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Review

Nano-Elastic Vesicles in Oncology: Bridging Formulation Design and Translational Outcomes

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Abstract

Nano-elastic vesicles (NEVs), including transferosomes, ethosomes, and elastic liposomes, have emerged as promising drug delivery systems to overcome the biopharmaceutical limitations of conventional anticancer therapies. Their unique deformability, nanoscale size, and ability to traverse biological barriers enable improved drug solubility, stability, bioavailability, and site-specific delivery. This review critically examines recent advances in the formulation design, physicochemical characterization, in vitro and in vivo performance, and translational prospects of nano-elastic vesicles in oncology. Emphasis is placed on formulation strategies, mechanisms governing enhanced permeation and retention, pharmacokinetic modulation, therapeutic efficacy, safety considerations, and regulatory challenges. The review aims to bridge the gap between laboratory-scale development and clinical translation, highlighting opportunities and future directions for NEV-based anticancer drug delivery.

Keywords: Nano-elastic vesicles, transferosomes, ethosomes, anticancer drug delivery, bioavailability, translational nanomedicine.

1. Introduction

Cancer remains a leading cause of morbidity and mortality worldwide despite significant progress in chemotherapy, targeted therapy, and immunotherapy. A major limitation of many anticancer drugs is their poor aqueous solubility, instability, non-specific biodistribution, dose-limiting toxicity, and low bioavailability. Nanocarrier-based drug delivery systems have been extensively investigated to address these challenges, with lipid-based vesicles occupying a central role [1-3].

Nano-elastic vesicles represent an advanced class of lipid vesicles characterized by high membrane flexibility and deformability. Unlike conventional liposomes, NEVs can squeeze through pores much smaller than their own diameter without vesicle rupture. This property allows enhanced penetration across biological barriers such as the skin, mucosa, tumor interstitium, and cellular membranes [4]. Consequently, NEVs have attracted increasing interest for the delivery of anticancer agents via oral, transdermal, topical, and parenteral routes. This review provides a comprehensive overview of NEVs in oncology, focusing on formulation design, mechanistic aspects, in vitro and in vivo evaluation, and translational outcomes.

2. Classification of Nano-Elastic Vesicles

2.1 Transferosomes: Transferosomes are ultra-deformable vesicles composed of phospholipids and an edge activator (e.g., Tween 80, Span 80, sodium cholate). The edge activator destabilizes the lipid bilayer, imparting elasticity and enabling penetration through narrow pores [5].

2.2 Ethosomes: Ethosomes contain high concentrations of ethanol (20–45%), which enhances membrane fluidity and improves drug permeation. Ethanol also acts as a penetration enhancer by interacting with biological membranes.

2.3 Trans-ethosomes and Other Hybrid Systems: Trans ethosomes combine the advantages of transferosomes and ethosomes by incorporating both edge activators and ethanol. Other hybrid NEVs include invasomes and glycerosomes, designed to further enhance permeability and stability [6].

3. Formulation Design Considerations

Figure 1. Schematic representation of nano-elastic vesicle architecture. A conceptual diagram illustrating the structural components of nano-elastic vesicles, including phospholipid bilayer, edge activators/ethanol, and encapsulated anticancer drug (hydrophilic and lipophilic domains).

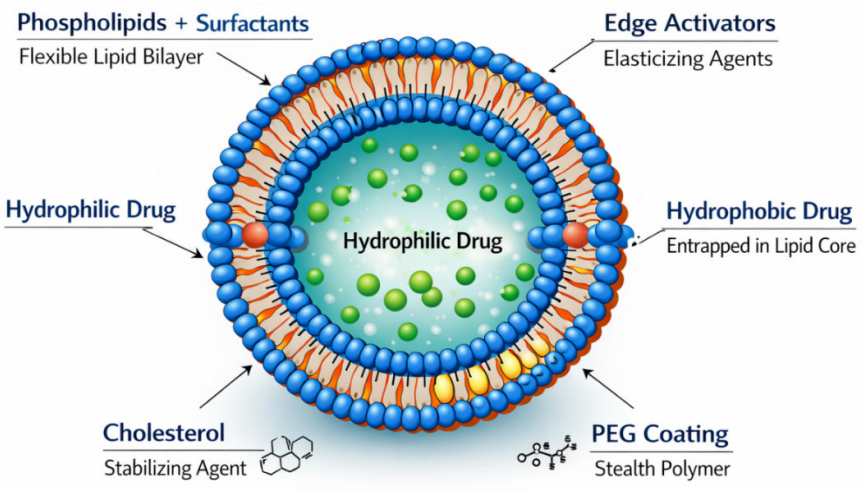

Figure 1. Schematic representation of nano-elastic vesicle architecture.

