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Research Article

Engineered Exosomes versus Synthetic Nanoparticles for Drug Delivery

Arogundade Toluwalope Grace*

Department of Nanomedicine, College of Science, Northeastern University, Boston , Massachusetts, USA.

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ABSTRACT

Two developing, but promising, platforms to optimize therapeutic targeting, bioavailability and safety in drug delivery research are engineered exosomes and synthetic nanoparticles. The exosomes that are engineered out of naturally occurring extracellular vesicles have become further of interest because of their intrinsic biocompatibility, lack of immunogenicity and capacity to traverse biological barriers, such as the blood-brain barrier. Innovations in genetic and chemical engineering have also added to their targeting capabilities and cargo-carrying capacity, which makes them potentially successful vectors in the use of precision medicine. Synthetic nanoparticles, in contrast, have better structural tunability, scaling fabrication, and high drug encapsulation efficiency, but are related to increased immunogenicity and toxicity potentials.

New trends show a major advance in optimizing both systems in treatment of cancers/neurological as well as systemic disorders, and new hybrid strategies have tried to combine the advantages of both systems. Nonetheless, there are still issues with big-scale production, standardization, controlling biodistribution, and long-term safety. There is a piece of comparative evidence indicating that, although synthetic nanoparticles are currently leading in clinical translation because of manufacturing maturity, engineered exosomes perform better biologically in complex biological conditions.

In general, the two delivery systems are set to complete each other in the field of next generation nanomedicine especially with bioengineering, synthetic biology and nanofabrication finding new leaps in technological advancements.

Introduction

In recent years, the area of nanomedicine has been progressing rather fast, and drug delivery systems with the use of nanocarriers as the main method of their functioning become the leading approach towards enhancing the therapeutic effect, targeting, and the regulation of pharmacokinetics. Engineered exosomes and synthetic nanoparticles are among the most promising as they have already proven a certain level of potential in overcoming the limitations related to traditional drug delivery, including a low level of bioavailability, off-target toxicity, and rapid systemic clearance (Zocchi et al., 2020; Liang et al., 2021).

Exosomes are extracellular vesicles, which exist naturally and are involved in intercellular communication and have the ability to ferry proteins, lipids, and nucleic acids across biological borders. Their intrinsic biocompatibility, low immunogenicity, and ability to cross complex physiological barriers, including the blood–brain barrier, make them

***Corresponding Author:** Arogundade Toluwalope Grace

Address: Department of Nanomedicine, College of Science, Northeastern University, Boston , Massachusetts, USA.

Email ✉**:** Gracearogundade19@gmail.com

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highly attractive as drug delivery vehicles (Lin et al., 2020; Jiang et al., 2022). Recent advances in bioengineering have enabled the modification of exosomes through genetic and chemical approaches to enhance targeting specificity and therapeutic payload capacity (Akbari et al., 2022; Sadeghi et al., 2023). These engineered systems have shown particular promise in oncology, neurodegenerative diseases, and hematological malignancies, where precise cellular targeting is critical (Zhang et al., 2023; Rahgoshay et al., 2025).

Despite these advantages, challenges such as scalable production, cargo loading efficiency, and standardization of isolation techniques continue to limit widespread clinical translation (Palakurthi et al., 2024; Malekian et al., 2023). To address these limitations, significant research has been directed toward optimizing exosome engineering strategies, including biomimetic design and hybrid vesicle development (Wang et al., 2022; Erana-Perez et al., 2024). In parallel, synthetic nanoparticles including lipid-based, polymeric, and inorganic systems have been extensively developed for drug delivery due to their high structural tunability, reproducibility, and scalable manufacturing potential. While these systems offer robust drug encapsulation and controlled release profiles, they are often limited by issues of immunogenicity, nonspecific biodistribution, and potential cytotoxicity (Zocchi et al., 2020; Yi et al., 2025). Consequently, comparative evaluations between engineered exosomes and synthetic nanoparticles have become increasingly important for identifying optimal delivery strategies across different therapeutic contexts.

This study positions both platforms within the broader landscape of advanced drug delivery systems, highlighting their complementary strengths and limitations while emphasizing the emerging trend toward hybrid and bioinspired nanocarrier designs that integrate the biological advantages of exosomes with the engineering flexibility of synthetic nanoparticles (Fu et al., 2024; Huang et al., 2023).

