguishes exosomes mechanistically from other extracellular vesicle subtypes, such as microvesicles, which bud directly outward from the plasma membrane, and apoptotic bodies, which form during programmed cell death. Because these subtypes overlap substantially in size and can co-purify, biogenesis alone is rarely sufficient to classify a given isolated vesicle population with certainty.

2.2 Molecular composition

Exosome composition is determined by the parental cell type, its physiological or pathological state, and the culture or isolation conditions used to obtain the vesicles. Commonly reported protein constituents include tetraspanins (e.g., CD9, CD63, CD81), ESCRT-associated proteins (e.g., Alix, TSG101), heat-shock proteins, and membrane-trafficking proteins, several of which are used as operational markers of exosomal identity rather than as proof of a single biogenesis route. Lipid composition is typically enriched in cholesterol, sphingomyelin and phosphatidylserine relative to the parental plasma membrane, contributing to bilayer rigidity and stability. The nucleic-acid cargo can include messenger RNA, microRNA, long non-coding RNA, and fragments of DNA, which together with the protein cargo can contribute to intercellular signalling in the recipient cell (3,8,13).

2.3 Biological properties relevant to drug delivery

Table 1: Potential advantages of exosomes as drug-delivery vehicles and associated caveats

Potential advantage	Relevance to drug delivery	Caveat
Biological origin	Potential biocompatibility and favourable cellular interaction	Depends strongly on source, donor cell state and processing
Lipid bilayer	May protect some cargo classes from enzymatic degradation	Does not guarantee efficient intracellular release of cargo
Natural uptake mechanisms	Can enter recipient cells via endocytosis or membrane fusion	Uptake is not automatically tissue-specific
Cargo diversity	Can in principle carry drugs, proteins and nucleic acids	Loading efficiency varies substantially by cargo class and method
Engineerability	Surface and genetic engineering can add targeting or functional elements	Engineering can alter safety, immunogenicity and pharmacokinetics
Precision-delivery potential	Disease- or cell-specific delivery may be achievable	Clinical evidence for superiority over synthetic carriers remains limited

Several biological properties underpin interest in exosomes as delivery vehicles: a biological (rather than fully synthetic) origin that may confer biocompatibility and reduced immunogenicity depending on source and processing; a lipid bilayer that can protect some classes of cargo from enzymatic degradation; a natural capacity for uptake by recipient cells through mechanisms including endocytosis, membrane fusion and receptor-mediated interactions; and the ability to carry chemically diverse cargo - small molecules, proteins and nucleic acids - within a single carrier. Surface engineering can further extend these properties toward tissue- or cell-specific targeting. Table 1 summarizes these potential advantages alongside the caveats that qualify each one; the central methodological point is that these are properties that make exosomes attractive candidates, not evidence, in isolation, that they outperform synthetic carriers in a given application (1,5,6).

3. Exosomes as drug-delivery vehicles

Building on the biological properties, exosomes have been investigated as delivery vehicles for a broad range of cargo classes, including chemotherapeutic small molecules, proteins and peptides, and nucleic acids such as siRNA, miRNA and mRNA. The workflow common to most exosome-based delivery systems comprises four stages: (i) selection and culture of a donor cell source; (ii) isolation and purification of the secreted vesicles; (iii) loading of the therapeutic cargo, achieved either by modifying the parent cell (endogenous loading) or by direct manipulation of isolated vesicles (exogenous loading); and (iv) administration and biodistribution to the intended target tissue, optionally guided by surface engineering (Figure 2) (6,9,12).

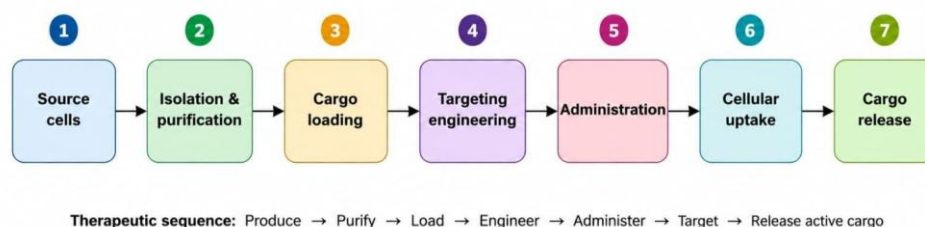


Figure 2: General exosome-based drug-delivery workflow, from donor-cell selection to administration.