Table 1. Common formulation components used in nano-elastic vesicles for anticancer drug delivery [7].

Component Type	Examples	Functional Role
Phospholipids	Soy PC, Egg PC, DSPC	Vesicle formation, biocompatibility
Edge Activators	Tween 80, Span 80, Sodium cholate	Impart elasticity, enhance deformability
Solvents	Ethanol, Isopropyl alcohol	Increase membrane fluidity, permeation
Stabilizers	Cholesterol	Improve vesicle stability
Drugs	Doxorubicin, Paclitaxel, Curcumin	Anticancer activity

3.1 Selection of Lipid Components: Phospholipids such as phosphatidylcholine are commonly used due to their biocompatibility. Cholesterol content is carefully optimized, as excessive cholesterol can reduce vesicle elasticity.

3.2 Role of Edge Activators: Edge activators regulate membrane flexibility and vesicle deformability. Their concentration significantly influences vesicle size, entrapment efficiency, and stability [8].

3.3 Drug Properties and Loading Strategies: Both hydrophilic and lipophilic anticancer drugs can be incorporated into NEVs. Drug–lipid compatibility, partition coefficient, and molecular weight influence encapsulation efficiency and release behaviour.

3.4 Preparation Methods

Common methods include thin-film hydration, ethanol injection, reverse-phase evaporation, and micro-fluidization. Process parameters such as hydration time, sonication, and extrusion affect vesicle characteristics [9].

4. Physicochemical Characterization

Figure 2. Characterization workflow for nano-elastic vesicles. A flowchart depicting key characterization steps including vesicle preparation, size and zeta potential analysis, morphology assessment, deformability testing, and entrapment efficiency evaluation [9].

Table 2. Physicochemical characterization parameters and analytical techniques.

Parameter	Technique	Significance
Vesicle size & PDI	Dynamic light scattering	Size uniformity and stability
Zeta potential	Electrophoretic mobility	Colloidal stability
Morphology	TEM, Cryo-TEM	Vesicle shape and lamellarity
Elasticity	Deformability index measurement	Penetration capability
Entrapment efficiency	Ultracentrifugation	Drug loading capacity

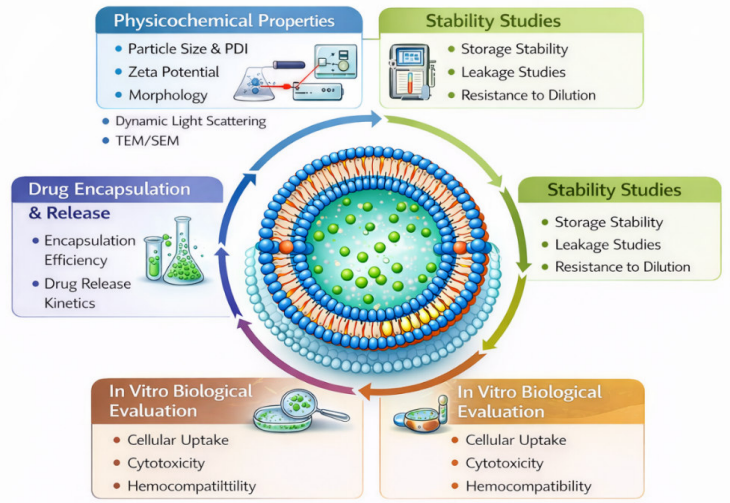

Figure 2. Characterization workflow for nano-elastic vesicles.

4.1 Vesicle Size, PDI, and Zeta Potential

Dynamic light scattering is used to determine size distribution and polydispersity index. Zeta potential provides insight into colloidal stability [10].

