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A Review on "Nanovesicular Drug Delivery Systems: Recent Advances, Challenges, and Future Perspectives

Ajay Sunil Thorat[1], Kalyani Jaywant Bhor[2], Payal Dnyaneshwar Nannaware[3], Soham Sandeep Lokare[4], Sharad Balu Narhe[5].

[1]Student, [2]Assistant Professor, [3]Student, [4]Student, [5]Student,
Samarth Institute of Pharmacy, Belhe, Maharashtra, India
[1]ajaythorat3864@gmail.com,[2]bhorkalyani63@gmail.com ,[3]nannawarepayal2@gmail.com
,[4]lokaresoham84@gmail.com,[5]sharadnarhe18@gmail.com

Abstract: *Nanovesicular drug delivery systems have emerged as a significant advancement in modern pharmaceutics due to their ability to enhance drug solubility, stability, bioavailability, and targeted delivery. These nanoscale carriers overcome limitations of conventional drug delivery systems, such as poor absorption, rapid degradation, and lack of site specificity. They include various types such as liposomes, niosomes, ethosomes, transferosomes, and phytosomes, and are widely used in applications like cancer therapy, transdermal delivery, vaccine delivery, gene therapy, and management of chronic diseases. The objective of this review is to present a comprehensive overview of nanovesicular systems, including their classification, formulation strategies, therapeutic applications, recent advancements, and associated challenges. Recent developments such as surface-functionalized vesicles, ligand-targeted systems, and stimuli-responsive nanocarriers have significantly improved targeted and controlled drug delivery. Additionally, advancements in fabrication techniques and hybrid vesicular systems have enhanced drug loading capacity, permeability, and stability. Despite these advantages, several challenges persist, including physical and chemical instability, drug leakage, high production costs, scalability issues, and regulatory barriers that restrict large-scale clinical use.*

Keywords: Nanovesicles , Drug delivery, Liposomes, Niosomes, Targeted delivery, Nanocarriers, Controlled release.

I. INTRODUCTION

The therapeutic management of complex diseases demands not merely efficacious drug molecules but sophisticated delivery architectures capable of overcoming the multifaceted biological barriers that impede drug efficacy. Conventional pharmaceutical formulations tablets, capsules, and simple injectable solutions while clinically indispensable, are fundamentally constrained by limitations including non-specific biodistribution, rapid systemic clearance, poor aqueous solubility of many modern therapeutic entities, gastrointestinal degradation, and the inability to achieve sustained local concentrations at target sites. These shortcomings translate directly into suboptimal therapeutic outcomes, dose-limiting toxicities, and diminished patient compliance, particularly in the management of chronic conditions such as cancer, neurodegenerative disorders, and autoimmune diseases. 1

The advent of nanotechnology has profoundly transformed the landscape of pharmaceutical sciences over the past four decades. The strategic application of nanoscale engineering principles to drug delivery has enabled the design of carrier systems with exquisite control over drug loading, release kinetics, surface functionalization, and biological targeting. Among the diverse array of nanocarrier platforms including polymeric nanoparticles, solid lipid nanoparticles, dendrimers, carbon nanotubes, and inorganic nanocarriers vesicular systems occupy a privileged position by virtue of

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their structural versatility, biocompatibility, and capacity to accommodate both hydrophilic and lipophilic therapeutic agents simultaneously.

The importance of NVDDS in contemporary pharmaceutical research and clinical practice is evidenced by the regulatory approval of landmark formulations including Doxil (liposomal doxorubicin), AmBisome (liposomal amphotericin B), Onpattro (lipid nanoparticle siRNA delivery), and the mRNA COVID-19 vaccines, which collectively demonstrate the transformative clinical potential of lipid-based nanovesicular platforms. These approvals have catalyzed enormous investment in next-generation nanovesicular technologies incorporating biological targeting moieties, stimuli-responsive elements, and gene delivery capabilities. The present review provides a comprehensive and critical appraisal of the current state of knowledge regarding nanovesicular drug delivery systems. It systematically addresses the classification, composition, methods of preparation, physicochemical characterization, mechanisms of drug release and targeting, and therapeutic applications of the major classes of nanovesicular systems. Furthermore, the review highlights transformative recent advances including smart and stimuli-responsive vesicles, biologically derived exosomes, ligand-conjugated targeted carriers, and AI-assisted formulation development, while critically examining the challenges that must be addressed to accelerate the clinical translation of these promising platforms.

II. OVERVIEW OF NANO VESICULAR DRUG DELIVERY SYSTEMS

Nano vesicular systems are defined as colloidal particles in the nanometre size range (typically 10–1000 nm) that adopt a closed, bilayer or multilamellar vesicular architecture spontaneously formed by the self-assembly of amphiphilic molecules in an aqueous medium. The thermodynamic driving force for vesicle formation is the hydrophobic effect, wherein the energetically unfavorable exposure of hydrophobic acyl chains to aqueous environments is minimized through the formation of closed bilayer membranes. The precise geometry of the resulting self-assembled structure spherical vesicles, tubules, or bicelles is governed by the critical packing parameter (CPP) of the amphiphilic molecule, defined as the ratio of the molecular volume to the product of the interfacial area per headgroup and the critical chain length. 2

The architectural organization of a typical nanovesicle consists of an outer hydrophilic shell formed by the polar headgroups of the bilayer-forming amphiphiles, a hydrophobic intramembranous domain composed of the acyl chains, and an aqueous inner core. This tripartite architecture confers exceptional versatility in drug encapsulation: hydrophilic drugs (e.g., peptides, oligonucleotides, water-soluble anticancer agents) are sequestered within the aqueous lumen, while lipophilic drugs (e.g., poorly water-soluble chemotherapeutics, steroidal hormones) partition into the hydrophobic bilayer domain. Amphiphilic drug molecules can simultaneously occupy interfacial positions between the headgroup region and the acyl chain domain.

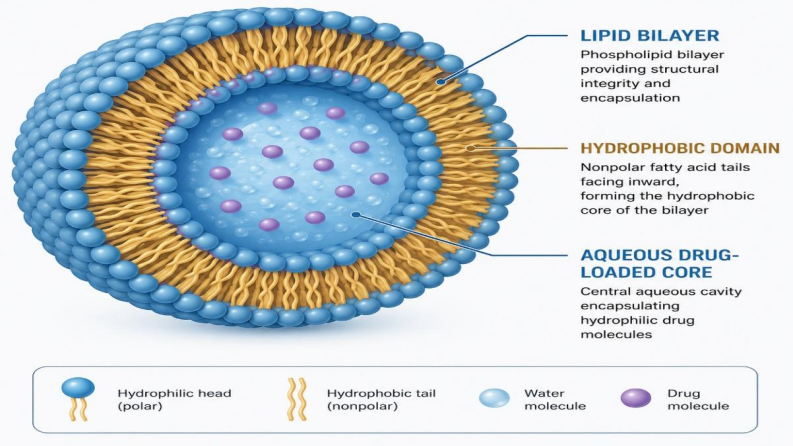

Figure 1: Schematic representation of nanovesicle structure showing the lipid bilayer, hydrophobic domain, and aqueous drug-loaded core

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The fundamental advantages of nanovesicular systems over conventional drug delivery approaches are multifold and have been extensively substantiated in preclinical and clinical studies. Enhanced bioavailability, resulting from improved drug solubilization, reduced first-pass metabolism, and prolonged systemic circulation enabled by PEGylation (stealth technology), represents one of the most clinically significant attributes. The enhanced permeability and retention (EPR) effect facilitates passive accumulation of nanovesicles in solid tumors due to the fenestrated tumor vasculature and impaired lymphatic drainage, providing a natural mechanism for selective tumor targeting without the need for active targeting ligands. Surface functionalization with targeting ligands antibodies, aptamers, peptides, and small molecules further enables receptor-mediated endocytosis and precise intracellular drug delivery, minimizing off-target toxicity. 3

III. CLASSIFICATION OF NANOVESICULAR DRUG DELIVERY SYSTEMS

The taxonomy of nanovesicular systems is primarily based on the chemical nature of the membrane-forming amphiphile, the architectural organization of the bilayer, and the biological origin of the vesicle. Six principal classes of nanovesicular systems have achieved significant pharmaceutical and clinical relevance, each with distinctive physicochemical properties, formulation considerations, and therapeutic applications.