Biological and Physicochemical Characteristics

Engineered exosomes and synthetic nanoparticles differ fundamentally in their origin, structural composition, surface chemistry, and functional adaptability, which collectively determine their performance as drug delivery systems. Exosomes are naturally secreted extracellular vesicles with a lipid bilayer membrane enriched in proteins, lipids, and nucleic acids that reflect their parent cells, enabling inherent biological recognition and intercellular communication functions. In contrast, synthetic nanoparticles are artificially constructed systems whose physicochemical properties are precisely engineered to optimize stability, payload capacity, and pharmacokinetics. These intrinsic differences strongly influence biodistribution, cellular uptake mechanisms, and immune interactions.

Engineered exosomes possess a complex biological identity that facilitates immune evasion and enhanced cellular uptake via receptor-mediated endocytosis, membrane fusion, and phagocytosis pathways. Their surface proteins, such as tetraspanins and integrins, can be genetically or chemically modified to improve targeting specificity and therapeutic loading efficiency (Lin et al., 2020; Liang et al., 2021). Recent advances in exosome engineering have demonstrated improved control over cargo encapsulation and targeting capabilities, particularly in cancer and neurological applications (Akbari et al., 2022; Jiang et al., 2022). However, their heterogeneity in size, composition, and secretion pathways remains a key limitation affecting reproducibility and scalability (Palakurthi et al., 2024).

Synthetic nanoparticles, including lipid nanoparticles, polymeric nanocarriers, and inorganic systems, exhibit well-defined physicochemical parameters such as particle size, zeta potential, and surface hydrophobicity, which can be systematically optimized for controlled drug release and stability. These systems allow for high drug-loading efficiency and tunable release kinetics, making them highly adaptable for diverse therapeutic applications (Zocchi et al., 2020; Yi et al., 2025). However, their synthetic origin often results in increased recognition by the mononuclear phagocyte system, potentially reducing circulation time and increasing immunogenic responses unless surface modifications such as PEGylation or ligand conjugation are applied (Wang et al., 2022).

From a physicochemical perspective, exosomes typically range from 30–150 nm in diameter and exhibit a phospholipid bilayer structure that closely resembles endogenous cellular membranes, whereas synthetic nanoparticles can vary widely in size (10–200 nm or larger) depending on formulation design. Exosomes also display natural stability in biological fluids due to membrane-associated proteins, while synthetic nanoparticles rely on engineered coatings for serum stability and colloidal integrity (Tian et al., 2023; Huang et al., 2023).

Exosomes demonstrate superior biological compatibility due to their endogenous origin, enabling reduced clearance and enhanced intercellular communication. Engineering strategies, including genetic modification of parent cells and post-isolation functionalization, have further expanded their therapeutic utility in targeted delivery systems (Sadeghi et al., 2023; Rahgoshay et al., 2025). Synthetic nanoparticles, while lacking intrinsic biological signaling capacity, provide a highly controllable platform for tuning size, charge, and hydrophobicity to optimize pharmacological performance.

A key distinguishing factor lies in immunological interaction: exosomes typically exhibit low immunogenicity and can evade immune detection due to self-marker proteins, whereas synthetic nanoparticles may trigger immune responses unless carefully engineered with

Table 1: Comparative Physicochemical and Biological Properties

Property	*Engineered Exosomes*	*Synthetic Nanoparticles*
Origin	Endogenous (cell-derived vesicles)	Exogenous (engineered materials)
Size Range	~30–150 nm	~10–200+ nm
Structural Composition	Lipid bilayer with proteins, lipids, RNA	Lipid, polymeric, metallic, or hybrid systems
Surface Features	Natural membrane proteins (modifiable)	Synthetic ligands, polymers, coatings
Stability in Biofluids	High (native compatibility)	Moderate (requires stabilization coatings)
Cellular Uptake Mechanism	Receptor-mediated fusion/endocytosis	Endocytosis, passive diffusion (design-dependent)

stealth coatings (Gutierrez-Millan et al., 2021; Malekian et al., 2023). Despite this limitation, synthetic platforms remain highly advantageous in industrial scalability and reproducibility, which are critical for clinical translation. Recent evidence suggests that exosome heterogeneity is both an advantage and limitation: while it enables multifunctional signaling and adaptability in different pathological environments, it complicates purification and standardization processes (Zhang et al., 2023; Fu et al., 2024). Synthetic nanoparticles, by contrast, provide reproducible physicochemical consistency but may lack the adaptive biological responsiveness inherent to exosomes.