A central and still-unresolved question for the field is whether unmodified exosomes offer a meaningful delivery advantage over engineered synthetic carriers in a like-for-like comparison, or whether their principal value lies specifically in applications where a biological membrane, natural targeting ligands, or reduced immunogenicity are decisive - for example, in crossing the blood-brain barrier or evading rapid mononuclear phagocyte system clearance.

4. Therapeutic cargo and loading strategies

Table 2: Exosome drug-loading strategies: principle and major limitation.

Method	Main principle	Major limitation
Passive incubation	Cargo associates with vesicles by diffusion or physicochemical interaction	Often low loading efficiency, particularly for hydrophilic or large cargo
Electroporation	Electrical pulses transiently increase membrane permeability	Risk of vesicle aggregation or cargo precipitation/loss
Sonication	Ultrasound transiently disrupts the membrane to permit cargo entry	Possible membrane damage or alteration of vesicle integrity
Extrusion	Vesicles and cargo are co-forced through membranes of defined pore size	May alter vesicle size distribution and surface properties
Freeze-thaw cycling	Repeated freezing and thawing transiently changes membrane permeability	Risk of structural damage and vesicle fusion or aggregation
Endogenous loading	Parent cells are engineered (e.g., transfection/transduction) to overexpress or package cargo before secretion	Depends on parent-cell expression efficiency; scale-up and batch consistency are challenging

Efficient, reproducible drug loading is central to exosome-based delivery, and remains one of the field's most consequential unresolved variables: loading efficiency differs markedly by cargo class, loading method and vesicle source, and is rarely reported using standardized units that allow cross-study comparison. Loading strategies are

broadly grouped as passive (incubation-based), active (physical or chemical disruption of the vesicle membrane), or endogenous (engineering of the parent cell prior to vesicle secretion) (6,9,12). Table 2 summarizes the principle and major limitation of each approach; each is then discussed in turn.

4.1 Passive loading

Passive (incubation-based) loading exposes isolated exosomes to the cargo of interest, relying on diffusion or noncovalent association for incorporation. It is procedurally simple and avoids exposing vesicles to physical or chemical stress, but efficiency is generally low, particularly for hydrophilic small molecules and macromolecular cargo, limiting its practical use to lipophilic agents or applications tolerant of low payload.

4.2 Electroporation

Electroporation applies brief electrical pulses to transiently permeabilize the exosomal membrane, allowing nucleic acids or other charged cargo to enter. It is widely used for siRNA and miRNA loading but is associated with variable efficiency between studies, a tendency toward vesicle aggregation, and potential cargo precipitation, all of which complicate standardization and dose calculation.

4.3 Sonication

Sonication uses ultrasound energy to transiently disrupt the lipid bilayer, facilitating cargo entry before the membrane reseals. This can improve loading of certain hydrophobic drugs relative to passive incubation, but the mechanical stress involved raises the possibility of membrane alteration or vesicle damage that may affect downstream stability and biological activity.

4.4 Extrusion

Extrusion forces a mixture of exosomes and cargo through membranes or filters of defined pore size, promoting cargo incorporation through repeated membrane disruption and resealing. While extrusion can achieve relatively high loading efficiencies for some cargo, it can also alter the native size distribution and surface characteristics of the vesicles, which may in turn affect biodistribution and targeting behaviour.

4.5 Freeze-thaw

Repeated freeze-thaw cycling exploits ice-crystal formation and membrane phase transitions to transiently increase permeability and promote cargo association. It is technically straightforward but carries a recognized risk of structural damage, vesicle fusion or aggregation, and is therefore often used in combination with, rather than as a substitute for, other loading methods.