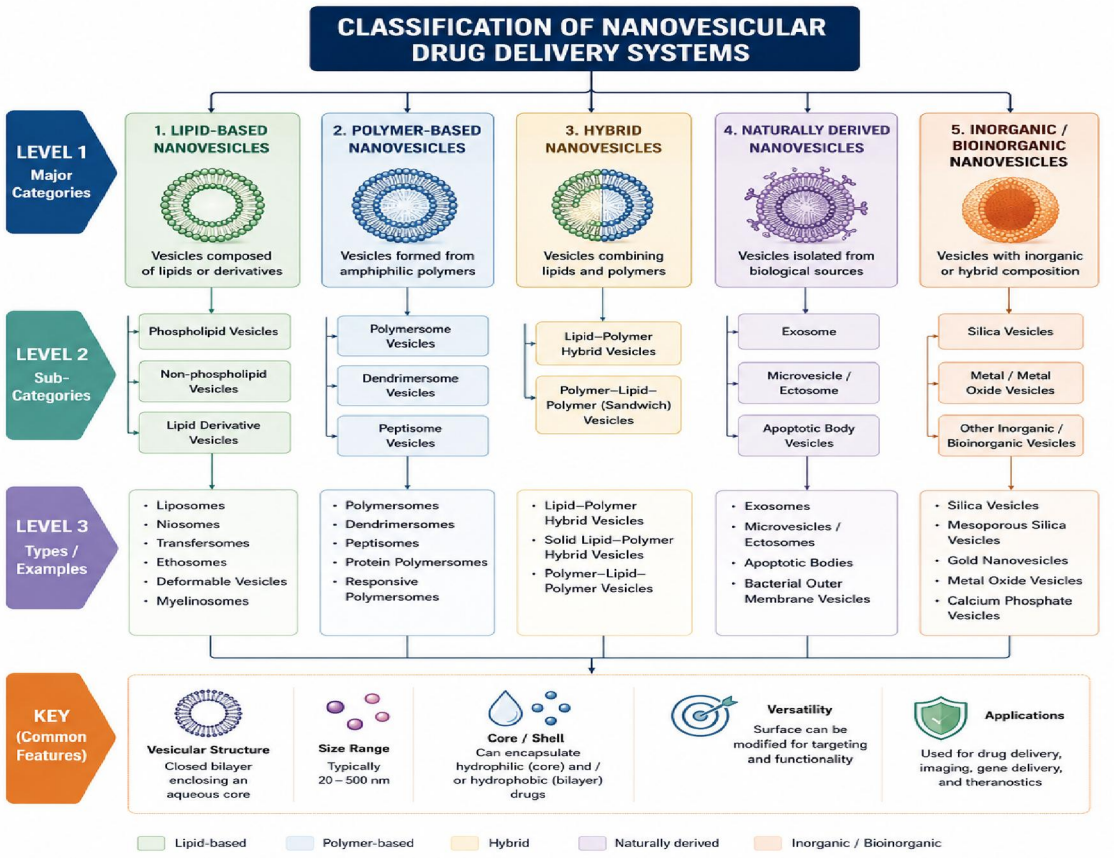

Figure 2: Classification of nanovesicular drug delivery systems — major categories and their hierarchical relationships

3.1 Liposomes

Liposomes are the archetypal and most extensively studied class of nanovesicular drug delivery systems, first described by Alec Bangham in 1965. These spherical vesicular structures are composed of one or more concentric phospholipid

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bilayers enclosing an aqueous core and are formed by the spontaneous self-assembly of amphiphilic phospholipid molecules in aqueous media. The phospholipid bilayer closely mimics the structural organization of biological cell membranes, conferring exceptional biocompatibility and biodegradability. Structurally, liposomes are classified by the number of lamellae: unilamellar vesicles (ULV), comprising a single bilayer and further subdivided into small unilamellar vesicles (SUV, 20–100 nm) and large unilamellar vesicles (LUV, 100–1000 nm); multilamellar vesicles (MLV, >500 nm) consisting of multiple concentric bilayers; and multivesicular vesicles (MVV) containing multiple non-concentric aqueous compartments.

The composition of liposomes typically encompasses phospholipids such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), and phosphatidylglycerol (PG) sourced from natural origins (soy lecithin, egg lecithin) or synthesized as high-purity defined-chain species (DPPC, DSPC, DOPC). Cholesterol is an indispensable structural component incorporated at molar ratios of 30–50% to modulate bilayer fluidity, reduce permeability, and enhance mechanical stability by intercalating between phospholipid acyl chains and filling packing defects. Charged lipids such as DOTAP (cationic) and DOPA (anionic) are incorporated to modulate electrostatic interactions with nucleic acids (for gene delivery) or charged drug molecules. PEGylated lipids (DSPE-PEG2000) are incorporated in stealth liposomal formulations to create a hydrophilic steric barrier that suppresses opsonization and extends systemic circulation half-life from minutes to many hours. 4

The principal advantages of liposomes include their structural resemblance to biological membranes, capacity for co-encapsulation of hydrophilic and hydrophobic drugs, surface engineering flexibility, biodegradability and minimal immunogenicity of natural phospholipids, and their well-established clinical track record. Clinically approved liposomal formulations include Doxil/Caelyx (pegylated liposomal doxorubicin), DaunoXome (liposomal daunorubicin), AmBisome (liposomal amphotericin B), Depocyt (liposomal cytarabine), and Onpattro (LNP-siRNA). The principal limitations of liposomes include relatively high production costs for pharmaceutical-grade phospholipids, susceptibility to oxidative and hydrolytic degradation of unsaturated phospholipids, challenges in large-scale manufacturing reproducibility, and limited drug loading efficiency for many hydrophobic molecules.

3.2 Niosomes

Niosomes are non-ionic surfactant-based vesicles, structurally analogous to liposomes but formed from the self-assembly of non-ionic surfactants principally Spans (sorbitan esters), Tweens (polysorbates), and Brij series in the presence of cholesterol and, optionally, charge-inducing agents such as dicetyl phosphate or stearylamine. The bilayer-forming capacity of non-ionic surfactants is governed by their HLB (hydrophilic-lipophilic balance) value and their critical packing parameter; surfactants with HLB values between 3 and 8 generally form stable bilayer vesicles. Niosomes encapsulate hydrophilic drugs within their aqueous core and lipophilic drugs within the surfactant bilayer membrane, offering a versatile dual-compartment encapsulation strategy comparable to liposomes.