4.2 Morphology and Elasticity

Transmission electron microscopy and cryo-TEM reveal vesicle morphology. Deformability index is a critical parameter distinguishing NEVs from conventional liposomes [11].

4.3 Entrapment Efficiency and Drug Loading

High entrapment efficiency is essential for therapeutic efficacy and dose reduction. Factors influencing entrapment include lipid composition and drug physicochemical properties.

5. In Vitro Evaluation

Figure 3. Mechanisms of cellular uptake of nano-elastic vesicles. A schematic illustrating endocytosis, membrane fusion, and lipid exchange mechanisms facilitating enhanced intracellular delivery of anticancer drugs [12].

Table 3. Representative in vitro evaluation models used for nano-elastic vesicles.

Study Type	**Model/System**	**Outcome Measured**
Drug release	Dialysis method	Release kinetics
Cytotoxicity	MCF-7, HeLa, A549 cells	Cell viability
Cellular uptake	Fluorescent-tagged NEVs	Internalization efficiency
Permeation	Franz diffusion cell	Barrier penetration

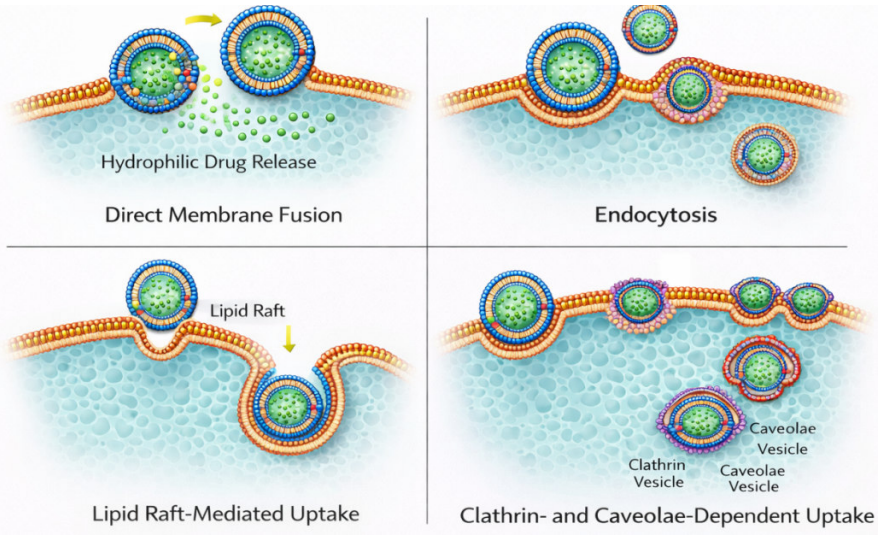

Figure 3. Mechanisms of cellular uptake of nano-elastic vesicles.

5.1 Drug Release Studies

In vitro release studies provide information on release kinetics and mechanism. NEVs often exhibit sustained or controlled drug release profiles [13].

5.2 Cell Line Studies

Cytotoxicity and cellular uptake studies using cancer cell lines (e.g., MCF-7, HeLa, A549) demonstrate enhanced intracellular drug accumulation and anticancer activity.

5.3 Mechanistic Insights

Enhanced uptake occurs via endocytosis, membrane fusion, and lipid exchange, leading to improved intracellular drug delivery [15].

6. In Vivo and Preclinical Assessment

Figure 4. Biodistribution and tumor accumulation of NEVs in preclinical models. A conceptual illustration showing enhanced tumor targeting and reduced off-target distribution compared to free drug.

Table 4. Summary of reported preclinical outcomes of nano-elastic vesicle-based anticancer formulations [16].

