LIPOSOMES AS DRUG DELIVERY SYSTEMS: A COMPREHENSIVE REVIEW WITH RECENT ADVANCES

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Abstract

Liposomes are spherical vesicular drug delivery systems composed of phospholipid bilayers enclosing an aqueous core, capable of encapsulating both hydrophilic and lipophilic drugs. Due to their structural similarity to biological membranes, excellent biocompatibility, and ability to improve drug solubility, stability, and bioavailability, liposomes have emerged as one of the most promising nanocarriers in modern drug delivery. Over the years, advancements in formulation techniques, lipid composition, and surface engineering have enabled the development of specialized systems such as PEGylated stealth liposomes, stimuli-responsive liposomes, ligand-targeted liposomes, and lipid nanoparticle-based mRNA delivery platforms. These innovations have significantly expanded their therapeutic applications in cancer therapy, antimicrobial treatment, gene delivery, vaccine development, and dermatological and ocular drug delivery. Despite their clinical success, challenges such as physical and chemical instability, rapid clearance by the mononuclear phagocyte system, large-scale manufacturing difficulties, and high production costs still limit their widespread commercialization. Ongoing research focused on smart nanocarriers, precision targeting, and advanced manufacturing technologies is expected to further enhance the clinical potential of liposomal drug delivery systems in the future.

Keywords: *Liposomes; nanocarriers; drug delivery systems; phospholipid vesicles; PEGylation; stealth liposome.*

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Received: 05/06/2026
Revised: 25/06/2026
Accepted: 01/07/2026
DOI: http://doi.org/10.66204/GJPSR-1124-2026-2-7-6

How to Cite
Pal A, Maurya VK, Kumar K. Liposomes as drug delivery systems: a comprehensive review with recent advances. Global Journal of Pharmaceutical and Scientific Research. 2026, ISSN: 3108-0103. 2026;2(7):1124–1144. ISSN: 3108-0103. http://doi.org/10.66204/GJPSR-1124-2026-2-7-6.

1. INTRODUCTION

Conventional drug delivery systems often suffer from limitations such as poor aqueous solubility, low bioavailability, rapid systemic clearance, and dose-related toxicity, which significantly reduce therapeutic efficacy and patient compliance. These challenges have driven the development of novel drug delivery approaches aimed at improving drug stability, targeted delivery, and controlled release profiles (Allen & Cullis, 2013; Pattni et al., 2015).

In recent decades, nanotechnology-based drug delivery systems have emerged as a promising strategy to overcome these limitations. Among various nanocarriers, liposomes have gained significant attention due to their unique structural characteristics, high biocompatibility, and ability to encapsulate both hydrophilic and hydrophobic drugs within a single system. Liposomes are spherical vesicles composed of one or more phospholipid bilayers enclosing an aqueous core, closely resembling biological membranes, which enhances their compatibility with physiological systems (Akbarzadeh et al., 2013).

Since their discovery, liposomes have evolved from simple model membrane systems to clinically approved drug delivery vehicles used in cancer therapy, antifungal treatment, and vaccine development. Their ability to modify pharmacokinetics, reduce systemic toxicity, and enhance drug accumulation at target sites has made them one of the most extensively studied nanocarrier systems in pharmaceutical research (Bozzuto & Molinari, 2015).

Despite their advantages, conventional liposomes face challenges such as instability in biological fluids, rapid clearance by the mononuclear phagocyte system, and limited control over drug release. These limitations have led to the development of advanced liposomal systems, including PEGylated stealth liposomes, stimuli-responsive formulations, and ligand-targeted vesicles, which aim to improve circulation time and targeting efficiency (Sercombe et al., 2015).

This review provides a comprehensive overview of liposomes as drug delivery systems, focusing on their structure, composition, preparation methods, characterization techniques, mechanisms of drug delivery, therapeutic applications, recent advancements, and associated challenges. The paper also highlights emerging trends and future perspectives in liposomal research, emphasizing their growing importance in modern precision and nanomedicine.

2. Liposomes: Structure and Physicochemical Basis

Liposomes are spherical, nanosized vesicular systems composed primarily of phospholipid bilayers enclosing an aqueous core. Due to their amphiphilic nature, liposomes are capable of encapsulating both hydrophilic and hydrophobic drugs, making them one of the most versatile drug delivery carriers in pharmaceutical science (Akbarzadeh et al., 2013; Pattni et

al., 2015). Structurally, phospholipids spontaneously organize into bilayers in aqueous environments, driven by hydrophobic interactions, forming closed vesicular systems that closely resemble biological membranes (Allen & Cullis, 2013). This biomimetic nature contributes to their excellent biocompatibility and low toxicity, which are critical for clinical applications (Sercombe et al., 2015).

2.1 Basic structure (lipid bilayer vesicles)

The basic structure of liposomes consists of a phospholipid bilayer arranged such that hydrophilic heads face the aqueous environment while hydrophobic tails orient inward, forming a stable membrane barrier (Bozzuto & Molinari, 2015). This organization results in the formation of a central aqueous compartment capable of entrapping hydrophilic drugs, while lipophilic compounds are incorporated within the lipid bilayer itself (Sercombe et al., 2015). Cholesterol is frequently incorporated into the bilayer to enhance membrane rigidity, reduce permeability, and improve in vivo stability (Pattni et al., 2015).