4.6 Endogenous loading

Endogenous loading engineers the exosome-producing parent cell - for example, by transfection or transduction - so that a therapeutic protein or nucleic acid is overexpressed and subsequently packaged into vesicles during normal biogenesis. This approach avoids direct physical or chemical manipulation of isolated vesicles and can, in principle, yield more physiologically integrated cargo incorporation, but its efficiency is constrained by parent-cell expression levels, and it introduces additional cell-line development, scale-up and batch-consistency considerations that are distinct from those of exogenous, post-isolation loading methods (6,9,12).

5. Exosome engineering and targeting

Beyond cargo loading, engineering strategies aim to improve the targeting specificity, circulation stability, and functional performance of exosomes. These strategies act at the level of the parent cell (genetic engineering), the isolated vesicle (surface engineering), the choice of targeting ligand (active targeting), the responsiveness of cargo

release to the local microenvironment (stimulus-responsive systems), or through combination with synthetic nanomaterials (hybrid systems) (5,8,9,11).

5.1 Genetic engineering

Genetic engineering modifies the parent cell so that a targeting peptide, antibody fragment, or other functional protein is incorporated into the vesicle membrane during biogenesis, commonly by expressing a fusion construct linking the targeting element to an abundant exosomal membrane protein. This produces a targeting ligand that is presented on essentially every vesicle secreted by the engineered cell line, but it requires stable and reproducible parent-cell engineering and, as with endogenous cargo loading, is subject to batch-to-batch variability tied to cell-line performance.

5.2 Surface engineering

Surface engineering instead modifies vesicles after isolation, using chemical conjugation (e.g., click chemistry), lipid insertion, or antibody/aptamer attachment to add targeting or functional moieties without requiring parent-cell modification. This offers greater flexibility to combine a single vesicle source with multiple targeting strategies, but post-isolation chemical processing can itself alter vesicle integrity, and the resulting surface density and orientation of the targeting ligand are harder to control precisely than with genetically encoded display.

5.3 Active targeting

Peptides, antibodies, aptamers and other ligands have been explored, via either genetic or surface engineering, to confer receptor-mediated targeting toward specific cell types or tissues. Targeting must be validated experimentally rather than assumed from ligand–receptor biology alone, because surface modification can simultaneously alter biodistribution, immunogenicity, opsonization and clearance kinetics in ways that are not always predictable from the unmodified vesicle (5,8,9).

5.4 Stimulus-responsive systems

Stimulus-responsive release - in which cargo release is triggered by a local physicochemical cue such as pH, enzymatic activity, or redox state - is a well-established design principle in synthetic nanocarrier engineering. Its application specifically to exosomes is comparatively less developed: most reported exosome engineering to date has focused on targeting ligand display and cargo loading rather than on programmed, microenvironment-triggered release, and rigorous, exosome-specific evidence for stimulus-responsive control is correspondingly sparse relative to the synthetic-nanoparticle literature.

5.5 Hybrid exosome–nanoparticle systems

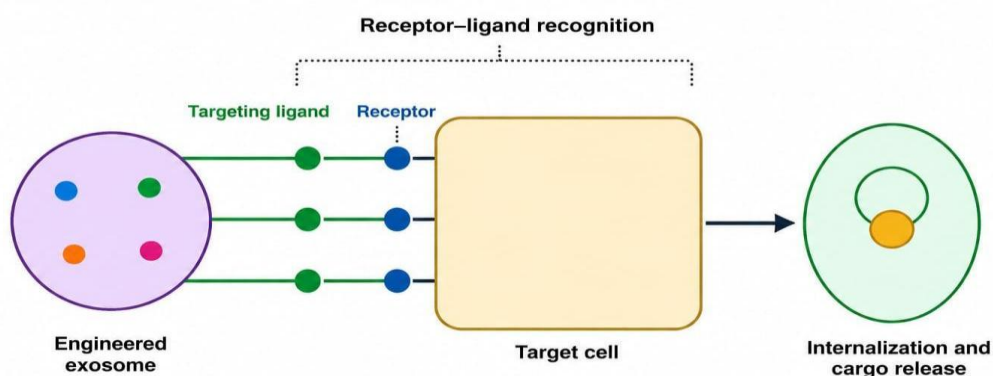


Figure 3: Active targeting of recipient cells by an engineered, surface-modified exosome

Hybrid systems combine biological exosomes with synthetic nanomaterials - for example, liposomal or polymeric components - with the intent of pairing the biological interaction and membrane properties of exosomes with the more precisely controllable physicochemical properties (size uniformity, loading capacity, manufacturability) of synthetic carriers. This is an emerging strategy rather than a mature one, and, as with stimulus-responsive systems, the functional advantage of hybridization over either parent platform used alone requires case-by-case experimental validation rather than being assumed a priori (6,9).