The principal advantage of niosomes over liposomes lies in their substantially lower raw material costs, superior chemical stability non-ionic surfactants lacking the oxidation-prone double bonds of unsaturated phospholipids exhibit significantly better shelf-life and greater physicochemical stability under physiological conditions. Niosomes demonstrate remarkable potential in transdermal, ophthalmic, and mucosal drug delivery due to their ability to interact with the stratum corneum and mucous membranes, enhancing local drug permeation. Span 60-cholesterol niosomes loaded with aceclofenac demonstrated 4.8-fold enhancement in transdermal flux compared to the free drug suspension. Limitations include potential surfactant-related cytotoxicity at higher concentrations, tendency toward aggregation and fusion on storage, and limited clinical validation compared to liposomes.

3.3 Transfersomes

Transfersomes,represent a class of ultradeformable or elastic vesicles specifically engineered for transdermal drug delivery via non-occluded intact skin. These modified vesicles are formulated using phospholipids (soy phosphatidylcholine) in combination with membrane-softening agents termed edge activators single-chain amphiphiles

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including sodium cholate, sodium deoxycholate, Tween 80, dipotassium glycyrrhizinate, and Span 80 incorporated at 10–25% w/w concentrations. The edge activators destabilize the lipid bilayer, dramatically reducing its bending energy and increasing vesicle deformability by orders of magnitude compared to conventional liposomes. Transfersomal vesicles can deform under the transepidermal osmotic gradient generated by the hydration difference between the hydrated vesicle exterior and the drier deeper skin layers. 5

The transdermal permeation mechanism of transfersomes involves their driving through pore channels in the stratum corneum with mean pore radii of approximately 20–30 nm, far smaller than the mean transfersome diameter of 150–300 nm by squeezing and deforming through these channels without disruption, driven by the transepidermal water activity gradient. This enables transfersomes to deliver drugs into the viable epidermis and dermis, and even into systemic circulation in some cases, without skin occlusion. Transfersomal formulations of diclofenac, ketoprofen, testosterone, insulin, and interferon have demonstrated significantly enhanced transdermal penetration and bioavailability. The key limitation of transfersomes is their relative instability under occluded conditions, which abolishes the osmotic driving force for transdermal penetration.

3.4 Ethosomes

Ethosomes are novel phospholipid-based vesicular carriers developed by Touitou et al. in 2000, distinguished from conventional liposomes by their high ethanol content (20–45% w/w) as the primary formulation component alongside phospholipids and water. The high ethanol concentration serves multiple complementary functions: it disrupts the ordered lipid packing of both the ethosomal bilayer and the stratum corneum lipid lamellae, reducing bilayer rigidity and enabling the carrier to penetrate through the tightly packed intercellular lipid matrix of the stratum corneum; it acts as a permeation enhancer by fluidizing epidermal lipids; and it modulates drug partitioning from the formulation into the skin. The net result is a synergistic enhancement of transdermal permeation and drug penetration into deeper viable skin layers and, in many cases, the systemic circulation. 6

Comparative permeation studies have consistently demonstrated 2–10 fold greater transdermal flux from ethosomal formulations compared to conventional liposomes and hydroalcoholic solutions, attributable to the combined membrane-fluidizing effects. Ethosomes have demonstrated particular utility for delivering lipophilic drugs such as testosterone, cannabidiol, minoxidil, acyclovir, erythromycin, and colchicine through intact skin. The ethosomal system is amenable to incorporation in hydrogel matrices for topical application, and has shown promising results in the management of skin conditions including psoriasis, alopecia, and herpes labialis. The primary limitations include drug leakage at high ethanol concentrations, potential skin irritation with prolonged application, and challenges in maintaining vesicle integrity during long-term storage.

3.5 Phytosomes

Phytosomes (also termed herbosomal complexes) represent a specialized class of lipid-compatible molecular complexes formed by the stoichiometric complexation of standardized plant extracts or purified phytoconstituents with phospholipids principally soy phosphatidylcholine or phosphatidylserine in non-protic organic solvents, followed by solvent removal to yield dry phytosome complexes. The complexation chemistry involves the formation of hydrogen bonds and other non-covalent interactions between the phosphate polar headgroup of the phospholipid and the polar functional groups (hydroxyl, carbonyl) of the phytoconstituent, generating a well-defined phospholipid-phytomolecule complex with distinct physicochemical properties. Unlike simple admixtures of plant extract and lecithin, phytosomes exhibit characteristic spectroscopic profiles (NMR, IR, DSC) that confirm true molecular complexation.

The principal pharmaceutical rationale for phytosome technology is the dramatic improvement in the oral bioavailability of polyphenolic phytoconstituents flavonoids, terpenes, and phenolic acids that are characterized by poor intestinal absorption due to inadequate membrane permeability and/or extensive presystemic metabolism. The phospholipid complexation renders these hydrophilic phytomolecules amphiphilic, facilitating their interaction with intestinal epithelial membranes and enhancing transcellular absorption. Landmark phytosomal products include Meriva

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(curcumin phytosome, 29-fold bioavailability enhancement), Siliphos (silybin phytosome, 4.6-fold enhancement), Greenselect Phytosome (green tea catechin complex), and Ginkgoselect Phytosome. These products have demonstrated clinically significant improvements in efficacy for conditions including osteoarthritis, liver diseases, and cognitive disorders. 7

3.6 Exosomes and Extracellular Vesicles

Exosomes are naturally secreted nanoscale extracellular vesicles (40–160 nm diameter) of endosomal origin, released by virtually all mammalian cell types through the fusion of multivesicular bodies (MVBs) with the plasma membrane. These biologically derived nanovesicles possess a lipid bilayer membrane enriched in sphingomyelin, cholesterol, and glycosphingolipids, and bear surface proteins including tetraspanins (CD9, CD63, CD81), heat shock proteins (HSP70, HSP90), and cell-type-specific surface markers that confer exosome-specific cell tropism and endosomal uptake capability. Their cargo encompassing proteins, mRNAs, miRNAs, and genomic DNA reflects their cellular origin and mediates intercellular communication across physiological and pathological contexts.

The biological properties of exosomes nanometric dimensions enabling passage through biological barriers, inherent biocompatibility, lack of immunogenicity (particularly for autologous exosomes), and endogenous targeting capability make them uniquely attractive drug delivery vehicles. Drug loading into exosomes can be achieved by passive incubation, electroporation, sonication, freeze-thaw cycling, or co-extrusion with lipid films. Surface engineering of exosomes with targeting peptides (iRGD, T7, RVG) has enabled targeted delivery to tumor cells, brain, and muscles. Exosome-based delivery of doxorubicin, paclitaxel, siRNA, miRNA, and CRISPR-Cas9 components has demonstrated superior efficacy and minimal toxicity in multiple preclinical cancer models. The principal current challenges are the complexity and limited scalability of exosome production from cell culture, batch-to-batch heterogeneity, and the absence of standardized manufacturing and characterization guidelines. 8

IV. MATERIALS USED IN NANOVESICLE FORMULATION

The functional and physicochemical properties of nanovesicular systems are critically determined by the nature, purity, and relative proportions of the constitutive materials. A rational, evidence-based approach to material selection is essential for optimizing encapsulation efficiency, bilayer stability, release kinetics, and in vivo performance.