2.2 Types of liposomes (uni- and multilamellar systems)

Liposomes are classified based on their lamellarity and size into unilamellar vesicles (ULVs) and multilamellar vesicles (MLVs). ULVs contain a single phospholipid bilayer surrounding an aqueous core and are further divided into small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs) (Akbarzadeh et al., 2013). In contrast, MLVs consist of multiple concentric lipid bilayers resembling an onion-like structure, which generally provide higher drug-loading capacity but relatively lower uniformity in size distribution (Bozzuto & Molinari, 2015). The type of liposome strongly influences drug release behavior, encapsulation efficiency, and pharmacokinetics (Allen & Cullis, 2013).

2.3 Key physicochemical properties influencing performance

The performance of liposomes is governed by several physicochemical parameters, including particle size, polydispersity index (PDI), surface charge (zeta potential), lipid composition, and membrane fluidity (Sercombe et al., 2015). Particle size plays a crucial role in biodistribution and cellular uptake, with smaller liposomes generally exhibiting prolonged circulation times (Pattni et al., 2015). Zeta potential influences colloidal stability by controlling electrostatic repulsion between vesicles, thereby preventing aggregation (Bozzuto & Molinari, 2015). Additionally, lipid composition and cholesterol content significantly affect membrane rigidity, permeability, and drug retention capacity (Allen & Cullis, 2013). Phase transition temperature of phospholipids further determines bilayer fluidity and drug release kinetics under physiological conditions (Akbarzadeh et al., 2013).

2.4 Stability considerations in biological systems

Despite their advantages, liposomes face major stability challenges in biological environments, including premature drug leakage, phospholipid oxidation, and rapid clearance by the mononuclear phagocyte system (MPS) (Sercombe et al., 2015). Opsonization by plasma proteins leads to recognition and uptake by macrophages in the liver and spleen, significantly reducing circulation half-life (Bozzuto & Molinari, 2015). To overcome these limitations, surface modification strategies such as PEGylation have been developed to form "stealth liposomes," which evade immune recognition and prolong systemic circulation (Pattni et al., 2015). Furthermore, incorporation of cholesterol and optimized lipid composition enhances membrane stability and reduces leakage of encapsulated drugs in vivo (Allen & Cullis, 2013).

Table 1: Comparison of Liposomes with Other Nanocarrier Systems

System	Structure	Drug Loading	Stability	Targeting	Clinical Use	Limitation
Liposomes	Phospholipid bilayer vesicles	High (both hydrophilic & lipophilic)	Moderate	High (modifiable)	Widely approved	Leakage, cost
Niosomes	Non-ionic surfactant vesicles	Moderate	High	Moderate	Limited	Lower encapsulation
Polymeric nanoparticles	Polymer matrix	High	High	High	Some approved	Toxicity concerns
Solid lipid nanoparticles	Solid lipid core	Moderate	High	Moderate	Approved products	Limited drug loading
Dendrimers	Branched polymers	High	High	High	Experimental	Cytotoxicity

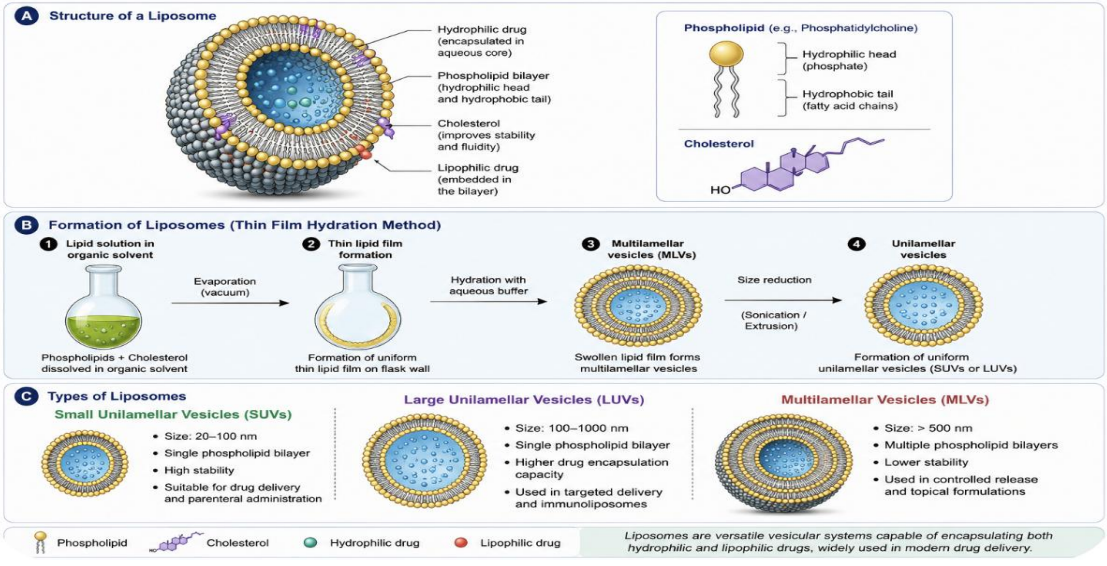

Figure 1: Structure, Formation, and Types of Liposomes

3. Composition and Functional Role of Lipid Components

The physicochemical behavior and biological performance of liposomes are largely determined by their lipid composition. Each lipid component contributes distinct structural and functional roles, influencing membrane integrity, drug loading capacity, circulation stability, and in vivo fate. The major components include phospholipids as the structural framework, cholesterol as a membrane stabilizer, and surface-modifying lipids such as PEGylated and charged lipids that enhance pharmacokinetic and targeting properties (Immordino et al., 2006; Pattni et al., 2015).

