# Unlocking Drug Delivery Potential: The Crucial Role of Liposome Mechanical Properties

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**Abstract** – *The mechanical properties of liposomes play a critical role in determining their stability, drug release behavior, biodistribution, and interaction with biological barriers. These properties are primarily governed by lipid composition, including the degree of acyl chain saturation, tail length, and headgroup charge. Cholesterol incorporation is a widely used strategy to increase membrane rigidity by condensing the bilayer and reducing permeability. Temperature also modulates mechanical behavior, with liposomes transitioning from a rigid gel phase below the lipid phase transition temperature to a more fluid and permeable liquid-crystalline phase above it. Structural features such as liposome size and lamellarity further influence mechanical performance, larger liposomes tend to be more flexible, whereas multilamellar vesicles exhibit greater stiffness. Precisely controlling liposome stiffness through careful manipulation of their mechanical properties is a fundamental design principle for creating more effective nanocarriers in cancer therapy. Achieving moderate liposome stiffness is particularly advantageous, as it can result in extended circulation within the bloodstream and enhanced accumulation within tumors by exploiting the enhanced permeability and retention effect.*

**Keywords:** *Elasticity; mechanical properties; nanomedicine; nanoparticles; liposomes.*

## 1. Introduction

Liposomes are spherical vesicles composed of one or more concentric lipid bilayers, typically 50–500 nm in size for biomedical applications [1]. They form spontaneously when natural or synthetic amphiphilic lipids are dispersed in an aqueous medium. These lipids contain hydrophilic headgroups and hydrophobic tails that self-assemble into bilayers, with the heads facing the surrounding water and the tails forming the membrane core (Fig. 1). Liposomes are widely recognized as effective drug carriers due to their biocompatibility [2], biodegradability, structural stability, ease of synthesis, high drug-loading capacity [3,4], and ability to enhance drug bioavailability [5]. In addition, they improve drug solubility, enable controlled distribution, and can be surface-modified for targeted delivery, prolonged circulation, and sustained release.

Phospholipids constitute the primary structural components of liposomes and biological membranes [6]. They are broadly classified into glycerophospholipids and sphingomyelins based on their alcohol backbone [7]. Common glycerophospholipids used in liposome fabrication include phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI), and phosphatidylglycerol (PG) [6,8].

Although the importance of liposome mechanical properties has gained increasing attention, the relationship between these properties and drug delivery performance remains incompletely understood. This review focuses on elucidating the role of liposome mechanics in cancer drug delivery. It outlines key mechanical concepts, summarizes measurement techniques, discusses major influencing factors, and highlights how mechanical properties impact therapeutic delivery efficiency.

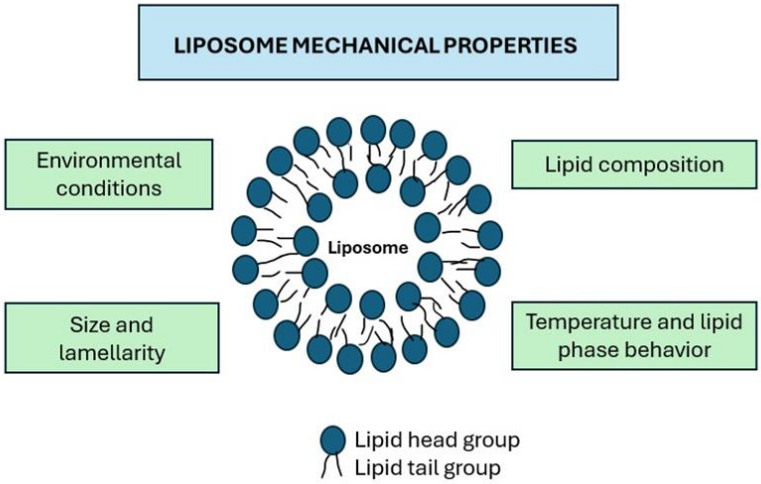


**Fig.1**. Factors affecting liposome mechanical properties.

## 2. Mechanical Properties

### *2.1. Area compressibility modulus*

The area compressibility modulus (*K*) is a fundamental parameter that quantifies the resistance of a lipid bilayer to changes in its surface area under applied tension. Essentially, it measures the bilayer's elasticity by indicating how much the membrane can be compressed or expanded before undergoing structural alterations.