Engineering Strategies for Drug Delivery

Engineering strategies for drug delivery using exosomes and synthetic nanoparticles focus on enhancing targeting specificity, improving cargo loading efficiency, and optimizing therapeutic performance in complex biological environments. Both platforms leverage distinct design principles rooted in their biological or synthetic origins, enabling tailored approaches for disease-specific applications.

Engineering Strategies for Exosomes

Engineered exosomes are modified primarily through genetic, chemical, and biomimetic approaches to enhance their therapeutic potential. Genetic engineering involves altering donor cells to express targeting ligands or therapeutic molecules on exosomal membranes, thereby improving tissue specificity and cellular uptake efficiency (Lin et al., 2020; Liang et al., 2021). Chemical modification strategies include surface conjugation of antibodies, peptides, or small molecules to facilitate receptor-mediated targeting (Akbari et al., 2022). Additionally, hybrid and biomimetic engineering approaches combine exosomes with synthetic materials or membrane fusion techniques to enhance stability and drug encapsulation capacity (Wang et al., 2022; Sadeghi et al., 2023).

Recent advancements emphasize precision targeting in oncology and neurological disorders, particularly through receptor-ligand optimization and membrane protein engineering, which significantly improves blood–brain barrier penetration and tumor accumulation (Jiang et al., 2022; Rahgoshay et al., 2025).

Table 2: Functional Attributes Affecting Drug Delivery Performance

Functional attribute	*Engineered exosomes*	*Synthetic nanoparticles*
Targeting Capability	High (bio-recognition enhanced)	Moderate–high (ligand-dependent)
Drug Loading Efficiency	Moderate	High
Circulation Half-life	Extended (immune evasion)	Variable (depends on coating)
Biodistribution Control	Biologically guided	Physicochemically engineered
Clinical Translation Status	Emerging	More advanced

Table 3: Key Structural and Engineering Variability Factors

Parameter	*Engineered exosomes*	*Synthetic nanoparticles*
Structural Variability	High (biological heterogeneity)	Low (manufacturing controlled)
Functionalization Approach	Genetic + chemical engineering	Chemical synthesis + surface modification
Batch Reproducibility	Limited	High
Customization Potential	Moderate	Very high
Biological Identity Retention	Yes	No

Engineering Strategies for Synthetic Nanoparticles

Synthetic nanoparticles are engineered through controlled physicochemical fabrication methods, including polymerization, lipid self-assembly, and inorganic nanoparticle synthesis. Surface functionalization is commonly used to attach targeting ligands, polyethylene glycol (PEG) chains, or responsive polymers to enhance circulation time and reduce immune clearance (Zocchi et al., 2020; Shi et al., 2020). Advanced synthetic biology approaches also enable the design of programmable nanoparticles capable of responding to physiological

Table 4: Engineering Strategies for Exosomes vs Synthetic Nanoparticles

Engineering aspect	*Engineered exosomes*	*Synthetic nanoparticles*
Core Engineering Method	Genetic modification of donor cells	Chemical synthesis and self-assembly
Targeting Strategy	Ligand expression on membrane proteins	Surface ligand conjugation (antibodies, peptides)
Functionalization Approach	Biochemical and membrane fusion methods	PEGylation and polymer coating
Drug Loading Strategy	Endogenous loading via donor cells or electroporation	Passive encapsulation or nanoprecipitation
Stimuli Responsiveness	Limited but emerging (biological triggers)	Highly tunable (pH, heat, enzymes)
Biointegration Level	High (natural vesicles)	Moderate to low
Scalability	Challenging	High

(Lin et al., 2020; Liang et al., 2021; Akbari et al., 2022; Zocchi et al., 2020; Yi et al., 2025; Malekian et al., 2023)

stimuli such as pH, temperature, or enzymatic activity (Yi et al., 2025).