3.1 Phospholipids (structural backbone)

Phospholipids are the fundamental building blocks of liposomal bilayers and spontaneously organize into vesicular structures due to their amphiphilic nature. They typically consist of a hydrophilic phosphate head group and hydrophobic hydrocarbon chains, enabling bilayer formation in aqueous environments (Bangham et al., 1965; Torchilin, 2005). Naturally derived phospholipids such as egg phosphatidylcholine and soybean lecithin are widely used, while synthetic phospholipids like DPPC, DSPC, and DOPC allow better control over membrane properties.

The physicochemical characteristics of phospholipids, particularly acyl chain length and degree of saturation, strongly influence bilayer fluidity and permeability. Saturated lipids with higher transition temperatures produce more rigid membranes with slower drug leakage, whereas unsaturated lipids enhance membrane fluidity and drug release rates (Drummond et al., 1999). This tunability makes phospholipids a critical determinant of liposomal performance.

3.2 Cholesterol (membrane rigidity and stability)

Cholesterol plays a vital role in modulating liposomal membrane structure by intercalating between phospholipid molecules within the bilayer. It reduces membrane permeability, decreases leakage of encapsulated drugs, and enhances mechanical stability (Lasic, 1998). By filling void spaces between lipid molecules, cholesterol restricts excessive membrane fluidity at physiological temperatures while preventing crystallization at lower temperatures, thereby maintaining bilayer integrity across a wide thermal range (Szoka & Papahadjopoulos, 1980).

The presence of cholesterol also improves resistance against serum-induced destabilization and fusion, thereby increasing in vivo circulation stability. This makes cholesterol-containing liposomes particularly suitable for systemic and long-circulating drug delivery applications (Immordino et al., 2006).

3.3 Surface modification (PEGylation and charge modulation)

Surface modification is a key strategy to improve the pharmacokinetic and biological performance of liposomes. PEGylation involves the covalent attachment of polyethylene glycol (PEG) chains to the liposomal surface, creating a hydrophilic steric barrier that reduces opsonization and recognition by the mononuclear phagocyte system (MPS) (Allen et al., 1991). This results in "stealth liposomes" with significantly prolonged circulation half-life and improved tumor accumulation via the enhanced permeability and retention (EPR) effect (Torchilin, 2005).

In addition to PEGylation, surface charge plays a major role in biological interactions. Cationic liposomes enhance electrostatic interactions with negatively charged cell membranes, improving cellular uptake and gene delivery efficiency. However, they may also increase plasma protein binding and toxicity. Neutral or slightly negative liposomes demonstrate better systemic stability and reduced nonspecific clearance (Malam et al., 2009). Therefore, optimizing surface charge and steric stabilization is essential for achieving a balance between targeting efficiency and biocompatibility.

4. Preparation Techniques of Liposomes

The preparation of liposomes is a crucial step that determines vesicle size, lamellarity, encapsulation efficiency, and long-term stability. Various conventional and advanced techniques have been developed to tailor liposomal characteristics according to drug properties and therapeutic requirements. These methods primarily rely on the self-assembly of phospholipids in aqueous environments or solvent displacement strategies, followed by processing steps to achieve nanoscale uniformity (Gubernator, 2011; Pattni et al., 2015).

4.1 Thin film hydration method

The thin film hydration method is one of the earliest and most widely adopted techniques for liposome preparation. In this method, phospholipids and lipophilic drugs are dissolved in a volatile organic solvent, which is subsequently evaporated under reduced pressure to form a thin lipid film. Hydration of this film with an aqueous phase above the lipid transition temperature leads to the spontaneous formation of multilamellar vesicles (MLVs) (Bangham, 1993).

Although the method is simple and versatile, it often produces heterogeneous vesicles with broad size distribution. Therefore, additional processing steps such as sonication or extrusion are typically required to obtain nanosized liposomes suitable for drug delivery applications (Liu et al., 2022). Despite scalability limitations, this method remains widely used in laboratory-scale formulation development due to its simplicity and adaptability to various lipid systems.

4.2 Solvent injection methods (ethanol/ether injection)

Solvent injection techniques are based on dissolving lipids in a water-miscible organic solvent followed by controlled injection into an aqueous phase, resulting in spontaneous vesicle formation due to solvent diffusion. The ethanol injection method is particularly popular as it avoids high shear forces and produces relatively uniform small unilamellar vesicles (Mozafari et al., 2008).

Upon solvent dilution, phospholipids self-assemble into bilayer structures, encapsulating drug molecules within the lipid membrane or aqueous core depending on their solubility. This method is considered more reproducible and scalable compared to thin film hydration; however, complete removal of organic solvent and moderate encapsulation efficiency for hydrophilic drugs remain key challenges (García-Manrique et al., 2018).

