



Liposomal Drug Delivery Systems: A Comprehensive Review

¹Ajay Sharma, ²Jitendra Jakhar, ¹Rahul saini, ¹Sushil singh Rajawat, ¹Vishnu kumar Saini, ²Dr. C.P Mishra

¹Scholar Sri Balaji College of Pharmacy, Rajasthan University of Health sciences, Jaipur, Rajasthan, India Mail: sharmacp.mishra@gmail.com

²Associate Professor, Sri Balaji College of Pharmacy, Rajasthan University of Health sciences Jaipur, Rajasthan, India

Received:- 20/06/2026, Revised:- 23/07/2026, Accepted:- 11/08/2026, Published:- 22/08/2026

Abstract

Liposomal drug delivery has emerged as one of the most successful nanotechnology-based approaches for improving the therapeutic performance of conventional drugs. Liposomes are spherical vesicular systems composed mainly of phospholipid bilayers surrounding an aqueous core. Their unique structure allows them to encapsulate both hydrophilic and lipophilic therapeutic agents, protect drugs from premature degradation, modify pharmacokinetics, improve drug accumulation at desired sites, and reduce systemic toxicity. Since the approval of the first liposomal formulation, Doxil® (liposomal doxorubicin), liposomal systems have progressed from experimental carriers to clinically established drug-delivery platforms. Recent developments include PEGylated, ligand-targeted, stimuli-responsive, immunoliposomes, and novel zwitterionic systems such as PMPCylated liposomes. These technologies aim to overcome limitations including rapid clearance, drug leakage, poor tissue penetration, manufacturing variability, and immune recognition. This review discusses the structure, composition, classification, preparation methods, drug-loading approaches, mechanisms of drug delivery, advantages, limitations, pharmaceutical applications, marketed products, evaluation parameters, recent advances, and future perspectives of liposomal drug delivery.

Keywords: Liposomes, nanocarriers, drug delivery, phospholipids, PE Gylated liposomes, targeted delivery, controlled release, nanomedicine.

1. Introduction

Conventional drug delivery systems frequently face problems such as poor aqueous solubility, limited bioavailability, rapid metabolism, nonspecific distribution, toxicity, and inadequate drug concentration at the target site. Nanotechnology-based drug delivery systems have therefore attracted considerable attention as strategies for improving therapeutic efficacy and reducing adverse effects.

Liposomes are among the most extensively investigated lipid-based nanocarriers. They are self-assembled vesicles consisting of one or more phospholipid bilayers enclosing an aqueous compartment. Their amphiphilic structure allows hydrophilic drugs to be incorporated into the aqueous core while hydrophobic drugs can be accommodated within the lipid bilayer.

The major pharmaceutical advantages of liposomes include improved drug solubility, protection of encapsulated drugs, prolonged circulation, controlled release, altered biodistribution, and reduction of drug-related toxicity. Surface modification can further provide passive or active targeting capabilities.

The clinical success of liposomal formulations has demonstrated the practical value of this technology. Doxil®, a pegylated liposomal formulation of doxorubicin, became the first FDA-approved liposomal drug in 1995. Subsequently, several liposomal products have been developed for cancer, infections, anesthesia, pulmonary disorders, vaccines, and other therapeutic applications.

2. Structure and Composition of Liposomes

A typical liposome consists of three major structural components:

1. Phospholipids
2. Cholesterol
3. Aqueous phase

2.1 Phospholipids

Phospholipids are the principal structural components of liposomes. They contain a hydrophilic head group and hydrophobic fatty-acid tails. In an aqueous environment, phospholipids spontaneously organize into bilayers, with hydrophilic groups facing the aqueous environment and hydrophobic chains oriented toward the interior of the membrane. Commonly used phospholipids include:

- Phosphatidylcholine
- Hydrogenated soybean phosphatidylcholine
- Phosphatidylethanolamine
- Phosphatidylglycerol

- Dioleoyl phosphatidylcholine

2.2 Cholesterol

Cholesterol is frequently incorporated into liposomal membranes to improve membrane rigidity and stability. It can reduce excessive membrane permeability and minimize premature leakage of the encapsulated drug.

2.3 Surface-modifying agents

Surface modification can alter circulation time, targeting, stability, and biological interactions. Polyethylene glycol (PEG) is commonly used to produce "stealth" liposomes that reduce recognition by components of the mononuclear phagocyte system.

More recently, zwitterionic polymers such as poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) have been investigated as alternatives to conventional PEGylation.

3. Classification of Liposomes

Liposomes can be classified according to size, lamellarity, composition, and surface characteristics.