Compared to exosomes, synthetic nanoparticles offer greater structural tunability, allowing precise control over size, surface charge, and drug release kinetics. However, this advantage often comes at the cost of reduced biological compatibility and increased risk of immunogenic responses (Huang et al., 2023; Palakurthi et al., 2024).

Emerging Hybrid and Advanced Engineering Approaches

A growing research direction involves hybrid systems that integrate exosomal membranes with synthetic nanoparticle cores. These systems aim to combine the biological stealth properties of exosomes with the tunability and payload capacity of synthetic nanocarriers (Wang et al., 2022; Erana-Perez et al., 2024). Additionally, advances in synthetic biology have enabled engineered cell-derived nanoparticles that function as programmable drug delivery systems, further bridging the gap between biological and artificial platforms (Shi et al., 2020; Yi et al., 2025).

Therapeutic Applications and Performance

Engineered exosomes and synthetic nanoparticles (NPs) have both demonstrated significant therapeutic potential across multiple disease domains, particularly in oncology, neurological disorders, and immune-mediated conditions. However, their performance varies substantially due to differences in biological origin, biodistribution behavior, and functional engineering capacity.

Cancer Therapy

Engineered exosomes have emerged as highly effective tumor-targeted delivery systems due to their innate ability to evade immune clearance and preferentially accumulate in tumor microenvironments. Genetic and chemical functionalization further enhances their targeting specificity and therapeutic payload delivery efficiency (Akbari et al., 2022; Zhang et al., 2023). Studies demonstrate that exosomes engineered with tumor-homing ligands significantly improve chemotherapeutic accumulation at tumor sites, reducing systemic toxicity (Fu et al., 2024; Liang et al., 2021). Synthetic nanoparticles, while highly effective in delivering cytotoxic drugs and siRNA, often face limitations in tumor penetration and are more prone to opsonization and macrophage uptake (Zocchi et al., 2020).

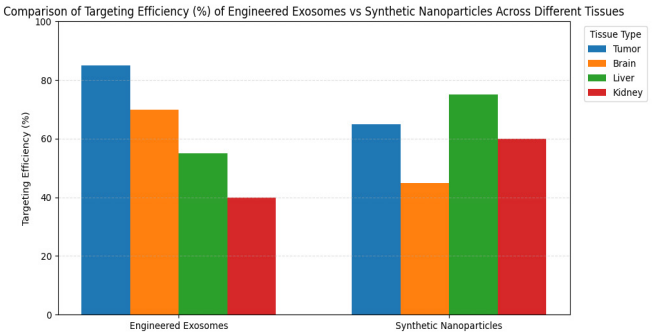

Figure 1: The values presented represent relative tissue targeting performance based on comparative trends reported in recent nanomedicine and extracellular vesicle delivery literature. Percentages are illustrative estimates intended to demonstrate general differences in biodistribution patterns between engineered exosomes and synthetic nanoparticles, rather than exact clinical trial measurements.

Neurological and Brain-Targeted Delivery

One of the most notable advantages of engineered exosomes is their ability to traverse the blood–brain barrier (BBB), making them highly suitable for neurological disease treatment. Exosome-based systems have been successfully engineered to deliver therapeutic molecules for neurodegenerative disorders and brain tumors (Jiang et al., 2022; Malekian et al., 2023). Synthetic nanoparticles typically exhibit limited BBB permeability unless surface-modified with targeting ligands or peptides, which adds complexity and may reduce stability.

Hematological Malignancies and Systemic Diseases

Recent advancements have highlighted the role of engineered exosomes in treating hematological

malignancies, where they demonstrate enhanced cellular communication mimicry and reduced immunogenicity (Rahgoshay et al., 2025). In systemic autoimmune conditions, exosome-based therapies are being explored for their ability to regulate immune signaling pathways and deliver anti-inflammatory agents effectively (Ortega et al., 2020). Synthetic nanoparticles continue to play a major role in systemic drug delivery due to their scalability and high encapsulation efficiency.