6. Therapeutic applications

Exosome-based delivery has been investigated across a range of disease areas, most extensively in oncology, with growing activity in neurological, cardiovascular, inflammatory, regenerative and gene/RNA-delivery applications. Table 3 summarizes representative cargo and the therapeutic objective pursued in each area.

Table 3: Exosome-based therapeutic applications by disease area

Application area	Representative cargo	Therapeutic objective
Cancer	Doxorubicin, paclitaxel, siRNA, miRNA	Targeted chemotherapy and gene-expression modulation
Neurological disease	siRNA, miRNA, proteins	Brain/CNS-directed delivery across the blood–brain barrier
Cardiovascular disease	miRNA, siRNA, proteins	Tissue repair and modulation of inflammation
Inflammatory disease	Anti-inflammatory molecules, RNA	Pathway-specific immune modulation
Regenerative medicine	Proteins, miRNA	Support of tissue repair processes
Gene and RNA delivery	mRNA, siRNA, other nucleic acids	Modulation of target gene expression

6.1 Cancer

Cancer is the most developed application area for exosome-based delivery. Reviews describe exosomes carrying anticancer small molecules, nucleic acids and proteins, with surface engineering used to improve tumour-selective delivery (17,18). A 2024 experimental report described dendritic-cell-derived exosomes loaded with doxorubicin and targeted toward breast cancer cells and cancer stem cells in preclinical models, illustrating a general shift from conceptual demonstrations toward more deliberately engineered therapeutic platforms (15). Even within this most-developed application area, evidence remains predominantly preclinical, and dose–response, biodistribution and long-term safety data comparable to those required for conventional oncology therapeutics are not yet consistently available.

6.2 Neurological diseases

Neurological delivery is a particularly challenging and particularly active application, given the restrictive nature of the blood–brain barrier. Recent work has investigated exosomes as carriers for therapeutic nucleic acids intended for the central nervous system, while explicitly highlighting unresolved questions of targeting specificity, in vivo tracking, safety, and translational pathway (16). Mesenchymal-stem-cell (MSC)-derived exosomes have also been extensively studied in this and related regenerative/inflammatory contexts (19).

6.3 Cardiovascular diseases

In cardiovascular applications, exosomes carrying miRNA, siRNA, or proteins have been explored for their potential to support tissue repair and modulate post-injury inflammation. As in other application areas, this

evidence base is predominantly preclinical, and the translational questions of dose, delivery route and long-term cardiac safety remain largely open.

6.4 Inflammatory diseases

Exosomes loaded with anti-inflammatory molecules or regulatory RNA have been investigated for pathway-specific modulation of immune and inflammatory signalling, an application area that overlaps mechanistically with both cardiovascular repair and regenerative medicine and that similarly awaits confirmatory clinical evidence.

6.5 Regenerative medicine

MSC-derived exosomes, in particular, have been studied for their capacity to support tissue repair through delivery of proteins and miRNA, reflecting the broader interest in MSC-derived vesicles as a cell-free alternative to cell-based regenerative therapies (19).

6.6 Gene and RNA delivery

Exosomes have been proposed as carriers for mRNA, siRNA, and other nucleic acids intended to modulate target gene expression, positioning them alongside lipid nanoparticles as a candidate platform for nucleic-acid therapeutics.

7. Research advances during 2020–2025

Table 4 summarizes the major research direction reported for each year between 2020 and 2025, illustrating a broad progression from foundational proof-of-concept work toward engineering refinement and, more recently, translational and quality-focused considerations.