3.1 Based on lamellarity

Unilamellar vesicles:

Contain a single phospholipid bilayer.

- Small unilamellar vesicles (SUVs)
- Large unilamellar vesicles (LUVs)

Multilamellar vesicles (MLVs):

Contain multiple concentric lipid bilayers separated by aqueous spaces.

The size and lamellarity influence drug loading, circulation, stability, and biological distribution.

3.2 Based on surface characteristics

- Conventional liposomes
- PEGylated or stealth liposomes
- Cationic liposomes
- Anionic liposomes
- Neutral liposomes
- Targeted liposomes
- Immunoliposomes
- Stimuli-responsive liposomes

4. Drug Encapsulation in Liposomes

One of the most important advantages of liposomes is their ability to accommodate drugs with different physicochemical properties.

Hydrophilic drugs

Hydrophilic drugs are primarily entrapped within the aqueous core.

Lipophilic drugs

Lipophilic drugs are incorporated into the hydrophobic region of the phospholipid bilayer.

Amphiphilic drugs

Amphiphilic molecules may be distributed between the aqueous compartment and lipid

membrane depending on their physicochemical properties. This versatility allows liposomes to act as carriers for small molecules, proteins, peptides, nucleic acids and other therapeutic agents.

5. Methods of Liposome Preparation

Several techniques are available for preparing liposomal formulations.

5.1 Thin-film hydration method

This is one of the most widely used laboratory methods.

Steps:

1. Phospholipids and cholesterol are dissolved in an organic solvent.
2. The solvent is evaporated to form a thin lipid film.
3. The lipid film is hydrated using an aqueous drug solution or buffer.
4. Vesicles are formed through agitation.
5. Sonication or extrusion may be used to reduce particle size.

5.2 Reverse-phase evaporation

Lipids are dissolved in an organic solvent and mixed with an aqueous phase to form a water-in-oil emulsion. Removal of the organic solvent results in vesicle formation.

5.3 Ethanol injection

The lipid components are dissolved in ethanol and rapidly injected into an aqueous phase. Lipid precipitation and self-assembly result in liposome formation.

5.4 Ether injection

A lipid-containing ether solution is slowly injected into a heated aqueous phase. Evaporation of ether leads to vesicle formation.

5.5 Sonication

Sonication reduces the size of larger vesicles and may produce smaller unilamellar vesicles.

5.6 Membrane extrusion

Liposomes are passed through membranes with defined pore sizes to obtain a more uniform particle-size distribution.

5.7 Micro fluidic methods

Microfluidic techniques provide better control of mixing and can improve reproducibility and scalability. Modern manufacturing approaches increasingly focus on controlling critical quality attributes such as particle size, encapsulation efficiency, lipid composition, and drug release.

6. Drug-Loading Techniques

Liposomal drugs can be loaded by passive or

active methods.

6.1 Passive loading

The drug is incorporated during liposome formation.

Examples include:

- Thin-film hydration
- Reverse-phase evaporation
- Solvent injection
- Dehydration-rehydration

6.2 Active or remote loading

Active loading involves establishing a chemical or ionic gradient across the lipid membrane that drives drug accumulation inside the liposome.

Remote loading has been particularly important for anthrax cycline drugs such as doxorubicin and can provide high encapsulation efficiency and improved formulation stability.

7. Mechanism of Liposomal Drug Delivery

After administration, liposomes undergo several biological processes:

Administration → Circulation → Biodistribution → Target-site accumulation → Cellular uptake → Drug release → Therapeutic action

Liposomes may reach tissues through passive distribution or through active targeting mechanisms.

7.1 Passive targeting

Passive targeting is associated with the physiological characteristics of certain pathological tissues. In tumors, abnormal vasculature and impaired lymphatic drainage can contribute to nanoparticle accumulation. However, the magnitude and reproducibility of this phenomenon vary considerably among tumors and patients, so passive targeting should not be considered universally reliable.

7.2 Active targeting

Active targeting involves attaching ligands to the liposome surface that recognize receptors expressed by particular cells or tissues.

Potential targeting molecules include:

- Antibodies
- Peptides
- Aptamers
- Folic acid
- Transferrin
- Carbohydrates

Several receptor-targeting strategies have been investigated for cancer and other diseases.

8. Advantages of Liposomal Drug Delivery

The major advantages are summarized below.