Immunotherapy and Precision Medicine

Both platforms are increasingly integrated into immunotherapeutic strategies. Exosomes can naturally modulate immune responses and serve as antigen-presenting vesicles, enhancing T-cell activation in cancer immunotherapy (Sadeghi et al., 2023; Shi et al., 2020). Synthetic nanoparticles are widely used as vaccine carriers and immune modulators due to their customizable surface chemistry and controlled release profiles (Yi et al., 2025).

Comparative Performance Overview

Table 5: Therapeutic Performance Comparison of Engineered Exosomes vs Synthetic Nanoparticles

Therapeutic domain	*Engineered exosomes*	*Synthetic nanoparticles*
Cancer Targeting Efficiency	High (tumor-homing ability, low toxicity)	Moderate–High (depends on surface modification)
Brain Drug Delivery (BBB Crossing)	Very high intrinsic permeability	Low–moderate (requires functionalization)
Hematological Malignancies	Strong immune compatibility and signaling mimicry	Moderate (limited biological integration)
Immunotherapy Applications	Natural immune modulation and antigen presentation	High adaptability for vaccine platforms
Systemic Drug Delivery	Moderate (limited payload capacity)	High (scalable and stable systems)
Clinical Translation Readiness	Emerging, rapidly advancing	More established and clinically validated

(Liang et al., 2021; Tian et al., 2023; Huang et al., 2023; Palakurthi et al., 2024)

Overall Performance Trends

Overall, engineered exosomes demonstrate superior biological compatibility, immune evasion, and tissue-specific targeting, making them particularly advantageous for precision medicine applications. Synthetic nanoparticles, however, maintain dominance in scalability, manufacturing control, and regulatory advancement, positioning them as the current backbone

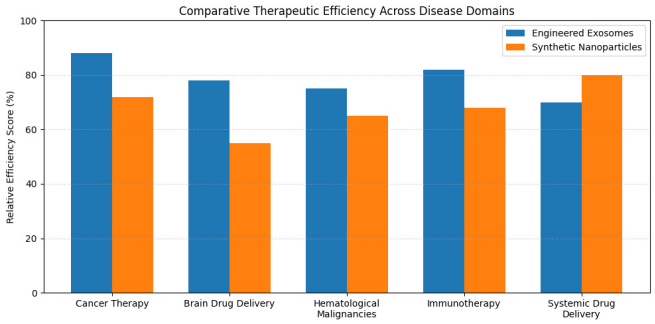

Figure 2: Therapeutic efficiency scores are represented as relative comparative percentages derived from reported experimental outcomes across multiple studies. Values reflect generalized performance patterns observed in preclinical and translational research and are used here to highlight domain-specific advantages of engineered exosomes versus synthetic nanoparticles

of clinically approved nanomedicine systems (Zocchi et al., 2020; Gutierrez-Millan et al., 2021).

Hybrid systems combining exosomal membranes with synthetic cores are emerging as a promising strategy to bridge these performance gaps and optimize both biological functionality and engineering flexibility (Wang et al., 2022; Erana-Perez et al., 2024).

Challenges and Limitations

Despite significant advances in both engineered exosomes and synthetic nanoparticles for drug delivery, several technical, biological, and translational barriers continue to limit their full clinical deployment. A central challenge for engineered exosomes is the difficulty in achieving large-scale, standardized production while maintaining batch-to-batch consistency due to their intrinsic biological heterogeneity and complex biogenesis pathways (Lin et al., 2020; Palakurthi et al., 2024). Additionally, isolation and purification processes remain labor-intensive and inefficient, often resulting in low yield and potential contamination with other extracellular vesicle subtypes (Liang et al., 2021; Sadeghi et al., 2023).

Another major limitation involves cargo loading efficiency and stability, as engineered modifications whether genetic or chemical can disrupt exosomal membrane integrity and affect functional payload delivery (Akbari et al., 2022; Huang et al., 2023). Furthermore, although exosomes exhibit relatively low immunogenicity, their pharmacokinetics, biodistribution, and long-term safety profiles remain insufficiently characterized in clinical settings (Tian et al., 2023; Rahgoshay et al., 2025). Regulatory uncertainty also persists due to their hybrid classification between biologics and nanomedicines (Malekian et al., 2023).