Table 4: Major research directions in exosome-based drug delivery, 2020–2025

Period	Major direction	Representative evidence
2020	Foundational studies, tumour targeting and early GMP considerations	(1,2,3,4,20)
2021	Targeted engineering, cancer delivery and MSC-derived exosomes	(5,17,18,19)
2022	Drug loading, surface modification and hybrid systems	(6,7)
2023	Engineered exosomes, systematic evaluation and bench-to-clinic translation	(8,9,10,11,12)
2024	Therapeutic cargo, clinical applications, quality control and experimental targeting	(13,14,15)
2025	Brain-targeted nucleic-acid delivery	(16)

2020–2022: Establishing the field

Literature from 2020 established much of the groundwork for the modern exosome drug-delivery discussion, with reviews reporting exosomes as carriers of anticancer drugs capable of reaching different tissues and cell types, alongside GMP-focused work on production quality and control that anticipated the manufacturing requirements (1,2,3,4,20). Engineering considerations became more prominent in 2021, with reviews addressing genetic and post-production modification strategies intended to improve targeted delivery to specific cell types, cancer-focused summaries of chemotherapeutic and nucleic-acid cargo, and growing interest in MSC-derived exosomes as both therapeutics and delivery vehicles in their own right (5,17,18,19). By 2022, attention had extended to

natural nanocarrier concepts and hybrid systems, with particular emphasis on loading strategies; in retrospect, 2022 marks an inflection from demonstrating that exosomes can carry therapeutic molecules toward designing carriers intended to deliver those molecules to specific cells (6,7).

2023–2024: Engineering maturation and translational focus

The 2023 literature placed greater emphasis on engineered exosomes and the transition from bench to clinic, addressing genetic and chemical vesicle modification, cargo encapsulation, and the influence of manufacturing choices on therapeutic properties; systematic studies of encapsulation methods revealed variability between approaches and reinforced the need for standardized quantification (8,9,10,11,12). In 2024, therapeutic delivery, quality control, and translational considerations became a focus of many reviews, alongside experimental work - such as the dendritic-cell-derived doxorubicin platform, illustrating engineering directed at specific cancer-targeting applications and delivery of established chemotherapeutics (13,14,15). The overall shift across this period is from asking whether exosomes can carry therapeutic molecules to determining how to manufacture reproducible, targeted, stable, and clinically useful exosome products (12,13,14,15).

8. Isolation, purification and characterization

Common isolation approaches include differential ultracentrifugation, size-exclusion chromatography, polymer-based precipitation, immunoaffinity capture, and newer, more scalable methods such as tangential-flow filtration and microfluidic separation. These methods differ substantially in achievable yield, purity, scalability, and equipment requirements, and no single method is universally preferred across applications: ultracentrifugation remains widely used but is comparatively low-throughput, while precipitation-based kits are rapid but tend to co-isolate non-vesicular contaminants. Preparations obtained by any of these methods may contain co-isolated proteins, lipoprotein particles, free nucleic acids, cellular debris, or other extracellular vesicle subtypes, so vesicle purity must be assessed rather than assumed.

Characterization should address particle concentration and size distribution (e.g., by nanoparticle tracking analysis or dynamic light scattering), morphology (e.g., by electron microscopy), molecular marker expression, contaminant burden, cargo content, and functional potency. The Minimal Information for Studies of Extracellular Vesicles (MISEV2023) guidance from the International Society for Extracellular Vesicles provides consensus recommendations for transparent reporting of EV production, separation and characterization methods, and is increasingly treated as a baseline reporting standard against which individual studies can be benchmarked (21). A persistent methodological limitation, consistent with the biogenesis, is that not every isolated small-EV preparation can automatically be termed an exosome in the strict biogenesis sense; because isolation methods cannot yet reliably separate exosomes from other similarly sized EV subtypes on the basis of biogenesis alone, rigorous, multi-parameter characterization is essential both for scientific reproducibility and for the identity and purity assessments required in a regulatory context (13,17,21).