Drug	Vesicle Type	Cancer Model	Key Outcome
Doxorubicin	Transferosomes	Breast cancer	Enhanced tumor inhibition
Paclitaxel	Ethosomes	Lung cancer	Improved bioavailability
Curcumin	Trans ethosomes	Colon cancer	Reduced systemic toxicity

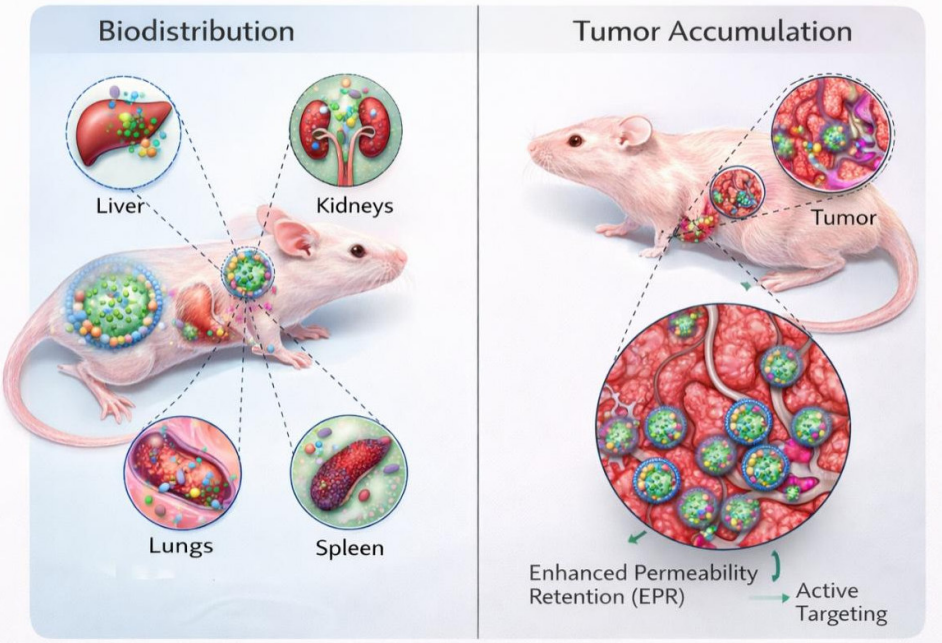

Figure 4. Biodistribution and tumor accumulation of NEVs in preclinical models.

6.1 Pharmacokinetics and Biodistribution

Pharmacokinetic (PK) behaviour and biodistribution are critical determinants of the therapeutic efficacy and safety of anticancer drug delivery systems. Conventional chemotherapeutic agents often exhibit rapid systemic clearance, non-specific tissue distribution, poor tumor accumulation, and dose-limiting toxicities. Nano-elastic vesicles (NEVs) significantly modify these parameters by altering drug absorption, distribution, metabolism, and elimination, thereby improving therapeutic index and clinical potential. NEVs improve plasma half-life, reduce clearance, and enhance tumor accumulation of anticancer drugs [17].

6.2 Antitumor Efficacy

Preclinical tumor models demonstrate superior tumor growth inhibition and reduced systemic toxicity compared to free drugs.

6.3 Safety and Toxicity

Biocompatible lipid components generally confer good safety profiles, though long-term toxicity and immunogenicity require further evaluation.

Influence of Nano-Elastic Vesicles on Pharmacokinetics

Absorption and Bioavailability Enhancement: NEVs enhance drug bioavailability through improved membrane permeability and prolonged systemic exposure. Their ultra-deformable lipid bilayers allow efficient traversal across biological barriers, including gastrointestinal epithelium, skin, and tumor vasculature. For orally administered anticancer drugs, NEVs protect labile compounds from enzymatic degradation and first-pass metabolism, resulting in increased plasma drug concentrations. Transdermal and topical NEV formulations similarly demonstrate superior drug permeation compared to conventional liposomes or free drugs [18].

Distribution and Plasma Circulation Time: Encapsulation of anticancer agents within NEVs leads to prolonged circulation time by reducing rapid renal clearance and reticuloendothelial system (RES) uptake. Surface modification with polyethylene glycol (PEGylation) further enhances stealth properties, minimizing opsonization and macrophage recognition. Extended plasma half-life (t½) facilitates sustained drug release and improved tumor exposure. Studies consistently report increased area under the concentration–time curve (AUC) and reduced clearance (CL) for NEV-encapsulated drugs compared to free formulations, indicating improved systemic retention [19].