Advantage	Pharmaceutical significance
Improved solubility	Useful for poorly water-soluble drugs
Protection from degradation	Reduces premature drug degradation
Controlled release	Maintains drug concentration over time
Reduced toxicity	Limits exposure of healthy tissues
Prolonged circulation	Can increase systemic exposure
Targeting	Facilitates preferential delivery to selected tissues
Improved pharmacokinetics	Modifies distribution and elimination
Biocompatibility	Phospholipids are generally biologically compatible
Versatile drug loading	Can carry hydrophilic and lipophilic drugs
Surface modification	Allows development of specialized systems

These properties explain why liposomes remain one of the most clinically successful nanocarrier platforms.

9. Limitations and Challenges

Despite their advantages, liposomes have several limitations.

9.1 Physical instability

Liposomes may undergo aggregation, fusion, oxidation, hydrolysis, or drug leakage during storage.

9.2 Premature drug release

Insufficient membrane stability may result in leakage before the liposome reaches its intended target.

9.3 Rapid clearance

Conventional liposomes may be recognized and removed by the mononuclear phagocyte system.

9.4 Manufacturing challenges

Reproducible large-scale manufacturing can be difficult because small variations in lipid composition, processing conditions, particle size, and encapsulation can affect product performance.

9.5 Limited tissue penetration

Although liposomes can improve drug distribution, their penetration into certain biological barriers and dense tissues remains challenging.

9.6 Immunological concerns

PEGylated systems may undergo immune recognition in some circumstances, including the development of anti-PEG antibodies and accelerated blood clearance. Recent research therefore investigates alternative surface coatings.

10. Pharmaceutical and Therapeutic Applications

10.1 Cancer therapy

Cancer remains one of the major therapeutic areas for liposomal drug delivery. Liposomal formulations can reduce exposure of normal

tissues while improving the pharmacological profile of anticancer agents.

Examples include liposomal:

- Doxorubicin
- Daunorubicin
- Irinotecan
- Cytarabine

Doxil® represents a landmark example of successful liposomal cancer therapy.

10.2 Antifungal therapy

Liposomal amphotericin B is an important example of lipid-based delivery used to improve the therapeutic profile of amphotericin B.

10.3 Antibacterial therapy

Liposomes can improve the delivery of antibiotics by increasing drug localization and potentially improving penetration into difficult-to-treat infection sites.

10.4 Vaccines and nucleic acid delivery

Lipid-based delivery technologies have demonstrated major potential for nucleic acids and vaccine-related applications. Liposomal systems can act as carriers and, depending on their composition, can facilitate cellular uptake and intracellular delivery.

10.5 Pulmonary delivery

Liposomal formulations have been investigated for inhalation and pulmonary delivery because they can provide localized drug delivery and sustained release.

10.6 Gene and RNA delivery

Lipid-based nanocarriers can transport nucleic acids such as DNA, RNA, and other genetic materials while protecting them from enzymatic degradation.

10.7 Dermatological applications

Liposomes have also been investigated for topical delivery of corticosteroids, antibiotics, antioxidants, cosmetic ingredients, and other active compounds.

11. Marketed Liposomal Drug Products

The clinical development of liposomal formulations has resulted in several approved products. Examples include:

Product	Drug	Major application
Doxil®	Doxorubicin	Cancer
DaunoXome®	Daunorubicin	Cancer
AmBisome®	Amphotericin B	Fungal infections
DepoCyt®	Cytarabine	Cancer
Onivyde®	Irinotecan	Pancreatic cancer
Exparel®	Bupivacaine	Local analgesia

The exact regulatory status and indications may vary by country and over time. Liposomal products have been developed for oncology, infectious disease, anesthesia, pulmonary therapy, vaccination, and other applications.

12. Evaluation of Liposomal Formulations

Quality evaluation is essential for ensuring reproducibility, safety, and therapeutic performance.

Important characterization parameters include:

Physical characterization

- Particle size
- Polydispersity index
- Zeta potential
- Morphology
- Lamellarity

Drug-related parameters

- Drug content
- Encapsulation efficiency
- Drug-loading capacity
- In-vitro drug release
- Stability

Biological evaluation

- Cellular uptake
- Cytotoxicity
- Hemocompatibility
- Biodistribution
- Pharmacokinetic studies
- Therapeutic efficacy

Stability studies

Important stability parameters include:

- Physical appearance
- Particle-size changes
- Drug leakage
- Lipid degradation
- Oxidation
- Hydrolysis
- pH changes

Critical quality attributes are particularly important when moving from laboratory development to commercial manufacturing.

13. Recent Advances in Liposomal Drug Delivery

13.1 PEGylated liposomes

PEGylation creates a hydrophilic surface layer

European Journal of Molecular Pharmacy

that can reduce nonspecific interactions and prolong circulation.

13.2 Ligand-targeted liposomes

Attachment of antibodies, peptides, aptamers, folate, or other ligands can improve cellular targeting.