Ether injection, though effective in forming vesicles, is less frequently used due to the toxicity and volatility of ether-based solvents, making ethanol-based systems more favorable for pharmaceutical applications (Mozafari et al., 2008).

4.3 Size reduction techniques (sonication and extrusion)

Liposomes produced by conventional methods typically exhibit large size and multilamellar structures, necessitating size reduction to achieve nanoscale uniformity. Sonication is a widely used technique where high-frequency ultrasonic energy disrupts multilamellar vesicles into small unilamellar vesicles (SUVs). However, prolonged sonication may lead to lipid degradation and potential drug leakage (Danaei et al., 2018).

Extrusion is a more controlled technique in which liposomal suspensions are forced through polycarbonate membranes with defined pore sizes under pressure. This method produces liposomes with narrow size distribution and improved reproducibility, making it highly suitable for pharmaceutical applications (Danaei et al., 2018). Compared to sonication, extrusion offers better scalability and less risk of thermal degradation of sensitive drug molecules.

4.4 Industrial-scale production approaches

Scaling up liposome production from laboratory to industrial level remains a significant challenge in nanopharmaceutical development. Traditional batch methods are often limited by poor reproducibility and solvent handling issues. To address this, advanced techniques such as high-pressure homogenization, microfluidization, and continuous flow systems have been developed (Jóhannesson et al., 2020).

Microfluidic-based approaches are gaining significant attention due to their ability to precisely control mixing at the microscale, enabling the production of highly uniform

liposomes with tunable size and encapsulation efficiency. These systems also support continuous manufacturing, making them highly attractive for industrial-scale production (van Swaay & deMello, 2013).

Furthermore, regulatory-driven manufacturing trends now emphasize solvent reduction, process intensification, and GMP-compliant continuous production systems to facilitate clinical translation of liposomal drug products (Jóhannesson et al., 2020).

5. Characterization and Evaluation of Liposomes

The physicochemical characterization of liposomes is essential for predicting their in vivo performance, stability, and therapeutic efficiency. Key evaluation parameters include particle size distribution, surface charge, encapsulation efficiency, morphological attributes, and in vitro release behavior. These parameters collectively determine biodistribution, cellular uptake, and overall clinical effectiveness of liposomal drug delivery systems (Fan et al., 2023; Kaur et al., 2022).

5.1 Particle size, PDI, and zeta potential

Particle size is one of the most critical quality attributes of liposomal systems, directly influencing biodistribution, cellular uptake, and clearance by the reticuloendothelial system. Nanoliposomes typically ranging from 50-200 nm demonstrate improved circulation time and enhanced tumor accumulation via the enhanced permeability and retention (EPR) effect (Kaur et al., 2022). Dynamic light scattering (DLS) is commonly used to determine particle size and polydispersity index (PDI), where a PDI value <0.3 indicates a uniform and stable formulation (Danaei et al., 2018).

Zeta potential reflects the surface charge of liposomes and plays a key role in colloidal stability. High positive or negative zeta potential values generate electrostatic repulsion between vesicles, preventing aggregation and improving physical stability during storage (Fan et al., 2023). Additionally, surface charge influences interactions with biological membranes, thereby affecting cellular uptake and biodistribution.

5.2 Entrapment efficiency and drug loading

Entrapment efficiency (EE%) and drug loading capacity are critical parameters that determine the therapeutic effectiveness of liposomal formulations. EE% represents the percentage of drug successfully encapsulated within liposomes compared to the total drug used during formulation, while drug loading indicates the amount of drug per unit weight of lipid carrier (Zhang et al., 2021).

Hydrophilic drugs are typically encapsulated in the aqueous core, whereas lipophilic drugs integrate into the lipid bilayer. Factors such as lipid composition, cholesterol content,

hydration conditions, and preparation method significantly influence EE% (Shi et al., 2020). Higher cholesterol content often reduces drug leakage, thereby improving encapsulation stability but may slightly reduce loading capacity due to reduced bilayer space (Zhang et al., 2021).

5.3 Morphological analysis (TEM/SEM)

Morphological characterization is essential for confirming vesicle formation, shape, lamellarity, and surface smoothness. Transmission electron microscopy (TEM) provides high-resolution imaging to visualize internal structure and lamellar organization of liposomes, while scanning electron microscopy (SEM) is used to analyze surface morphology and vesicle uniformity (Schoenmaker et al., 2021).

Typically, liposomes appear as spherical or near-spherical vesicles with smooth surfaces under TEM. Cryo-TEM is considered the most advanced technique, as it allows visualization of liposomes in their near-native hydrated state without structural distortion caused by drying (Allen & Cullis, 2020). Morphological consistency is strongly correlated with formulation stability and reproducibility.

5.4 In vitro drug release and stability assessment

In vitro drug release studies are performed to evaluate the release kinetics of encapsulated drugs from liposomes under physiological conditions. Common methods include dialysis bag diffusion and Franz diffusion cells. Release behavior is influenced by lipid composition, bilayer rigidity, particle size, and drug-lipid interactions (Sharma et al., 2022).