Metabolism and Drug Protection: NEVs provide a protective lipid environment that shields encapsulated drugs from premature metabolic degradation. This is particularly advantageous for drugs prone to hydrolysis or enzymatic metabolism, such as paclitaxel, curcumin, and doxorubicin. Reduced metabolic inactivation contributes to enhanced therapeutic efficacy at lower doses.

Elimination Kinetics: The elimination of NEV-encapsulated drugs is primarily governed by vesicle composition, size, and surface charge. Nano-sized vesicles (typically 80–200 nm) exhibit delayed renal filtration and controlled hepatic clearance. Controlled release from NEVs results in sustained plasma drug levels and reduced peak-related toxicity [20].

2. Biodistribution Patterns of Nano-Elastic Vesicles

Passive Tumor Targeting via the EPR Effect: NEVs preferentially accumulate in tumor tissues through the enhanced permeability and retention (EPR) effect. Tumor vasculature is characterized by leaky endothelial junctions and impaired lymphatic drainage, allowing nanoscale vesicles to extravasate and remain within the tumor microenvironment. The high deformability of NEVs further facilitates penetration into dense tumor matrices compared to rigid nanocarriers.

Organ Distribution: Biodistribution studies in preclinical models reveal that NEVs primarily localize in the liver, spleen, kidneys, and lungs due to RES activity. However, optimized NEV formulations with PEGylation or surface charge modulation demonstrate reduced hepatic and splenic accumulation, thereby lowering off-target toxicity. Compared to free drugs, NEVs show [21]:

Reduced cardiotoxic accumulation (notably for doxorubicin)

Lower renal toxicity

Controlled hepatic exposure

Active Targeting Strategies: Surface functionalization of NEVs with targeting ligands such as folic acid, peptides, antibodies, or transferrin enhances receptor-mediated uptake by cancer cells. Active targeting significantly improves tumor-to-normal tissue drug ratios, leading to enhanced therapeutic outcomes while minimizing systemic adverse effects.

Tumor Penetration and Retention: Beyond accumulation, effective tumor penetration is essential for therapeutic success. The elastic nature of NEVs enables deep tumor infiltration, overcoming high interstitial fluid pressure and dense extracellular matrix barriers. Sustained retention within tumor tissue ensures prolonged drug exposure, resulting in enhanced apoptosis and tumor growth inhibition [22].

Comparative Pharmacokinetic Advantages over Conventional Systems

Compared to conventional liposomes and polymeric nanoparticles, NEVs exhibit:

- Superior deformability and permeability
- Enhanced bioavailability across multiple administration routes
- Improved tumor accumulation and penetration
- Reduced systemic toxicity
- Prolonged circulation time with controlled drug release

These advantages position NEVs as a next-generation nanocarrier system for anticancer drug delivery.

Translational Implications: Improved pharmacokinetic profiles and favorable biodistribution patterns directly contribute to enhanced therapeutic efficacy and patient compliance. However, inter-species variability, tumor heterogeneity, and formulation-dependent behavior necessitate comprehensive PK-PD modeling and standardized evaluation protocols. Future clinical translation will depend on robust correlations between preclinical biodistribution data and human pharmacokinetics.

7. Translational and Clinical Perspectives

Figure 5. Translational pathway of nano-elastic vesicles from bench to bedside. A schematic outlining stages from formulation design and preclinical testing to scale-up, regulatory approval, and clinical application.