Phospholipids form the structural backbone of liposomes, transfersomes, ethosomes, and phytosomes. Naturally derived phospholipids soybean phosphatidylcholine (SPC) and egg phosphatidylcholine (EPC) are widely used for their cost-effectiveness and commercial availability, though the presence of unsaturated fatty acid chains renders them susceptible to oxidative degradation. Synthetic phospholipids with defined acyl chain compositions DPPC (dipalmitoyl phosphatidylcholine, Tm 41°C), DSPC (distearoylphosphatidylcholine, Tm 55°C), and DOPC (dioleoyl phosphatidylcholine, Tm -20°C) offer superior batch-to-batch consistency and tailorable phase transition temperatures. The choice of phospholipid acyl chain saturation and length directly governs membrane fluidity, permeability, and drug release rate. 9

Cholesterol (CHO) is incorporated into phospholipid membranes as a critical bilayer modulator. At physiological temperatures, cholesterol intercalates between phospholipid acyl chains, reducing bilayer permeability, increasing mechanical rigidity, and suppressing drug leakage through the liquid crystalline-gel phase transition. Optimal cholesterol content (30–50 mol%) in liposomal formulations has been shown to extend drug retention and improve stability. Non-ionic surfactants (Span 60, Tween 80, Brij 35, Brij 52) serve as primary vesicle-forming amphiphiles in niosomes, while also functioning as edge activators in transfersomal formulations.

PEGylated lipids, particularly DSPE-PEG2000, are incorporated into stealth liposomes and lipid nanoparticles to generate a dense hydrophilic polymer brush on the vesicle surface that sterically inhibits opsonin adsorption and recognition by mononuclear phagocyte system (MPS) components, extending plasma half-life from minutes (conventional liposomes) to 18–24 hours (PEGylated liposomes). Cationic lipids including DOTAP, DOTMA, DC-Chol, and ionizable lipids such as DLin-MC3-DMA are essential components of nucleic acid delivery nanoparticles,

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enabling electrostatic complexation with anionic nucleic acids. Stabilizers including trehalose, sucrose, mannitol, and hydroxypropyl-β-cyclodextrin are incorporated in lyophilized nanovesicle formulations to prevent aggregation and preserve vesicular integrity during freeze-drying and long-term storage.

V. METHODS OF PREPARATION OF NANOVESICLES

The method of nanovesicle preparation profoundly influences the resulting vesicle size, lamellarity, encapsulation efficiency, and batch reproducibility. The selection of an appropriate preparation method must consider the physicochemical properties of the drug (hydrophilicity, heat sensitivity, organic solvent compatibility), the desired vesicle characteristics, and the feasibility of scale-up to manufacturing scale. 10

Table 1: Summary of nanovesicle preparation methods, principles, advantages, and limitations

Preparation Method	Principle	Vesicle Type	Advantages	Limitations
Thin-Film Hydration	Lipid film formed by solvent evaporation; hydrated with aqueous buffer under agitation	MLV primarily	Simple, widely applicable; high drug loading for hydrophobic drugs	Large, heterogeneous vesicles; poor hydrophilic encapsulation
Reverse Phase Evaporation (REV)	Water-in-oil emulsion formed; solvent removed under reduced pressure	LUV	High entrapment of hydrophilic drugs (>60%); single bilayer	Organic solvent residues; lengthy process; fragile vesicles
Probe/Bath Sonication	Ultrasonic energy disrupts MLVs to form SUVs	SUV	Small uniform vesicles (<100 nm); rapid; simple	Metal contamination (probe); low encapsulation; shear heating
Extrusion	Vesicles forced through polycarbonate membranes of defined pore size	SUV/LUV	Narrow size distribution; scalable; no organic solvents in final step	Membrane clogging; moderate yield; specialized equipment
Solvent Injection	Lipid dissolved in ethanol injected into aqueous phase under agitation	SUV/LUV	Simple; rapid; organic solvent free product	Residual ethanol; polydisperse size distribution
Microfluidization	High-pressure homogenization through microchannels	SUV/LUV	Scalable; uniform; sterile processing compatible	High equipment cost; energy intensive; heat generation
Dehydration-Rehydration	Preformed vesicles lyophilized and rehydrated with drug solution	MLV/LUV	High hydrophilic drug encapsulation; stable dry formulation	Size increase on rehydration; requires optimization
Freeze-Thaw Method	Repeated freeze-thaw cycles applied to SUV suspension with drug	LUV	Enhanced drug entrapment; simple	Fusion/aggregation; size variability; slow

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Among these methods, the thin-film hydration technique remains the most universally employed laboratory-scale method for initial formulation screening, attributed to its operational simplicity and compatibility with virtually all phospholipid compositions. However, the large, polydisperse MLVs produced typically require downstream size reduction by extrusion or sonication to achieve the target size range. The extrusion method, employing stacked polycarbonate membranes with defined pore sizes (100, 200, 400 nm), consistently yields monodisperse populations with polydispersity indices (PDI) below 0.2 and is amenable to scale-up. Microfluidics-based nanovesicle preparation, exploiting herringbone or Y-junction mixer geometries, has emerged as a transformative technology for pharmaceutical manufacturing, enabling continuous, GMP-compatible production of nanovesicles with outstanding batch-to-batch reproducibility and near real-time process control.

VI.CHARACTERIZATION OF NANOVESICULAR SYSTEMS

Comprehensive physicochemical characterization is an obligatory component of nanovesicle development, serving to establish quality attributes, guide formulation optimization, ensure batch-to-batch reproducibility, and fulfill regulatory requirements. The following characterization parameters are universally recognized as critical quality attributes (CQAs) for nanovesicular drug delivery systems. 11

Table 2: Critical quality attributes for nanovesicle characterization methods, targets, and significance

Parameter	Analytical Method	Accepted Range/Target	Significance
Particle Size (Z-avg)	Dynamic Light Scattering (DLS)	100–300 nm (tumor targeting); <200 nm (IV)	Determines biodistribution, EPR effect, filtration
Polydispersity Index (PDI)	DLS	<0.2 (monodisperse)	Batch homogeneity; formulation stability
Zeta Potential	Laser Doppler Electrophoresis	>±30 mV (stable); ±10 mV (unstable)	Electrostatic stability; aggregation prediction
Entrapment Efficiency (EE%)	Ultracentrifugation/dialysis + HPLC/UV	>70% (acceptable); >85% (optimal)	Drug loading efficiency; economic feasibility
Drug Loading (DL%)	Gravimetric/spectroscopic	As high as possible	Therapeutic dose achievability
Morphology	TEM, cryo-TEM, AFM, FESEM	Spherical, intact bilayers	Structural integrity confirmation
Membrane Fluidity	Fluorescence anisotropy, DSC	Below gel-liquid crystal transition	Stability and release prediction
In Vitro Drug Release	Franz diffusion cell, dialysis bag	Sustained/controlled profile	Biopharmaceutical prediction
Stability	ICH Q1A protocols (25°C/60%RH; 40°C/75%RH)	No significant change over shelf-life	Shelf-life and storage conditions

Dynamic light scattering (DLS) remains the predominant workhorse for routine size and PDI determination, offering rapid, non-destructive measurements from nanogram quantities of material. However, DLS measures the hydrodynamic diameter of the vesicle including its hydration shell and any surface grafted polymer chains, which may overestimate

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the geometrical vesicle size measured by electron microscopy. Cryogenic transmission electron microscopy (cryo-TEM) is considered the gold standard for nanovesicle structural characterization, enabling direct visualization of vesicle morphology, lamellarity, and internal aqueous compartments in their near-native hydrated state without fixation or staining artifacts. Nanoparticle tracking analysis (NTA) complements DLS by providing particle-by-particle size measurement and absolute particle concentration determination, enabling more precise characterization of polydisperse or bimodal distributions.