$$\frac{A-A_0}{A_0} = \frac{\Sigma}{\mathrm{K}} \quad (1)$$

where: $\sum$ = surface tension, $A$ = current area, and $A_0$ = initial area of the bilayer [9].
Measuring the area compressibility modulus is essential for applications involving liposomes, particularly in drug delivery systems, as it directly affects their mechanical stability, deformability, and interactions with biological membranes. For liposomes composed of commonly used phospholipids, the area stretch modulus typically ranges between 200 and 300 mN/m. This value is highly sensitive to factors such as lipid composition, the presence of cholesterol, and various environmental conditions [10].

### *2.2. Bending modulus*

The bending modulus ($\kappa$) is a critical mechanical property that quantifies the energy required to bend a lipid bilayer, reflecting its resistance to deformation.

$$M = \kappa\Delta\left(\frac{1}{R_1} + \frac{1}{R_2}\right) \quad (2)$$

where $M$ =membrane bending moments, $\Delta\left(\frac{1}{R_1} + \frac{1}{R_2}\right)$ = the change in total membrane curvature, with $R_1$ and $R_2$ are the principal radii of curvature at a given position in the membrane [11].
In drug delivery, optimizing the bending modulus is crucial for ensuring that liposomes can encapsulate therapeutic agents effectively, circulate in the body without premature degradation, and release their payload at the targeted site. The value $\kappa$ varies significantly based on lipid composition, presence of cholesterol, and environmental conditions [12-14].

### *2.3. Young's modulus*

The Young's modulus (*E*) is a fundamental mechanical property that quantifies the stiffness or elasticity of a material, indicating its resistance to deformation under applied stress. In the context of liposomes, measuring *E* provides insights into membrane rigidity, which is crucial for applications such as drug delivery, where membrane flexibility can influence circulation time and drug release profiles.

$$E = \frac{K}{d} \quad (3)$$

where: $K$ = area compressibility modulus, and $d$ = bilayer thickness.

Reported values for liposomal membranes vary widely, often ranging from 10 to 100 MPa, influenced by factors such as lipid composition and temperature [15-18].

## 3. Techniques For Measuring Liposome Mechanical Properties

Accurate measurement of liposome mechanical properties is essential for optimizing drug delivery performance. A range of experimental and computational methods has been developed to quantify parameters such as area compressibility modulus, bending modulus, and Young's modulus [19–21].

### *3.1. Micropipette aspiration*

The micropipette aspiration (MPA) technique was first introduced by Evans and Needham [22-24], uses a glass micropipette to apply controlled suction pressure via a connected reservoir. Membrane deformation under defined tension enables determination of area compressibility and bending moduli from the pressure–deformation relationship [19,21].

### *3.2. Atomic Force Microscopy*

Atomic Force Microscopy (AFM) provides nanoscale imaging and force measurements by monitoring interactions between a sharp probe and the liposome surface. Cantilever deflection, detected optically, generates force–distance curves used to calculate Young's modulus and membrane elasticity through indentation or dynamic modes [19,21,25–27].

### *3.3. Optical Tweezers*

Optical tweezers (OT) employ a focused laser beam to trap and deform individual liposomes without physical contact. Piconewton-scale forces allow measurement of stiffness, bending modulus, and elasticity, with the advantage of high spatial precision and compatibility with fluorescence imaging [19,21,28].

### *3.4. Fluctuation analysis*

The fluctuation analysis technique examines thermally induced shape fluctuations captured by optical microscopy. Statistical analysis of these undulations yields bending rigidity ($\kappa$), although the method is limited to low-tension membranes where fluctuations remain observable [19, 29].

### *3.5. Molecular dynamics simulations*

Molecular dynamics (MD) simulations complement experiments by providing molecular-scale insight into membrane mechanics. Bending rigidity can be extracted from bilayer height fluctuations [30–33], force-deformation responses [34, 35], or membrane tubulation simulations [36].