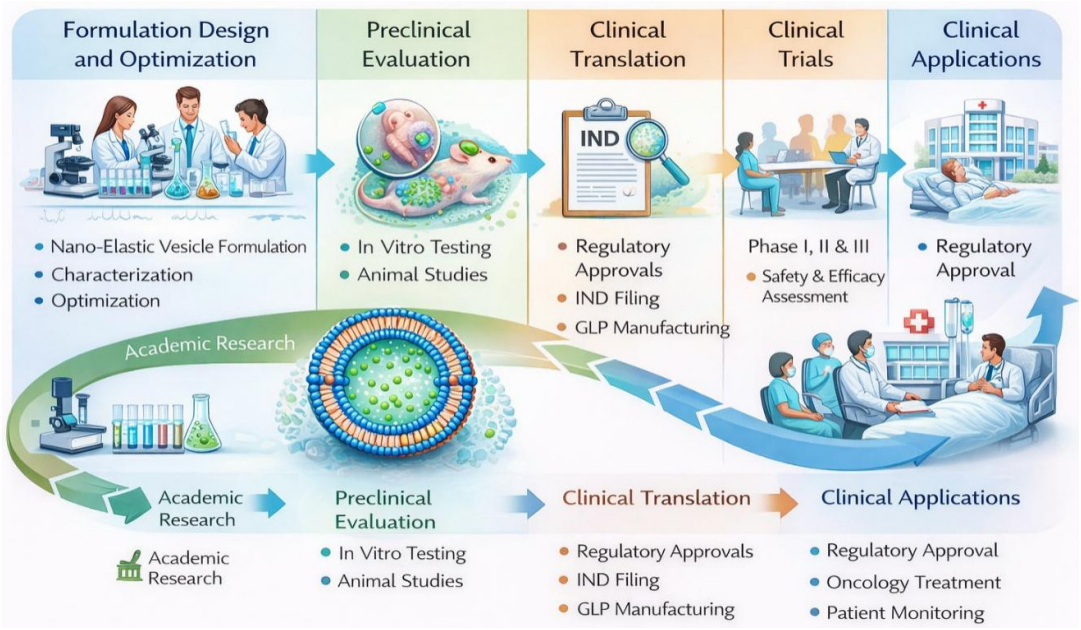

Figure 5. Translational pathway of nano-elastic vesicles from bench to bedside.

Despite promising preclinical results, clinical translation of NEVs faces challenges related to large-scale manufacturing, reproducibility, stability, and regulatory approval. Standardization of characterization methods and robust clinical data are essential for successful translation.

8. Regulatory and Manufacturing Challenges

Scalability, quality control, and compliance with regulatory guidelines remain major hurdles. Advanced manufacturing techniques such as microfluidics may offer solutions.

9. Future Directions

Future research should focus on targeted NEVs, stimulus-responsive systems, combination therapy, and personalized nanomedicine approaches. Integration with molecular oncology and biomarker-driven strategies may further enhance therapeutic outcomes. Despite significant progress in the development of nano-elastic vesicles (NEVs) for anticancer drug delivery, several scientific, technological, and translational challenges remain. Addressing these gaps will be critical for advancing NEVs from experimental platforms to clinically viable nanomedicines. Future research should focus on rational design, mechanistic understanding, clinical translation, and regulatory harmonization [24].

1. Advanced Formulation Strategies and Rational Design: Future NEV development should move beyond empirical formulation approaches toward rational, mechanism-driven design. Systematic optimization of lipid composition, edge activator type, and vesicle elasticity using design of experiments (DoE) and artificial intelligence–based modeling can significantly improve reproducibility and performance. Integration of molecular dynamics simulations may further elucidate bilayer behavior, drug–lipid interactions, and deformability

mechanisms at the nanoscale. Additionally, hybrid NEV systems incorporating polymers, inorganic nanoparticles, or stimuli-responsive materials may provide enhanced control over drug release and targeting.

2. Stimuli-Responsive and Smart Nano-Elastic Vesicles: Next-generation NEVs are expected to be stimuli-responsive, enabling site-specific drug release in response to internal or external triggers such as: pH gradients in tumor microenvironments. Enzymatic activity (e.g., matrix metalloproteinases). Redox potential (glutathione-rich intracellular environments). Temperature, ultrasound, or magnetic fields Such smart NEVs can minimize premature drug leakage, enhance intracellular drug delivery, and improve therapeutic precision.

3. Targeted and Personalized Cancer Therapy: Future research should prioritize ligand-functionalized NEVs tailored to tumor-specific biomarkers. Targeting moieties such as antibodies, peptides, aptamers, or small molecules can enhance selective uptake by cancer cells while sparing healthy tissues. Personalized NEV formulations based on patient-specific tumor profiles, genetic mutations, and pharmacogenomic data may further optimize therapeutic outcomes. Integration with precision oncology frameworks will be crucial for individualized cancer treatment.