Entrapment efficiency is typically determined by separating drug-loaded vesicles from free drug by ultracentrifugation (100,000×g, 1–2 hours), size exclusion chromatography, or equilibrium dialysis, followed by quantification of the entrapped drug by validated HPLC or UV spectrophotometric methods. Zeta potential, a measure of the electrostatic potential at the hydrodynamic shear plane of the vesicle surface, is a critical predictor of colloidal stability: vesicles with zeta potential magnitudes exceeding ±30 mV exhibit electrostatic repulsion sufficient to prevent aggregation, while values approaching neutrality indicate susceptibility to flocculation. However, PEGylated vesicles may display apparent neutrality despite good steric stabilization, underscoring the limitations of zeta potential as a universal stability predictor for sterically stabilized systems. 12

VII. MECHANISMS OF DRUG RELEASE AND TARGETING

The pharmacokinetic and pharmacodynamic performance of nanovesicular drug delivery systems is critically governed by the mechanisms through which encapsulated drugs are released and by which the carrier gains access to target tissues and cells. A nuanced understanding of these mechanisms is essential for the rational design of effective nanovesicular therapeutics.

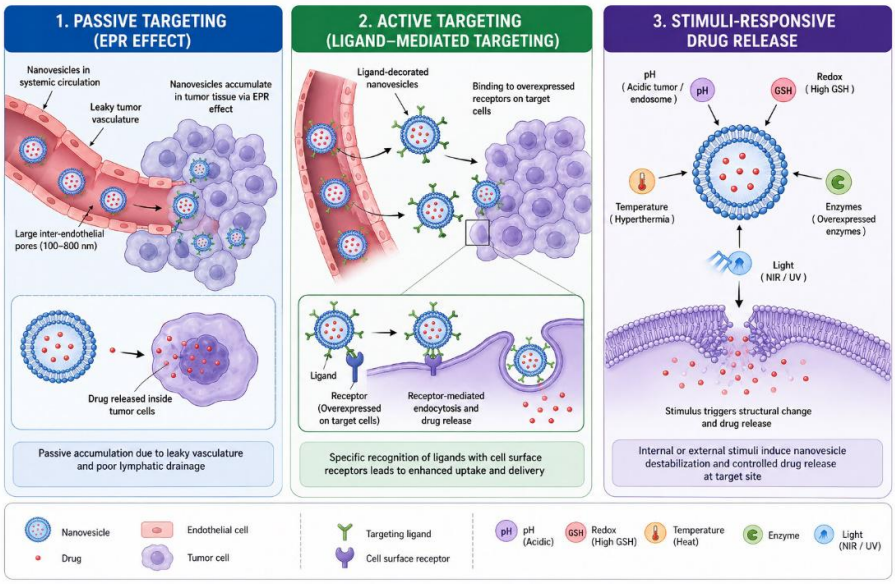

Figure 3: Schematic illustration of passive targeting (EPR effect), active ligand-mediated targeting, and stimuli-responsive drug release mechanisms

PASSIVE TARGETING

Passive targeting of nanovesicles to solid tumors exploits the enhanced permeability and retention (EPR) effect, a pathophysiological phenomenon arising from the abnormal characteristics of tumor vasculature and lymphatics. Tumor blood vessels, formed by rapid and aberrant angiogenesis, are poorly formed with irregular architecture, wide inter-endothelial junctions (200–1200 nm), and deficient pericyte coverage, creating fenestrations through which circulating nanoparticles extravasate into the tumor interstitium. Simultaneously, impaired or absent tumor lymphatic drainage

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fails to clear the extravasated nanoparticles, resulting in progressive accumulation at drug concentrations that may be 10–100 fold higher than in normal tissues. The EPR effect is maximized for nanoparticles in the 50–200 nm size range, with prolonged circulation times achieved through PEGylation. 13

ACTIVE TARGETING

Active targeting is achieved through the conjugation of targeting ligands on the nanovesicle surface that engage specific receptors overexpressed on target cells. Targeting moieties include monoclonal antibodies and antibody fragments (trastuzumab for HER2-positive breast cancer, cetuximab for EGFR-expressing tumors), peptides (RGD for integrin αvβ3, iRGD for tumor penetration, HAIYPRH for transferrin receptor), aptamers (AS1411 for nucleolin, EpCAM aptamers), folate ligands (for folate receptor-overexpressing cancers), and transferrin for the transferrin receptor. Upon ligand-receptor engagement, receptor-mediated endocytosis internalizes the nanovesicle into early endosomes, which mature into late endosomes/lysosomes, providing an intracellular drug release pathway. Active targeting does not necessarily increase tumor accumulation over passive EPR-mediated delivery but substantially enhances intracellular drug delivery and can overcome multidrug resistance mechanisms.

STIMULI-RESPONSIVE RELEASE

Stimuli-responsive or smart nanovesicular systems are engineered to release their drug payload selectively in response to specific endogenous or exogenous triggers, enabling on-demand drug liberation at the target site. Endogenous stimuli exploited in nanovesicular design include the acidic pH of tumor microenvironments (pH 6.5–6.8) and late endosomes (pH 5.0–5.5), elevated glutathione concentrations in tumor cytoplasm, and the overexpression of specific enzymes (matrix metalloproteinases, hyaluronidase, phospholipase A2). pH-sensitive nanovesicles incorporating ionizable lipids or pH-labile chemical bonds undergo structural destabilization and content release under acidic conditions. Glutathione-responsive vesicles incorporating disulfide cross-links undergo reductive cleavage in the cytoplasmic reducing environment, enabling selective intracellular drug release. 14

Exogenous stimuli-responsive nanovesicles respond to temperature elevation, light irradiation, ultrasound, and magnetic fields. Thermosensitive liposomes (TSL) incorporating phospholipids with gel-to-liquid crystal transition temperatures slightly above physiological temperature (e.g., DPPC/MSPC formulations, Tm ~41°C) release their drug cargo rapidly and completely upon mild local hyperthermia (40–42°C), enabling triggered drug release in tumors heated by focused ultrasound or radiofrequency energy. The clinical product ThermoDox (heat-activated liposomal doxorubicin) exemplifies the clinical translation of thermosensitive liposomal technology. Photosensitive vesicles incorporating photocleavable lipids or photoisomerizable amphiphiles enable light-triggered drug release in accessible superficial tissues. Magnetically responsive vesicles containing superparamagnetic iron oxide nanoparticles (SPIONs) enable MRI-guided targeting and alternating magnetic field-triggered hyperthermia for drug release.