9. Major challenges and research gaps

Table 5 summarizes the principal challenges identified across the preceding sections, together with their practical impact and the research need each implies.

Table 5: Major challenges and corresponding research needs in exosome-based drug delivery

Challenge	Impact	Research need
Heterogeneity	Variable composition and function between and within preparations	Defined cell sources and controlled, standardized production
Low yield/scalability	Difficult to translate into pharmaceutical-scale manufacture	Bioreactor-based production and scalable purification methods
Purification	Contaminants affect reproducibility and interpretation	Orthogonal, validated purification and purity-assessment methods
Loading efficiency	Limits achievable therapeutic dose per vesicle	Cargo-class-specific loading optimization and standardized reporting
Targeting	Off-target biodistribution reduces therapeutic index	Experimentally validated, quantitative surface-engineering strategies
Rapid clearance	Reduces effective exposure at the target site	Pharmacokinetic optimization, including circulation-extending strategies
Stability	Storage and handling can alter vesicle integrity and potency	Validated formulation and long-term stability studies
Batch variation	Undermines manufacturing reproducibility	Standardized manufacturing and in-process quality control
Safety	Long-term effects of repeated dosing remain incompletely defined	Repeated-dose and long-term preclinical and clinical safety studies
Regulation	Requirements for a clinical EV product remain complex and evolving	GMP-aligned standards and harmonized regulatory pathways
Stimulus-responsive release	Programmed, microenvironment-triggered release remains underdeveloped for exosomes specifically	Exosome-specific studies of responsive cargo release, building on synthetic-nanocarrier precedents

Considered together, the central research gap is translational: many individual studies demonstrate biological activity, but comparatively few establish a complete, reproducible chain running from a defined source and manufacturing process to a standardized product with quantitative biodistribution, dose–response, potency and safety data (5,16,18). A second, more definitional gap concerns terminology and identity: not every small-EV preparation can automatically be described as an exosome, making rigorous, MISEV-aligned characterization essential to comparing results across the literature (17,21).

10. Clinical translation and regulatory considerations

Clinical translation of exosome-based therapeutics requires consistent production, purification, characterization, storage, dosing, and safety evaluation. GMP-focused literature identifies upstream cell cultivation, downstream purification, and in-process quality control as major requirements for a viable clinical manufacturing process, and recent reviews continue to identify isolation, purification, standardization, characterization, and regulatory validation as the principal barriers to clinical progress (13,14,20).

Exosome-based products are generally expected to be regulated within existing biologic/advanced-therapy frameworks rather than under a bespoke regulatory category, which means that identity, purity, potency and stability must be defined and validated in ways broadly analogous to those required for other complex biologics - a considerably higher bar than that typically applied to early-stage preclinical characterization. Achieving this will require the field to converge on standardized potency assays and reference materials, which are not yet consistently established (13,14).

For scientific and regulatory accuracy alike, evidence for any specific exosome-based intervention should be explicitly separated into in vitro findings, animal/preclinical findings, and human clinical evidence, since the overwhelming majority of currently published work remains at the first two stages. Exosome-based drug delivery should therefore currently be described as an emerging, translationally immature technology rather than as a mature replacement for conventional drug-delivery systems.

11. Exosomes versus synthetic nanocarriers

Table 6: Qualitative comparison of exosomes with established synthetic nanocarrier platforms

Criterion	Exosomes	Liposomes / lipid nanoparticles	Polymeric nanoparticles
Manufacturing reproducibility	Limited by donor-cell and biological source variability	Well established, highly reproducible at scale	Well established, tunable and reproducible
Loading efficiency/control	Variable and cargo-class dependent	Generally high and well characterized, especially for nucleic acids	Generally high with tunable release kinetics
Immunogenicity	Potentially low, but source- and processing-dependent	Low for well-characterized clinical formulations	Depends on polymer chemistry; can be engineered to be low
Targeting capability	Natural and engineerable, but variable and requires validation	Well-established engineering toolkit (e.g., PEGylation, ligand conjugation)	Well-established engineering toolkit
Scalability / GMP readiness	Currently a major limitation	Mature, clinically validated manufacturing processes	Mature, clinically validated manufacturing processes
Regulatory pathway clarity	Evolving; treated broadly as a complex biologic	Well established, with approved clinical products	Well established, with approved clinical products
Biological barrier crossing (e.g., blood-brain barrier)	Reported natural capacity in some contexts	Achievable primarily through active engineering	Achievable primarily through active engineering