## 4. Factors Affecting Liposome Mechanical Properties

The mechanical properties of liposomes are influenced by a range of interrelated factors, including the lipid composition, temperature, lipid phase behavior, liposome size, degree of lamellarity (number of lipid bilayers), and surrounding environmental conditions such as pH and ionic strength (Fig. 1).

### *4.1. Lipid composition*

#### *4.1.1. Lipid acyl chain saturation*

Lipid saturation is a primary determinant of membrane rigidity. Liposomes composed of saturated phospholipids such as DPPC form tightly packed, rigid, and less permeable bilayers, whereas unsaturated phosphatidylcholines (e.g., egg or soybean PC) produce more fluid and mechanically unstable membranes [2,37]. Quantitative measurements by Rawicz et al. showed that saturated lipids including DPPC and DSPC possess higher area compressibility and bending moduli than unsaturated counterparts [10].

Molecular dynamics studies further demonstrate that mixtures of saturated and unsaturated lipids modulate mechanics through lipid–lipid interactions. Bilayers containing unsaturated DOPC combined

with saturated DSPC or DSPE revealed stronger intermolecular interactions in DSPE systems, highlighting the combined influence of saturation and headgroup chemistry on membrane stiffness [38].

#### *4.1.2. Lipid tail length*

Bilayer rigidity also depends strongly on acyl chain length. Longer lipid tails promote tighter hydrophobic packing and stronger van der Waals interactions, producing stiffer membranes, whereas shorter chains increase fluidity.

Simulations by Xu et al. showed that mixing long-chain DOPC with short-chain DHPC reduced membrane rigidity, with 65–75 mol% DOPC mixtures exhibiting ~10% lower compressibility than pure DOPC [39]. Micropipette aspiration experiments confirmed that 75:25 DOPC:DHPC vesicles had ~30% lower stretching moduli [40]. These findings agree with studies by Illya et al. and Kelley et al., demonstrating that chain-length mismatch disrupts packing and increases tail disorder, thereby softening membranes [41–43].

#### *4.1.3. Inclusion of cholesterol*

Cholesterol is widely used to modulate membrane stiffness due to its rigid sterol structure, which condenses lipid packing and restricts acyl chain motion. Numerous studies confirm this rigidifying effect. AFM measurements by Benne et al. showed that cholesterol content increased stiffness in antigen-loaded liposomes and correlated with enhanced immunological responses [44]. Needham and Nunn similarly reported improved structural stability following cholesterol incorporation [45]. AFM analysis of EggPC vesicles demonstrated increases in both Young's and bending moduli upon cholesterol addition [17], while Choi et al. observed delayed vesicle disintegration and increased rigidity in cholesterol-containing DMPC systems [46].

However, cholesterol effects are lipid-dependent. Garcia et al. reported increased flexibility in sphingomyelin membranes containing cholesterol, suggesting that cholesterol–lipid interactions vary with intrinsic packing properties [47].

#### *4.1.4. Lipid headgroup charge*

Charged lipids introduce electrostatic effects that can either stiffen or soften membranes depending on composition and environment. Negatively charged lipids such as PS and PA increase headgroup repulsion and aggregation stability, whereas cationic lipids like DOTAP alter biomolecular interactions and membrane mechanics [9].

AFM studies by Takechi-Haraya et al. showed that both positively and negatively charged lipids reduced nanoscale liposome stiffness by 30–60%, independent of acyl saturation [13,48]. In contrast, optical tweezer measurements on giant vesicles demonstrated that lipid charge and molecular geometry significantly influence mechanical behavior at larger length scales [49]. Additional work by Xu et al. revealed that among negatively charged lipids, DSPG produced the softest DOPC mixtures, emphasizing headgroup-specific mechanical effects [38].

### *4.2. Temperature and lipid phase behavior*

Membrane phase state, governed by temperature and lipid composition, critically determines liposome mechanics. Below the lipid melting temperature ($T_m$), bilayers exist in a rigid gel phase; above $T_m$ they transition to a fluid liquid-crystalline phase with higher permeability and flexibility [50].