VIII. THERAPEUTIC APPLICATIONS OF NANOVESICULAR SYSTEMS

The versatility of nanovesicular drug delivery systems in accommodating diverse drug classes, targeting diverse disease sites, and enabling sophisticated release kinetics has facilitated their application across an exceptionally broad spectrum of therapeutic areas. 15

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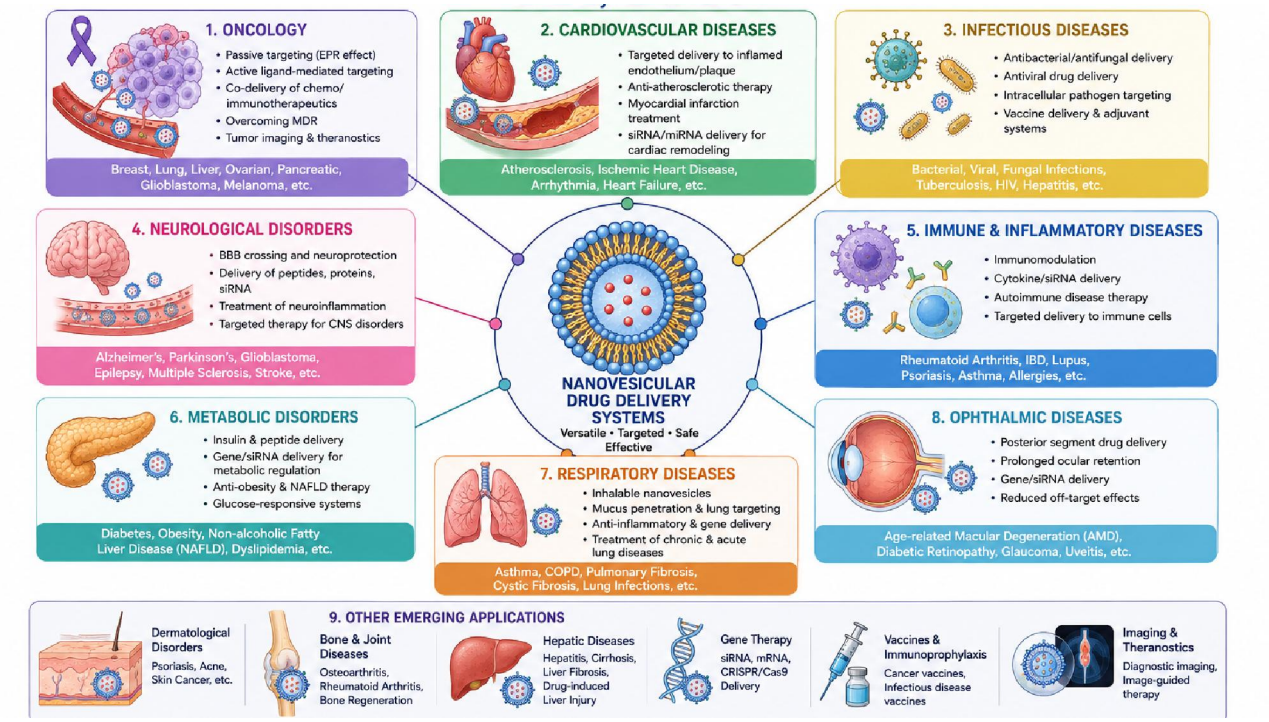

Figure 4: Therapeutic application domains of nanovesicular drug delivery systems across major disease areas

8.1 Cancer Therapy

Oncology represents the dominant therapeutic application domain for nanovesicular drug delivery systems, driven by the compelling need to overcome the profound limitations of conventional cytotoxic chemotherapy — severe systemic toxicity, multidrug resistance, and poor tumor penetration. Liposomal formulations of doxorubicin (Doxil/Caelyx), daunorubicin (DaunoXome), vincristine (Marqibo), and irinotecan (Onivyde) have received regulatory approval based on demonstrated improvements in therapeutic index compared to free drug. PEGylated liposomal doxorubicin achieves tumor drug concentrations approximately 4–16 fold higher than equivalent free doxorubicin doses in clinical studies, while substantially reducing cardiotoxicity (the dose-limiting toxicity of free doxorubicin) and alopecia. Targeted nanovesicles bearing HER2-specific antibodies (MM-302 anti-HER2 liposomal doxorubicin), folate receptor ligands, and transferrin receptor aptamers have demonstrated receptor-specific uptake and enhanced antitumor efficacy in preclinical tumor models.

Beyond small molecule chemotherapeutics, nanovesicular platforms have become indispensable vehicles for the delivery of nucleic acid therapeutics siRNA, miRNA, antisense oligonucleotides, mRNA, and CRISPR-Cas9 components that are precluded from direct systemic administration by their rapid nuclease degradation, renal clearance, and inability to penetrate cell membranes. Onpattro (patisiran, Alnylam), the first FDA-approved RNA interference therapeutic, employs ionizable lipid nanoparticles to deliver siRNA targeting transthyretin mRNA in hepatocytes, establishing the clinical proof-of-concept for lipid nanovesicle-mediated gene silencing. The dramatic clinical success of LNP-mRNA COVID-19 vaccines (Comirnaty, Spikevax) has further demonstrated the transformative potential of lipid nanovesicle technology for nucleic acid delivery. 16

8.2 Transdermal Drug Delivery

The skin presents formidable physicochemical barriers to drug permeation, with the outermost stratum corneum (SC) a 10–15 µm layer of cornified, terminally differentiated keratinocytes embedded in a continuous matrix of organized lipid

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lamellae comprising ceramides, free fatty acids, and cholesterol constituting the primary rate-limiting barrier. Conventional topical formulations achieve only superficial drug deposition in the SC, limiting their utility to drugs targeting the skin surface or requiring local cutaneous activity. Nanovesicular systems transfersomes, ethosomes, niosomes, and glycerosomes enhance transdermal drug delivery through multiple synergistic mechanisms: vesicle-SC lipid interactions that perturb the ordered lipid bilayer architecture, vesicle deformability enabling mechanical squeezing through SC lipid channels, and hydration-mediated enhancement of SC lipid fluidity.

Transfersomal formulations of diclofenac have demonstrated systemic bioavailability approaching 50% of equivalent oral doses through intact skin in human volunteers, with the major advantage of eliminating gastrointestinal side effects. Ethosomal testosterone gel has been evaluated as a transdermal hormone replacement platform with bioavailability superior to conventional gels. Niosomal formulations of flurbiprofen, indomethacin, and piroxicam demonstrated 3–7 fold enhancement of in vitro permeation through excised human skin compared to conventional topical gels, with corresponding improvements in anti-inflammatory efficacy in rat paw edema models.

8.3 Ocular Drug Delivery

Effective drug delivery to ocular target tissues particularly the posterior segment (retina, choroid, vitreous) confronts an exceptional array of anatomical, physiological, and pharmacokinetic barriers including corneal epithelium, aqueous humor dilution and drainage, blood-aqueous barrier, and blood-retinal barrier. Nanovesicular systems offer unique advantages for ocular drug delivery: their nanometric dimensions facilitate corneal epithelial penetration; their composition can be optimized to minimize ocular irritation; and surface modification with mucoadhesive polymers (chitosan, hyaluronic acid) prolongs corneal contact time and enhances conjunctival uptake. Liposomal formulations of cyclosporine A, triamcinolone acetonide, and ganciclovir demonstrated enhanced precorneal retention and improved ocular bioavailability in rabbit models. Niosomal timolol maleate eye drops demonstrated significantly prolonged intraocular pressure reduction compared to conventional eye drops in glaucoma models, supporting the potential for reduced dosing frequency and improved patient compliance. 17

8.4 Pulmonary Drug Delivery

Inhalation delivery of nanovesicular drug formulations exploits the large absorptive surface area of the pulmonary epithelium (70–140 m^2), thin alveolar epithelium enabling rapid absorption, extensive subepithelial capillary network, and avoidance of first-pass hepatic metabolism for both local and systemic therapeutic applications. Liposomal amikacin inhalation suspension (Arikayce, Insmed) received FDA approval in 2018 for treatment of refractory Mycobacterium avium complex (MAC) lung infection, representing the first approved inhaled liposomal antibiotic. Arikayce liposomes are specifically designed to be phagocytosed by alveolar macrophages the intracellular sanctuary of mycobacterial infections delivering high intramacrophage amikacin concentrations that eradicate intracellular bacteria inaccessible to systemic aminoglycosides. Niosomal and transfersomal formulations for pulmonary delivery of salbutamol, budesonide, and beclomethasone have demonstrated superior bronchodilator and anti-inflammatory effects with prolonged duration of action in animal models.