A recurring theme of this review is that exosomes should be evaluated against synthetic nanocarrier platforms - principally liposomes, lipid nanoparticles (LNPs) and polymeric nanoparticles - on a criterion-by-criterion basis rather than through a general claim of biological superiority. Table 6 sets out a qualitative comparison across the criteria most relevant to therapeutic development; because few studies directly compare exosomes with synthetic carriers under matched conditions, the comparison is presented as a synthesis of the general properties reported for each platform class in the literature reviewed above, rather than as a quantitative meta-analysis.

This comparison indicates that the principal, currently demonstrable advantage of exosomes lies less in any single physicochemical property and more in specific biological contexts - for example, reported natural blood-brain-barrier traversal or low baseline immunogenicity from an autologous or well-matched source - where a biological membrane may offer genuine benefit over an engineered synthetic surface. Conversely, on manufacturing reproducibility, scalability, and regulatory pathway clarity, synthetic carriers such as liposomal and lipid-nanoparticle systems remain considerably more mature, reflecting decades of clinical development compared with the still-emerging exosome manufacturing base. This asymmetry supports a pragmatic conclusion: exosomes are best positioned, at the current stage of the field, as a complementary platform for applications where their specific biological properties are decisive, and as a candidate component of hybrid systems, rather than as a universal replacement for synthetic nanocarriers (1,5,6,9).

12. Future prospects

Building on the challenges and comparative assessment above, priority areas for future research include:

- Scalable, reproducible manufacturing platforms, including bioreactor-based production suited to pharmaceutical-scale output.
- Cargo-specific loading strategies with higher and more consistently reported efficiency.
- Experimentally validated, receptor- or tissue-specific targeting strategies, assessed against matched unmodified controls.
- Controlled, stimulus-responsive cargo-release systems that extend established synthetic-nanocarrier design principles to exosomes.
- Rigorous biodistribution, pharmacokinetic, and dose-response studies conducted to a standard comparable with conventional therapeutics.
- Standardized identity, purity, potency, and safety assays, aligned with MISEV2023 and emerging regulatory expectations.
- Hybrid exosome-nanoparticle platforms with clearly defined, experimentally demonstrated functional advantages over either parent platform alone.
- Precision and patient-specific delivery approaches, including autologous or closely matched exosome sources.
- Exosome mimetics with improved manufacturing control, as an intermediate strategy between fully biological and fully synthetic carriers.
- Clearer, harmonized GMP and regulatory pathways specific to exosome-based products.

13. Conclusions

Exosomes represent a promising, biologically distinctive platform for drug delivery, arising from their natural role in intercellular communication and their intrinsic capacity to transport diverse molecular cargo. Research since

2020 has substantially advanced drug loading, surface and genetic engineering, targeted delivery, hybrid systems and therapeutic applications across cancer, neurological, cardiovascular, inflammatory, regenerative and gene/RNA-delivery contexts, with cancer and neurological delivery currently the most active areas.

Nevertheless, and consistent with the critical framing adopted throughout this review, exosome technology remains translationally immature. Vesicle heterogeneity, purification and characterization difficulties, variable loading efficiency, incompletely validated targeting, rapid clearance, storage instability, manufacturing scalability, safety characterization, and regulatory standardization remain substantial and, in most cases, unresolved barriers. The comparative assessment indicates that exosomes are not yet a general-purpose substitute for mature synthetic nanocarrier platforms, but they may offer decisive advantages in specific biological contexts and as components of hybrid delivery systems. Future progress will depend on standardized, reproducible, and scalable manufacturing, supported by rigorous pharmacokinetic, biodistribution, potency, and safety studies conducted and reported to a standard consistent with conventional drug-delivery systems, and aligned with emerging consensus guidance such as MISEV2023.

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