Et-Thakafy et al. demonstrated that at 20 °C, fluid-phase DOPC vesicles exhibited far lower elastic modulus (~13 ± 30 MPa) than gel-phase DPPC vesicles (~116 ± 45 MPa) [51]. Duan et al. further showed that gel-phase DPPC liposomes resisted repeated compression cycles, whereas fluid-phase vesicles underwent irreversible deformation and structural collapse [52]. These findings confirm that phase state strongly dictates mechanical resilience and stability.

### *4.3. Size and lamellarity*

Liposome size and bilayer number also influence mechanical performance and drug delivery suitability [53]. Vesicles are commonly classified as SUVs (<100 nm), LUVs (100–1000 nm), GUVs (>1 μm), multilamellar vesicles (MLVs), and multivesicular vesicles (MVVs). Structural differences arise from fabrication methods such as extrusion, sonication, homogenization, and microfluidics [46,54–59].

AFM measurements showed that sub-micron DOPC liposomes exhibited bending moduli of $10^{-18}$–$10^{-20}$ J, with stiffness decreasing as diameter increased [60,61]. Additional AFM studies revealed that vesicles containing multiple bilayers were more spherical and mechanically stiffer, indicating that lamellarity provides a means to tune mechanical strength [62].

### *4.4. Environmental conditions*

External conditions, particularly pH, strongly influence liposome mechanics by altering headgroup ionization and intermolecular forces. Optical tweezer studies on PG giant vesicles demonstrated pronounced stiffness changes with pH variation [49]. Sulkowski et al. reported that membranes formed in acidic environments were stiffer below $T_m$ but became more fluid above $T_m$, indicating pH-dependent phase behavior [63].

Micropipette aspiration experiments on SOPC vesicles showed that compressibility remained stable between pH 3–9 but decreased ~30% at pH 2, while bending stiffness increased at pH 4 and 9 relative to neutral conditions [64]. These findings highlight pH as a key parameter in designing responsive liposomal systems.

## 5. The Role of Liposome Mechanical Properties in Cancer Drug Delivery Efficiency

Optimizing liposomal membrane rigidity is a critical design parameter for enhancing the performance of liposomes as long-circulating nanocarriers in cancer drug delivery. A growing body of research highlights how mechanical tuning of liposomes, particularly their stiffness, can significantly influence their behavior in biological systems, including circulation time, cellular uptake, and tumor penetration.

Wu et al. demonstrated the role of cholesterol-mediated modulation of liposomal rigidity on tumor penetration and therapeutic efficacy [65]. In their study, liposomes were composed of hydrogenated soybean phosphatidylcholine (HSPC), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (DSPE-PEG2000), and varying levels of cholesterol. Their results revealed that cholesterol incorporation within this specific lipid matrix led to a decrease in membrane rigidity. Notably, liposomes with moderate stiffness exhibited the most effective tumor tissue penetration and significantly improved anti-tumor responses, underscoring the importance of fine-tuning liposomal mechanics for optimal therapeutic outcomes.

Complementing these findings, Xu et al. explored how lipid chain length influences membrane properties by combining short-chain (DHPC) and long-chain (DOPC) phospholipids in liposomal formulations [39,40]. They reported that introducing 25–35 mol% DHPC into DOPC bilayers reduced the area compressibility modulus by approximately 10%, resulting in softer membranes. These mechanically compliant liposomes demonstrated enhanced cellular uptake in both healthy and cancerous cells, suggesting that modulating membrane softness through lipid chain length can improve intracellular delivery of therapeutic agents.

In a related study, Dai et al. fabricated liposomes with extracellular matrix-mimetic surfaces and systematically varied their membrane rigidity by altering lipid saturation and chain length [66]. Rigid liposomes composed of DSPC (C18:0) showed the highest cellular uptake and cytotoxicity in standard invitro assays. However, in multicellular spheroids (MCS) that simulate the fibrotic tumor microenvironment, moderately rigid liposomes (e.g., DPPC, C16:0) achieved the best penetration and retention, highlighting the importance of balancing rigidity to overcome tumor stromal barriers.