4. Combination Therapy and Co-Delivery Systems: NEVs offer a versatile platform for co-delivery of multiple therapeutic agents, including: Chemotherapeutics. Gene therapy agents (siRNA, miRNA). Immunomodulators. Autophagy or apoptosis regulators. Future NEVs should be designed to deliver synergistic drug combinations with controlled release kinetics, enabling simultaneous modulation of multiple cancer signaling pathways and overcoming drug resistance.

5. Deeper Mechanistic Insights at Cellular and Molecular Levels: While enhanced uptake and efficacy of NEVs have been demonstrated, deeper understanding of their intracellular trafficking, endosomal escape, and interaction with cellular signaling pathways remains limited. Advanced imaging techniques, omics-based analyses, and systems biology approaches should be employed to elucidate: Endocytosis pathways. Organelle-specific drug release. Impact on apoptosis, autophagy, and immune responses. Such mechanistic insights will guide more effective NEV design and therapeutic optimization.

6. Improved In Vivo Models and Translational Relevance: Conventional xenograft models often fail to accurately predict clinical outcomes. Future NEV research should incorporate advanced preclinical models such as: Patient-derived xenografts (PDX). Organoids and tumor-on-chip systems. Humanized mouse models. These models will provide more predictive data on pharmacokinetics, biodistribution, efficacy, and safety, facilitating successful clinical translation.

7. Scale-Up, Manufacturing, and Quality Control: One of the major barriers to clinical translation of NEVs is large-scale manufacturing. Future efforts should focus on scalable, reproducible, and cost-effective production methods such as: Microfluidics-based manufacturing. Continuous-flow systems. Automated lipid assembly techniques. Establishing robust quality control parameters, including vesicle elasticity, batch-to-batch consistency, and long-term stability, will be essential to meet regulatory requirements.

8. Regulatory Science and Standardization: Lack of standardized regulatory guidelines for nano-elastic vesicles remains a significant challenge. Future research should align formulation development with regulatory

expectations by: Defining critical quality attributes (CQAs). Establishing standardized characterization protocols. Developing validated safety and toxicity assessment frameworks. Early engagement with regulatory agencies will accelerate approval pathways and reduce translational risk.

9. Long-Term Safety, Immunogenicity, and Toxicological Profiling: Although NEVs are generally composed of biocompatible lipids, long-term safety data remain limited. Future studies should emphasize: Chronic toxicity and immunogenicity. Biodistribution following repeated dosing. Interaction with the immune system and microbiome. Comprehensive toxicological profiling will be critical for clinical acceptance.

10. Integration with Emerging Cancer Therapies: NEVs are well-positioned to synergize with emerging therapeutic modalities, including: Immunotherapy. Photodynamic and photothermal therapy. Radiotherapy. CRISPR-based gene editing. Future NEV platforms may act as multifunctional carriers, combining diagnostic and therapeutic capabilities (theranostics) to enable real-time monitoring of treatment response.

11. Artificial Intelligence and Data-Driven Optimization: Artificial intelligence (AI) and machine learning (ML) tools can revolutionize NEV research by predicting optimal formulations, drug loading efficiencies, and in vivo performance. Data-driven approaches will accelerate discovery, reduce experimental costs, and improve translational success.

12. Outlook and Clinical Perspective: The future of nano-elastic vesicles in oncology lies in their evolution from passive carriers to intelligent, patient-specific therapeutic platforms. With continued interdisciplinary collaboration among formulation scientists, oncologists, engineers, and regulatory experts, NEVs hold strong potential to redefine cancer drug delivery and improve patient outcomes [25].

10. Conclusion

Nano-elastic vesicles represent a versatile and powerful platform for anticancer drug delivery. By bridging formulation design with translational outcomes, NEVs have the potential to significantly improve cancer therapy. Nano-elastic vesicles significantly modulate pharmacokinetics and biodistribution of anticancer drugs, offering prolonged circulation, enhanced tumor targeting, controlled release, and reduced toxicity. These attributes make NEVs a promising platform for translational oncology and personalized cancer therapy. Continued interdisciplinary research is necessary to realize their full clinical potential.

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