Liposomes often exhibit biphasic release patterns characterized by an initial burst release followed by sustained drug release. Stability studies are conducted under different temperature and humidity conditions to assess changes in particle size, PDI, zeta potential, and drug leakage over time (ICH guidelines Q1A). Instability mechanisms include lipid oxidation, hydrolysis, aggregation, and drug leakage, which can be minimized through PEGylation, cholesterol incorporation, and lyophilization techniques (Fan et al., 2023).

6. Drug Delivery Mechanism and Targeting

The therapeutic effectiveness of liposomal drug delivery systems is largely determined by their interaction with biological barriers, cellular uptake mechanisms, and ability to selectively accumulate at the target site. Liposomes enhance drug bioavailability by protecting encapsulated agents from enzymatic degradation and enabling controlled transport across biological membranes through passive, active, and stimuli-responsive mechanisms (Hossen et al., 2019; Bobo et al., 2016).

6.1 Cellular uptake pathways (endocytosis and fusion)

Liposomes are internalized by cells primarily through endocytic pathways, including clathrin-mediated endocytosis, caveolae-mediated uptake, and macropinocytosis. Once internalized, liposomes may localize within endosomes and subsequently undergo lysosomal processing, leading to intracellular drug release (Bobo et al., 2016). The uptake pathway is strongly influenced by liposome size, surface charge, and lipid composition.

In addition to endocytosis, membrane fusion is another important mechanism, particularly for fusogenic or cationic liposomes. In this process, liposomal bilayers merge directly with the cellular membrane, enabling rapid cytoplasmic delivery of the encapsulated drug while bypassing endosomal degradation (Bozzuto & Molinari, 2015; Pattni et al., 2015). This mechanism is especially relevant in gene delivery and vaccine applications.

6.2 Passive targeting (EPR effect in tumors)

Passive targeting is one of the most widely exploited mechanisms in liposomal drug delivery, particularly in oncology. It relies on the enhanced permeability and retention (EPR) effect, where nanoparticles preferentially accumulate in tumor tissues due to leaky vasculature and poor lymphatic drainage (Maeda et al., 2013).

Liposomes with optimized size (typically 100-200 nm) can extravasate through fenestrated tumor blood vessels and remain retained in the tumor microenvironment for prolonged periods. This passive accumulation enhances local drug concentration while reducing systemic toxicity (Sindhwani et al., 2020). However, the efficiency of the EPR effect varies significantly among tumor types and patient conditions, which remains a key limitation in clinical translation.

6.3 Active targeting using ligands

Active targeting involves the functionalization of liposome surfaces with ligands that specifically bind to overexpressed receptors on target cells. These ligands may include antibodies, peptides, aptamers, folic acid, transferrin, or small molecules (Allen & Cullis, 2013; Wang et al., 2021).

Upon ligand-receptor binding, receptor-mediated endocytosis enhances selective uptake of liposomes into target cells, thereby improving therapeutic index and reducing off-target effects. For example, folate-conjugated liposomes demonstrate high affinity for cancer cells overexpressing folate receptors, while antibody-targeted systems enable highly specific tumor recognition (Wang et al., 2021). Active targeting is particularly important for overcoming limitations of passive EPR-based accumulation.

6.4 Drug release behavior in biological environment

Drug release from liposomes in biological systems is governed by multiple factors, including lipid composition, membrane permeability, enzymatic degradation, pH, temperature, and interaction with serum proteins. Release mechanisms typically follow diffusion-controlled, degradation-mediated, or stimulus-responsive pathways (Bozzuto & Molinari, 2015).

In systemic circulation, liposomes may remain stable or undergo gradual drug leakage depending on membrane rigidity and cholesterol content. At the target site, environmental triggers such as acidic tumor pH, elevated enzyme levels, or temperature changes can accelerate drug release, enabling site-specific therapy (Zhang et al., 2020). Many modern liposomal systems are designed as stimuli-responsive carriers to achieve controlled and on-demand drug release, improving therapeutic precision and reducing systemic exposure.