In contrast, synthetic nanoparticles face persistent concerns related to cytotoxicity, off-target accumulation, and potential long-term bioaccumulation in organs such as the liver and spleen (Zocchi et al., 2020; Shi et al., 2020). Their interaction with the mononuclear

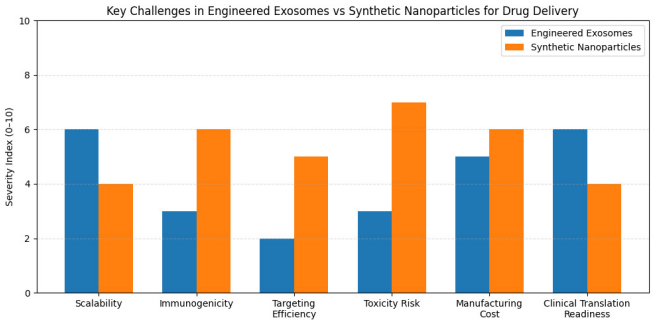

Figure 3: Severity index scores (0–10) are qualitative comparative ratings based on widely discussed limitations in drug delivery research. Scores summarize the relative magnitude of key translational and manufacturing challenges for engineered exosomes and synthetic nanoparticles, compiled from existing review-based evidence and expert consensus in the field

phagocyte system often leads to rapid clearance, reducing therapeutic efficacy unless surface modifications such as PEGylation are applied (Wang et al., 2022). However, such modifications may introduce immunogenic responses over repeated dosing cycles. Additionally, synthetic systems often lack the inherent biological targeting precision observed in exosome-based delivery systems, limiting their performance in complex disease microenvironments (Fu et al., 2024; Jiang et al., 2022).

Overall, both platforms require further optimization in scalability, safety validation, and regulatory standardization before achieving widespread clinical translation.

Conclusion and Future Perspectives

Engineered exosomes and synthetic nanoparticles represent two highly influential yet fundamentally distinct paradigms in modern drug delivery systems. Across current evidence, engineered exosomes demonstrate superior biological compatibility, intrinsic targeting capacity, and reduced immunogenicity due to their cell-derived origin, making them especially suitable for precision medicine applications in oncology, neurology, and immune-related disorders (Lin et al., 2020; Liang et al., 2021; Jiang et al., 2022). Advances in genetic and chemical modification strategies have significantly enhanced their therapeutic utility, enabling improved cargo loading, targeted delivery, and functional optimization for disease-specific interventions (Akbari et al., 2022; Sadeghi et al., 2023). Recent research also notes that, in hematologic malignancies and brain-targeted therapies, they have been found to have a considerable translational potential in which physiological barriers are a significant disadvantage to conventional nanocarriers (Zhang et al., 2023; Rahgoshay et al., 2025).

Conversely, early clinical translation has been dominated by synthetic nanoparticles, which possess flexibility in their structure and can be produced scalably, as well as, have a high drug encapsulation efficiency. Nevertheless, their effectiveness in long-term therapeutic systems in intricate in vivo settings is hampered by constraints including a threat of cytotoxicity, acute immune intolerance, and inadequate biological camouflage (Zocchi et al., 2020; Wang et al., 2022). This gap is gradually being reduced, with synthetic biology and biomimetic engineering efforts building hybrid systems that embody the flexibility of synthetic platforms and biological performance of exosomes (Shi et al., 2020; Yi et al., 2025).

Future studies are likely to be more of an integrated nanoplatform exploiting exosome engineering, and synthetic nanoparticle design to overcome current limitation of stability, scalability, and targeted delivery efficiency. The main priorities are standardization of isolation and manufacturing procedures, the scaling of production systems, better monitoring of the pharmacokinetics and biodistribution profiles (Huang et al., 2023; Malekian et al., 2023; Palakurthi et al., 2024). Moreover, the cell-based technologies of the engineering of extracellular vesicles and synthetic cells will tend to increase the pace of clinical translation of the next-generation drug delivery system, especially to the central nervous system-linked disease or to metastatic cancers (Erana-Perez et al., 2024; Gutierrez-Millan et al., 2021).

Generally speaking, synthetic nanoparticles still have the upper hand in production and regulatory compliance, but engineered exosomes are quickly developing as biologically superior carriers with revolutionary capability. Biomimetic and hybrid nanotechnologies are expected to introduce the next frontiers in targeted drug delivery with a convergence of the two systems.

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