8.5 Brain-Targeted Drug Delivery

Drug delivery to the central nervous system confronts the blood-brain barrier (BBB) an extraordinarily selective physiological barrier constituted by tight junction-connected brain microvascular endothelial cells expressing P-glycoprotein and other efflux transporters, supported by astrocytic endfeet and pericytes that excludes >98% of small molecule drugs and virtually all macromolecular therapeutics from brain parenchyma. Nanovesicular systems functionalized with BBB-penetrating targeting ligands transferrin, lactoferrin, low-density lipoprotein receptor-related protein (LRP1) ligands (angiopep-2, ApoE peptide), glucose transporter ligands, and cell-penetrating peptides have demonstrated receptor-mediated transcytosis across the BBB in vitro and in rodent models. PEGylated liposomes bearing OX26 anti-transferrin receptor antibody achieved 5–10 fold higher brain concentrations of encapsulated

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doxorubicin compared to free drug in glioma-bearing rats. Exosomes naturally expressing the RVG peptide (derived from rabies virus glycoprotein) have demonstrated remarkable brain targeting and delivery of siRNA to neurons in vivo through acetylcholine receptor-mediated transport, exemplifying the potential of biologically derived nanovesicles for CNS targeting. 18

8.6 Gene and Vaccine Delivery

The clinical validation of lipid nanoparticle-mRNA vaccine technology by the BNT162b2 (Comirnaty, Pfizer-BioNTech) and mRNA-1273 (Spikevax, Moderna) COVID-19 vaccines with mRNA encapsulated in ionizable lipid nanoparticles achieving robust protein expression and immune responses has fundamentally established lipid nanovesicles as the preeminent platform for mRNA therapeutics. Ionizable lipid nanoparticles (iLNPs), incorporating ionizable lipids that are cationic at acidic endosomal pH but neutral at physiological pH, enable efficient nucleic acid complexation, cellular uptake, and endosomal escape through a proton sponge or membrane fusion mechanism. Beyond infectious disease vaccines, mRNA-LNP technology is being rapidly advanced for cancer neoantigen vaccines, protein replacement therapy, and in vivo gene editing. Lipid nanovesicle-based siRNA therapeutics have advanced through clinical trials for targets including PCSK9 (hypercholesterolemia), transthyretin (amyloidosis), HIF-1α, and multiple oncology targets.

XI. RECENT ADVANCES AND NOVEL APPROACHES

The nanovesicular drug delivery field is undergoing a period of transformative innovation, with convergent advances in materials science, molecular biology, computational modeling, and manufacturing technology enabling a new generation of sophisticated, clinically relevant nanovesicular therapeutics.

9.1 Ligand-Conjugated Targeted Nanovesicles

The field of ligand-targeted nanovesicular delivery has matured substantially, with a growing portfolio of surface functionalization chemistries enabling the precise conjugation of targeting moieties while preserving vesicle integrity and ligand binding affinity. Post-insertion of ligand-lipid conjugates into preformed PEGylated liposomes using micellar lipid exchange the post-insertion technique enables facile surface decoration without exposure of ligands or drugs to harsh synthesis conditions. Site-specific antibody conjugation using maleimide-thiol chemistry, copper-free click chemistry (DBCO-azide), and enzymatic ligation approaches has enabled the generation of immunoliposomes with defined antibody orientation and valency, achieving superior receptor binding affinity compared to randomly coupled immunoconjugates. MM-302 anti-HER2 immunoliposomal doxorubicin demonstrated dose-dependent antitumor responses in HER2-overexpressing breast cancer patients in Phase I/II clinical evaluation. 19

9.2 Smart and Stimuli-Responsive Vesicles

The engineering of next-generation stimuli-responsive nanovesicles has expanded beyond the established pH and thermosensitive platforms to encompass increasingly sophisticated multi-stimuli responsive systems. Dual pH/redox-responsive liposomes incorporating both pH-sensitive lipids and disulfide-crosslinked PEG coatings enable sequential de-PEGylation in the acidic tumor microenvironment followed by glutathione-triggered intracellular drug release, achieving a two-stage targeting strategy that overcomes the PEG dilemma. Reactive oxygen species (ROS)-responsive vesicles incorporating arylboronic acid-modified lipids undergo selective oxidation-triggered disassembly in the elevated ROS environment of tumor cells and inflamed tissues. Ultrasound-responsive echogenic liposomes (ELIPs) encapsulating perfluorocarbon gases produce cavitation upon exposure to focused ultrasound, enabling site-specific drug release under image guidance.

Enzyme-responsive nanovesicles exploiting the overexpression of tumor-associated enzymes represent an emerging class of smart delivery systems. Matrix metalloproteinase-2 (MMP-2)-responsive liposomes bearing MMP-2-cleavable PEG-peptide-lipid conjugates shed their protective PEG corona selectively within MMP-2-rich tumor

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microenvironments, exposing underlying targeting ligands or cell-penetrating peptides for enhanced tumor cell internalization. Phospholipase A2-responsive liposomes undergo bilayer hydrolysis by tumor-secreted PLA2, enabling controlled intratumoral drug release.

9.3 Hybrid Nanovesicular Systems

Hybrid nanovesicles integrating the complementary properties of biological membranes and synthetic lipid bilayers represent a significant frontier in nanovesicular innovation. Cell membrane-coated nanovesicles, fabricated by coating synthetic lipid nanoparticles or polymer nanoparticles with purified plasma membranes from red blood cells, platelets, cancer cells, macrophages, or stem cells, inherit the surface antigen repertoire and biointerfacing properties of the source cell membrane. Red blood cell membrane-coated nanoparticles exhibit extended circulation (elimination half-life >72 hours compared to ~24 hours for PEGylated liposomes) by evading immune recognition through CD47 and other self-recognition signals. Platelet membrane-coated nanovesicles selectively home to damaged vasculature, collagen-rich atherosclerotic plaques, and circulating tumor cells expressing platelet-binding receptors, enabling targeted therapeutic intervention in thrombosis and cancer metastasis.