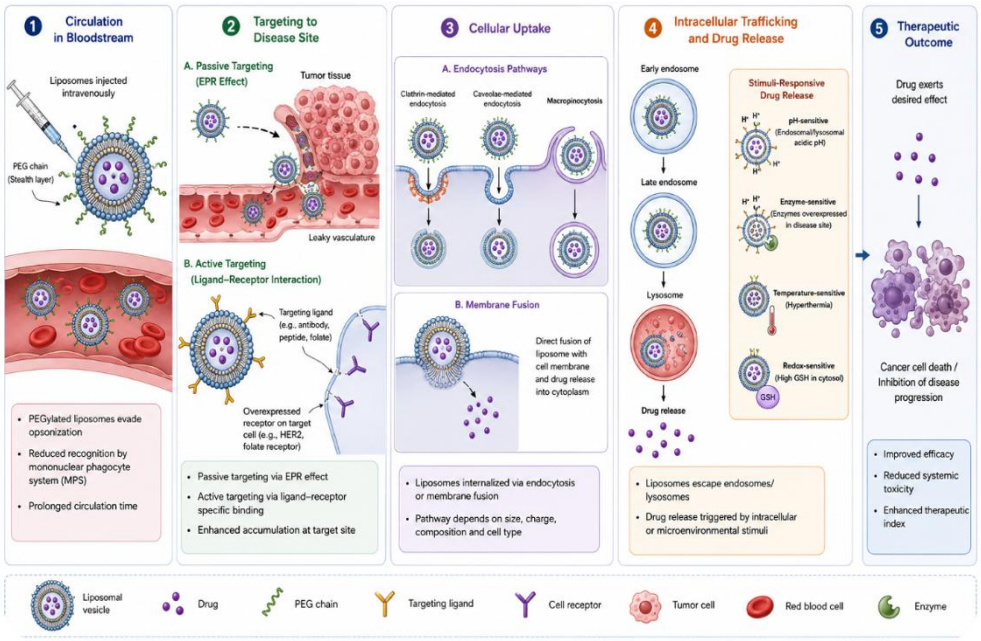

Figure 2: Mechanism of Liposomal Drug Delivery and Targeting

7. Therapeutic Applications of Liposomal Systems

Liposomes have emerged as one of the most successful nanocarrier systems in clinical medicine due to their ability to enhance drug solubility, improve pharmacokinetics, reduce systemic toxicity, and enable targeted delivery. Their versatility has led to applications across oncology, infectious diseases, gene therapy, and topical/ocular drug delivery (Bulbake et al., 2017; Yadav et al., 2021).

7.1 Cancer therapy

Cancer treatment is the most extensively explored application of liposomal drug delivery systems. Liposomes improve the therapeutic index of anticancer agents by enhancing tumor accumulation through the enhanced permeability and retention (EPR) effect and reducing systemic toxicity (Barenholz, 2012). Several liposomal formulations, such as liposomal

doxorubicin and liposomal paclitaxel, have demonstrated improved safety profiles compared to conventional chemotherapy.

PEGylated liposomes further enhance circulation time by evading recognition by the mononuclear phagocyte system, thereby increasing passive tumor targeting. Additionally, ligand-targeted liposomes are being developed to achieve receptor-specific delivery to tumor cells, improving selectivity and reducing off-target effects (Zylberberg & Matosevic, 2016). Stimuli-responsive liposomes are also gaining attention for controlled drug release within the tumor microenvironment.

7.2 Antimicrobial and antifungal delivery

Liposomes have shown significant potential in the delivery of antimicrobial and antifungal agents, particularly for drugs with poor solubility, high toxicity, or limited bioavailability. Encapsulation of antibiotics such as amphotericin B in liposomal systems has significantly reduced nephrotoxicity while maintaining antifungal efficacy (Stone et al., 2016).

Liposomes enhance drug penetration into infected tissues and can be engineered for sustained release, improving therapeutic outcomes in systemic and localized infections. Moreover, cationic liposomes exhibit enhanced interaction with negatively charged microbial membranes, increasing antimicrobial activity (Malik et al., 2020). This makes liposomal formulations highly valuable in treating resistant infections and intracellular pathogens.

7.3 Gene and nucleic acid delivery

Liposomes, particularly cationic liposomes, play a crucial role in gene therapy and nucleic acid delivery, including DNA, siRNA, and mRNA. These systems protect genetic material from enzymatic degradation and facilitate cellular uptake via endocytosis (Hou et al., 2021).

Lipid nanoparticles (LNPs), a specialized form of liposomal systems, have gained global attention due to their role in mRNA vaccine delivery. Ionizable lipids in LNPs enable efficient endosomal escape, allowing cytoplasmic release of nucleic acids for protein expression (Kulkarni et al., 2021). This technology has revolutionized vaccine development and holds strong potential for genetic disease therapy and cancer immunotherapy.

7.4 Ocular and dermatological applications

Liposomes are widely used in ocular and dermatological drug delivery due to their ability to enhance drug penetration through biological barriers such as the corneal epithelium and stratum corneum. In ophthalmic applications, liposomes improve drug retention time on the ocular surface and enhance bioavailability of poorly soluble drugs (Gaudana et al., 2010).

In dermatology, liposomes facilitate enhanced penetration into deeper skin layers, making them useful for the treatment of psoriasis, fungal infections, and inflammatory skin disorders.

Their biocompatibility and ability to incorporate both hydrophilic and lipophilic drugs make them ideal for topical formulations (Pandey et al., 2020). Additionally, liposomal gels and creams provide controlled drug release and improved patient compliance.

8. Recent Advances in Liposomal Drug Delivery

Recent advancements in liposomal drug delivery have significantly improved their stability, targeting efficiency, and clinical applicability. Modern liposomal systems are no longer simple vesicular carriers but have evolved into smart, multifunctional nanoplatforms capable of controlled release, immune evasion, and molecular targeting. These innovations have expanded their role in precision medicine and next-generation therapeutics (Mitchell et al., 2021; Tenchov et al., 2022).

8.1 Stealth liposomes (PEGylated systems)

Stealth liposomes are surface-modified with polyethylene glycol (PEG), which creates a hydrophilic steric barrier that reduces protein adsorption and recognition by the mononuclear phagocyte system. This modification significantly prolongs systemic circulation time and enhances passive tumor accumulation via the EPR effect (Mitchell et al., 2021).

PEGylated liposomes have become a clinically validated strategy, especially in anticancer therapy, where prolonged circulation improves drug exposure at tumor sites while reducing off-target toxicity. However, repeated administration may induce "accelerated blood clearance (ABC)" due to anti-PEG antibody formation, which is a current challenge in clinical use (Knop et al., 2010; Tenchov et al., 2022).