A study by Abumanhal-Masarweh et al. examined how lipid saturation and chain length influence liposomal uptake in triple-negative breast cancer (TNBC) cells [67]. Their results revealed that monounsaturated lipids such as DOPC (C18:1) facilitated higher uptake than saturated lipids of equal length. Among saturated lipids, longer chains like HSPC (C18:0) promoted uptake and even stimulated cancer cell proliferation, whereas short-chain lipids like DMPC (C14:0) and DLPC (C12:0) destabilized cell membranes, leading to cell death. Interestingly, cholesterol addition to DMPC membranes increased their rigidity and enhanced cellular uptake, suggesting a possible way to rescue the performance of otherwise unstable liposomal formulations.

In an in vitro model using 3D HeLa cell spheroids, Takechi-Haraya et al. assessed how liposome mechanical properties influence tissue penetration [68]. Using confocal laser scanning microscopy, they tracked fluorescently labeled liposomes composed of phosphatidylcholines with varying levels of

cholesterol and PEGylation. Liposomes with a higher bending modulus penetrated more efficiently into the spheroids, indicating that increased stiffness may enhance interstitial transport under certain conditions.

Building on this, Kong et al. studied layer-by-layer nanoparticles (LbL NPs) and found that their overall stiffness is governed by the mechanical characteristics of the inner liposomal core, which can be modulated via cholesterol incorporation into saturated lipid membranes [69]. Softer LbL NPs demonstrated a longer elimination half-life, improved tumor accumulation, and enhanced penetration, while maintaining the stealth and targeting properties provided by the outer polymeric layers.

Yuan et al. further expanded the understanding of how liposome elasticity affects immune interactions and transport dynamics [70]. Their study revealed that soft liposome nanoparticles (Lipo-NPs) preferentially adhered to cell membranes, medium-elasticity particles facilitated membrane fusion-mediated delivery to macrophages, and rigid particles were internalized via conventional endocytic pathways. These observations emphasize the elasticity-dependent biodistribution and immune cell engagement of liposomal carriers.

Taken together, these studies illustrate that precise control over liposomal mechanical properties, whether by adjusting lipid chain length, saturation, or cholesterol content, profoundly affects their pharmacokinetic and pharmacodynamic profiles. Modulating rigidity enables the tuning of critical factors such as circulatory half-life, tumor accumulation, tissue penetration, and cellular internalization, making it a powerful tool for engineering next-generation liposomal therapeutics tailored for cancer treatment.

## 6. Conclusions

The mechanical properties of liposomes are primarily governed by lipid composition and structural design. Parameters such as acyl chain saturation, chain length, and headgroup charge strongly influence membrane rigidity, elasticity, and permeability. Saturated and long-chain lipids promote tightly packed, rigid bilayers, whereas unsaturated and short-chain lipids increase fluidity. Charged lipids introduce electrostatic interactions that can either stabilize or soften membranes depending on composition and environment. Cholesterol is widely used to modulate liposome mechanics by condensing lipid packing, increasing rigidity, and reducing permeability, although its effects remain lipid-dependent. Temperature further regulates mechanics through phase transitions: gel-phase membranes below $T_m$ are stiff and ordered, while liquid-crystalline membranes above $T_m$ are more fluid and permeable. Liposome size and lamellarity also contribute, with larger vesicles showing lower bending rigidity and multilamellar structures exhibiting greater stiffness and stability. Mechanically softer liposomes have been associated with prolonged circulation and improved tumor accumulation via reduced clearance and enhanced passive targeting. However, the role of liposome mechanics in complex biological environments remains incompletely understood due to variability in tissue properties, pH, and ionic conditions. Future studies should systematically integrate mechanical properties with other physicochemical parameters, such as size, surface charge, ligand functionalization, and drug loading, using combined experimental, computational, and in vivo approaches to better optimize liposomal drug delivery performance.

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