Lipid-polymer hybrid nanoparticles (LPHNPs) combining a biodegradable PLGA polymer core for controlled drug release with a lipid monolayer or bilayer shell for biocompatibility and surface functionalization offer a versatile architecture that synergistically combines the sustained release characteristics of polymeric nanoparticles with the biomimetic surface properties of lipid vesicles. Co-delivery nanovesicles engineered to simultaneously encapsulate two or more synergistic therapeutic agents in their respective compartments hydrophilic in the aqueous core, hydrophobic in the lipid bilayer enable fixed-ratio co-delivery that overcomes the distinct pharmacokinetic profiles of individual drug components, maintaining synergistic drug ratios at tumor sites. 20

9.4 Artificial Intelligence in Nanovesicle Formulation

The application of artificial intelligence (AI) and machine learning (ML) approaches to nanovesicle formulation development is a rapidly emerging paradigm that promises to dramatically accelerate the iterative formulation optimization process and unlock structure-property relationships that are intractable by traditional univariate experimental approaches. Quantitative structure-property relationship (QSPR) models trained on curated datasets of formulation composition-property relationships have demonstrated capability to predict key quality attributes particle size, zeta potential, encapsulation efficiency from formulation input variables (lipid composition, drug-to-lipid ratio, cholesterol content, preparation method parameters) with prediction errors of 10–20%, sufficient for initial formulation screening. Neural network models incorporating physicochemical descriptors of lipid components have enabled the identification of novel ionizable lipid structures with predicted endosomal escape efficiency for mRNA delivery.

Design of experiment (DoE) methodologies Box-Behnken design, central composite design, and D-optimal design combined with response surface methodology and artificial neural network analysis have become standard tools for the systematic multivariable optimization of nanovesicle formulations, enabling simultaneous optimization of multiple critical quality attributes across a vast formulation space with minimal experimental runs. High-throughput nanoparticle screening platforms employing automated liquid handling, real-time in-process analytics, and ML-guided experimental design have been deployed in academic and industrial settings to explore lipid nanoparticle formulation space at unprecedented throughput evaluating thousands of formulations per week to identify novel compositions for organ-selective mRNA delivery. 21

X. CHALLENGES AND LIMITATIONS

Despite the remarkable scientific advances and growing clinical validation of nanovesicular drug delivery systems, numerous fundamental and practical challenges continue to impede the rapid and widespread translation of laboratory discoveries into approved therapeutic products. 22

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Table 3: Key challenges in nanovesicular drug delivery and current mitigation strategies

Challenge Category	Specific Challenge	Current Mitigation Strategies
Physical Stability	Vesicle aggregation, fusion, and size growth during storage	Lyophilization with cryoprotectants; controlled storage conditions; sterically stabilized PEG coatings
Chemical Stability	Phospholipid hydrolysis and oxidation reducing drug retention	Synthetic saturated phospholipids; antioxidants (α-tocopherol); inert headspace; refrigerated storage
Drug Leakage	Loss of encapsulated drug during storage and circulation	Optimized bilayer composition; cholesterol incorporation; drug-lipid interaction optimization
Scale-Up	Batch-to-batch variability; loss of size distribution control at scale	Microfluidics-based continuous manufacturing; process analytical technology (PAT)
Toxicity	Cationic lipid cytotoxicity; immune activation by PEG antibodies	Ionizable lipids; anti-PEG antibody monitoring; biodegradable lipid design
Regulatory	Absence of universal nanomedicine characterization guidelines	Adherence to EMA/FDA nanotechnology guidance; collaboration with regulatory bodies
Targeting Efficiency	Low in vivo active targeting efficiency (<5% of injected dose to tumor)	Enhanced EPR strategies; co-administration of vessel normalizing agents
Manufacturing Cost	High cost of GMP-grade phospholipids and specialized equipment	Process intensification; continuous manufacturing; novel excipient sourcing
Protein Corona	Non-specific plasma protein adsorption altering targeting specificity	PEGylation optimization; zwitterionic coatings; biomimetic surface engineering
Biomarker Heterogeneity	Intra-tumoral heterogeneity in receptor expression reducing targeting	Multi-ligand targeting; combinatorial approaches; patient stratification

The protein corona phenomenon the rapid adsorption of plasma proteins onto nanovesicle surfaces upon systemic injection, forming a dynamic biomolecular corona that effectively replaces the engineered surface with a protein layer represents one of the most consequential and underappreciated challenges in translational nanomedicine. 23 The composition and organization of the protein corona is determined by the nanoparticle surface chemistry, size, and charge, and profoundly alters the in vivo fate, biodistribution, targeting efficiency, and toxicity profile of nanovesicles in ways that are poorly predictable from in vitro characterization. PEGylation substantially reduces but does not eliminate protein corona formation, and the phenomenon of accelerated blood clearance (ABC effect) following repeated dosing of PEGylated liposomes attributable to anti-PEG IgM production represents a significant clinical challenge for multi-dose PEGylated nanovesicle regimens. 24 The regulatory landscape for nanomedicines remains incompletely harmonized globally, with divergent requirements between FDA, EMA, and Asian regulatory authorities complicating multinational development programs. 25

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XI. FUTURE PERSPECTIVES

The future of nanovesicular drug delivery systems is moving toward highly precise and personalized therapeutics driven by advances in nanotechnology, artificial intelligence, synthetic biology, and genome editing. Personalized nanomedicine, including patient-specific exosomes and AI-guided formulation design, has the potential to revolutionize targeted therapy by enabling individualized treatment based on genetic and molecular profiles. In parallel, the integration of CRISPR-Cas9 technology with lipid nanoparticle delivery systems is opening new possibilities for the permanent correction of genetic disorders, with early clinical success already being observed in inherited diseases and gene-editing therapies. Biologically derived vesicles such as exosomes, along with hybrid biomimetic nanocarriers, are expected to gain major clinical importance as scalable manufacturing technologies continue to improve. The remarkable success of mRNA-LNP vaccines during the COVID-19 pandemic has further accelerated interest in nanovesicle-based vaccines for infectious diseases, cancer immunotherapy, and autoimmune disorders. Moreover, innovations in microfluidic manufacturing, continuous production systems, and regulatory harmonization are expected to enhance large-scale commercialization and global accessibility. Collectively, these advances position nanovesicular drug delivery systems as a cornerstone of next-generation precision medicine and targeted therapeutics.

Conclusion

Nanovesicular drug delivery systems have emerged as highly promising platforms in modern pharmaceutical and biomedical sciences due to their ability to overcome the limitations of conventional drug delivery methods. From the discovery of liposomes to the successful development of lipid nanoparticle-based mRNA vaccines, these systems have demonstrated remarkable potential in improving drug stability, bioavailability, controlled release, and targeted delivery. Various nanovesicular carriers such as liposomes, niosomes, transfersomes, ethosomes, phytosomes, and exosomes have shown broad therapeutic applications in oncology, transdermal delivery, pulmonary therapy, ophthalmology, CNS disorders, infectious diseases, and gene therapy. Advances in lipid engineering, ligand-mediated targeting, and stimuli-responsive formulations have further enhanced their therapeutic efficiency and precision. Despite significant progress, challenges including stability issues, large-scale manufacturing reproducibility, immunogenicity, protein corona formation, regulatory complexities, and high production costs continue to affect their widespread clinical translation. Nevertheless, ongoing developments in artificial intelligence-assisted formulation design, biomimetic nanovesicles, microfluidic manufacturing, and personalized medicine are accelerating the evolution of next-generation nanotherapeutics. With continuous interdisciplinary research and technological innovation, nanovesicular drug delivery systems are expected to play a central role in the future of precision medicine by enabling safer, more effective, and highly targeted therapeutic strategies across diverse disease conditions.

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