8.2 Stimuli-responsive liposomes (pH/temperature/enzyme-sensitive)

Stimuli-responsive liposomes represent a major advancement in controlled drug delivery. These systems are engineered to release their payload in response to specific internal or external triggers such as pH changes, temperature variations, enzymatic activity, or light exposure (Meng et al., 2019).

pH-sensitive liposomes exploit the acidic microenvironment of tumors and inflamed tissues to trigger drug release, while thermosensitive liposomes release drugs upon localized hyperthermia. Enzyme-responsive systems utilize overexpressed enzymes in diseased tissues for site-specific degradation of lipid bilayers (Wang et al., 2022). These smart systems enhance therapeutic precision and minimize systemic toxicity.

8.3 Lipid nanoparticle (LNP) systems for mRNA delivery

Lipid nanoparticles (LNPs) represent the most advanced evolution of liposomal technology and have gained global recognition due to their role in mRNA vaccine delivery. LNPs

typically consist of ionizable lipids, cholesterol, phospholipids, and PEG-lipids, forming stable nanostructures that protect nucleic acids from degradation (Hou et al., 2021).

A key innovation is the use of ionizable lipids that remain neutral in circulation but become positively charged in acidic endosomes, facilitating endosomal escape and cytoplasmic delivery of mRNA. This mechanism was critical in the success of mRNA-based COVID-19 vaccines, marking a milestone in nanomedicine (Cullis & Hope, 2017; Hou et al., 2021).

8.4 Hybrid and targeted liposomal systems

Hybrid liposomal systems combine liposomes with polymers, proteins, or inorganic nanoparticles to enhance stability, targeting, and multifunctionality. These systems integrate the advantages of multiple nanocarriers, resulting in improved circulation stability and controlled drug release (Li et al., 2022).

Targeted liposomes are surface-functionalized with ligands such as antibodies, peptides, or small molecules that recognize specific receptors on diseased cells. This receptor-mediated targeting enhances cellular uptake and reduces systemic toxicity, making them highly effective in cancer and gene therapy applications (Allen & Cullis, 2013; Li et al., 2022).

8.5 Clinically approved and emerging formulations

Several liposomal formulations have received regulatory approval and are widely used in clinical practice. These include liposomal doxorubicin for cancer therapy, liposomal amphotericin B for fungal infections, and liposomal irinotecan for pancreatic cancer (Bulbake et al., 2017).

Recent developments focus on next-generation formulations with improved targeting, reduced immunogenicity, and enhanced pharmacokinetics. Emerging clinical candidates include stimulus-responsive liposomes, siRNA-loaded liposomes, and multifunctional theranostic systems that combine imaging and therapy in a single platform (Tenchov et al., 2022).

Table 2: Types of Liposomal Systems and Their Characteristics

Liposome Type	Description	Key Feature	Advantages	Limitations	Applications
Conventional liposomes	Basic phospholipid vesicles	Simple bilayer structure	Biocompatible, easy to prepare	Rapid clearance, instability	Drug delivery, basic DDS
PEGylated (stealth) liposomes	Surface-modified with PEG	Long circulation time	Reduced RES uptake	Cost, ABC phenomenon	Cancer therapy
Targeted liposomes	Ligand-conjugated systems	Receptor-specific delivery	High selectivity	Complex preparation	Tumor targeting
Stimuli-	pH/temp/enzyme	Triggered drug	Controlled	Stability	Smart drug

responsive liposomes	sensitive	release	release	issues	delivery
LNP systems	Ionizable lipid-based nanoparticles	Efficient nucleic acid delivery	High transfection efficiency	Complex design	mRNA vaccines

9. Challenges and Limitations

Despite significant advances in liposomal drug delivery systems, several challenges still limit their widespread clinical translation. These limitations are associated with physicochemical instability, biological barriers, manufacturing difficulties, and economic as well as regulatory constraints. Understanding these issues is essential for improving next-generation liposomal formulations (Sercombe et al., 2015; Bozzuto & Molinari, 2015).

9.1 Physical and chemical instability

One of the major limitations of liposomal systems is their inherent physical and chemical instability. Liposomes are prone to aggregation, fusion, phospholipid hydrolysis, and oxidative degradation, which can compromise vesicle integrity and drug retention over time (Mozafari, 2005).

Phospholipid oxidation leads to membrane destabilization, while hydrolysis results in leakage of encapsulated drugs, particularly hydrophilic molecules. Additionally, changes in temperature, pH, and ionic strength can alter bilayer structure and trigger premature drug release (Liu et al., 2020). To overcome these issues, strategies such as cholesterol incorporation, PEGylation, and lyophilization are commonly employed, but complete stabilization remains challenging.

9.2 Rapid clearance by RES system

Liposomes administered systemically are rapidly recognized and cleared by the mononuclear phagocyte system (MPS), particularly in the liver and spleen. This process is mediated by opsonization, where plasma proteins bind to liposomal surfaces and mark them for macrophage uptake (Allen & Cullis, 2013).

This rapid clearance significantly reduces circulation half-life and limits drug accumulation at target sites. Although PEGylation has been developed to create “stealth liposomes” that evade immune recognition, repeated administration may still trigger accelerated blood clearance (ABC phenomenon), reducing long-term effectiveness (Wang et al., 2016).