13.3 Stimuli-responsive liposomes

These systems are designed to release drugs in response to specific stimuli such as:

- pH
- Temperature
- Enzymes
- Light
- Ultrasound
- Redox conditions

Such approaches provide opportunities for site-specific drug release.

13.4 Immunoliposomes

Antibodies or antibody fragments are incorporated into the liposomal surface to recognize specific cellular targets.

13.5 Theranostic liposomes

Theranostic systems combine therapeutic and diagnostic functions, potentially enabling simultaneous drug delivery and imaging.

13.6 PMPCylated liposomes

A particularly recent direction is the use of PMPC, a zwitterionic polymer inspired by phosphatidylcholine. Recent research suggests PMPCylation may reduce nonspecific protein adsorption and improve immune evasion while providing opportunities for mucus, biofilm, and biological-barrier penetration.

13.7 Personalized liposomal therapy

Future liposomal systems may increasingly incorporate patient-specific disease characteristics, molecular biomarkers, and precision-targeting strategies.

14. Regulatory and Manufacturing Considerations

The successful development of a liposomal

drug requires control over both formulation composition and manufacturing processes.

Important variables include:

- Lipid identity and purity
- Lipid ratio
- Particle size
- Surface characteristics
- Encapsulation efficiency
- Drug release
- Sterility
- Endotoxin levels
- Stability
- Manufacturing reproducibility

Regulatory assessment of liposomal products therefore requires detailed characterization of composition, manufacturing processes, critical quality attributes, and product performance.

15. Future Perspectives

The future of liposomal drug delivery is likely to involve more sophisticated systems capable of overcoming biological barriers and providing highly controlled drug release.

Important research directions include:

1. Next-generation targeted liposomes
2. Stimuli-responsive drug release
3. Improved alternatives to PEGylation
4. RNA and gene delivery
5. Combination therapy
6. Theranostic applications
7. Improved tumor penetration
8. Mucosal and oral delivery
9. Artificial-intelligence-assisted formulation optimization
10. Continuous and scalable manufacturing

Recent research is particularly focused on overcoming premature clearance, biological-barrier penetration, immune recognition, and manufacturing reproducibility.

16. Conclusion

Liposomal drug delivery represents a mature yet continuously evolving platform in pharmaceutical nanotechnology. The unique phospholipid bilayer structure enables liposomes to accommodate both hydrophilic and hydrophobic drugs while providing opportunities for controlled release, altered pharmacokinetics, improved biodistribution, and reduced toxicity. The clinical success of products such as Doxil®, AmBisome®, and other liposomal formulations demonstrates that liposomal technology has moved beyond theoretical research into practical therapeutic applications.

Nevertheless, challenges related to stability, drug leakage, manufacturing scale-up, immune recognition, tissue penetration, and reproducibility remain. Recent innovations

including targeted, stimuli-responsive, theranostic, and PMPCylated liposomes provide promising approaches to address these limitations. Thus, continued integration of nanotechnology, pharmaceuticals, molecular biology, and precision medicine is expected to expand the role of liposomes in next-generation drug delivery.

17. Reference

1. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: an updated review. *Pharmaceutics*. 2017;9(2):12.
2. Sercombe L, Veerati T, Moheimani F, Wu SY, Sood AK, Hua S. Advances and challenges of liposome assisted drug delivery. *Front Pharmacol*. 2015;6:286.
3. Bozzuto G, Molinari A. Liposomes as nanomedical devices. *Int J Nanomedicine*. 2015;10:975-999.
4. Akbarzadeh A, Rezaei-Sadabady R, Davaran S, et al. Liposome: classification, preparation, and applications. *Nanoscale Res Lett*. 2013;8:102.
5. Bulbake U, et al. Liposomal formulations in clinical use: an updated review. *Pharmaceutics*. 2017;9(2):12.
6. Wang N, et al. A review of liposomes as a drug delivery system: current status of approved products, regulatory environments, and future perspectives. *Molecules*. 2022;27(4):1372.
7. Pattni BS, Chupin VV, Torchilin VP. New developments in liposomal drug delivery. *Chem Rev*. 2015;115(19):10938-10966.
8. Shi Y, Huang Z, Zhu S, et al. PMPCylated liposomes in drug delivery and beyond. *Materials Today Bio*. 2026;37:102960.
9. Shadab A, Ansari AF. Translational insights into liposomal drug delivery: recent advances, therapeutic applications, and clinical trials. *Drug Res (Stuttg)*. 2026;76(2/3):65-81.
10. Liposomes: A breakthrough in advanced drug delivery systems. *Advances in Colloid and Interface Science*. 2026;353:103887.