9.3 Scale-up and manufacturing issues

Translating laboratory-scale liposomal formulations into industrial-scale production remains a major challenge. Conventional methods such as thin film hydration lack reproducibility and

are difficult to scale due to batch variability and solvent handling issues (Zylberberg & Matosevic, 2016).

Large-scale production requires strict control over particle size distribution, encapsulation efficiency, and sterility, which is difficult to achieve using traditional batch processes. Advanced manufacturing techniques such as microfluidics, high-pressure homogenization, and continuous flow systems are emerging but still face limitations in cost and regulatory acceptance (Pattni et al., 2015).

9.4 Cost and regulatory constraints

The development and commercialization of liposomal drug products are associated with high production costs due to expensive phospholipids, complex manufacturing processes, and stringent quality control requirements. These factors significantly increase the final cost of liposomal therapeutics compared to conventional formulations (Bulbake et al., 2017).

From a regulatory perspective, ensuring batch-to-batch consistency, sterility, stability, and safety is challenging due to the complex nature of nanocarriers. Regulatory agencies require extensive characterization and clinical validation, which increases development time and cost (Zylberberg & Matosevic, 2016). These barriers collectively slow down the approval and commercialization of novel liposomal systems.

10. Future Perspectives

The future of liposomal drug delivery is strongly oriented toward the development of intelligent, multifunctional, and clinically translatable nanocarriers. With continuous advancements in lipid chemistry, nanotechnology, and bioengineering, liposomes are evolving from simple drug carriers into sophisticated therapeutic platforms capable of diagnosis, targeted delivery, and controlled release. The integration of precision medicine principles is expected to further enhance their role in individualized therapy (Mitchell et al., 2021; Tenchov et al., 2022).

A major future direction is the development of **next-generation smart liposomes** capable of responding to multiple biological stimuli simultaneously. These systems are being engineered to release drugs in response to tumor-specific triggers such as acidic pH, redox gradients, enzymatic overexpression, or external stimuli like heat and light. Such multi-responsive systems are expected to significantly improve site-specific drug delivery while minimizing systemic toxicity (Meng et al., 2019; Wang et al., 2022).

Another promising area is the advancement of **precision-targeted liposomal systems**. The incorporation of high-affinity ligands, antibodies, peptides, and aptamers is being explored to achieve cell- and tissue-specific delivery. These strategies aim to overcome the limitations of

passive targeting and enhance therapeutic selectivity, particularly in heterogeneous diseases such as cancer and inflammatory disorders (Li et al., 2022).

The evolution of **lipid nanoparticle (LNP) technology** has opened new possibilities in gene therapy and vaccine development. Ionizable lipid-based systems have already demonstrated success in mRNA vaccine delivery, and ongoing research is focusing on expanding their application to genetic disorders, protein replacement therapy, and cancer immunotherapy. Future improvements are expected to focus on enhancing endosomal escape efficiency, reducing immunogenicity, and improving long-term stability (Hou et al., 2021; Cullis & Hope, 2017).

In addition, **artificial intelligence (AI) and computational modeling** are expected to play a crucial role in liposome design and optimization. AI-driven predictive models can assist in selecting optimal lipid compositions, predicting stability, and optimizing drug loading and release profiles. This approach may significantly reduce experimental trial-and-error and accelerate formulation development (Mitchell et al., 2021).

From a translational perspective, future research will increasingly focus on **scalable and cost-effective manufacturing technologies**, such as microfluidics and continuous flow production systems. These approaches are essential to bridge the gap between laboratory research and industrial-scale production, ensuring batch consistency and regulatory compliance (Zylberberg & Matosevic, 2016).

Finally, the future of liposomal systems lies in their integration into **theranostic platforms**, combining therapeutic and diagnostic functions in a single nanocarrier. Such systems could enable real-time monitoring of drug distribution and therapeutic response, paving the way for highly personalized and adaptive treatment strategies in clinical practice.

11. Conclusion

Liposomes have emerged as one of the most advanced and clinically successful nanocarrier systems for drug delivery, owing to their unique vesicular structure, excellent biocompatibility, and ability to encapsulate both hydrophilic and lipophilic drugs. Continuous advancements in lipid composition, surface modification, and formulation technologies have significantly improved their stability, circulation time, and targeting efficiency, enabling broad applications in cancer therapy, antimicrobial treatment, gene delivery, and dermatological as well as ocular drug delivery. Recent developments such as PEGylated stealth liposomes, stimuli-responsive systems, and lipid nanoparticle-based mRNA delivery have further expanded their therapeutic potential and clinical relevance. However, challenges including physical and chemical instability, rapid clearance by the mononuclear phagocyte

system, scale-up difficulties, and high production costs still limit widespread commercialization. Future progress in smart multifunctional systems, ligand-based targeting, and advanced manufacturing technologies is expected to overcome these barriers, establishing liposomes as a cornerstone of next-generation precision and personalized medicine.

6. Acknowledgements

The authors sincerely acknowledge the support of their institution and colleagues who provided valuable insights during the preparation of this review.

7. Conflict of Interest

The authors declare that there are no conflicts of interest.

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