Review

Liposomal Formulations in Clinical Use Progress Challenges and Future Directions

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Liposomal Formulations in Clinical Use Progress Challenges and Future Directions

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Abstract: Liposomal drug delivery has been identified to be a potentially useful method for the modulation of the therapeutic index of drugs by enhanced bioavailability, reduced toxicity, and site-specific delivery. Historical development and chief progress in liposomal formulations, mechanism, formulation, and clinical application are elaborated in this article. Lipid polymorphism, cholesterol stabilization, and pharmacokinetic properties in drug entrapment retention are elaborated upon. FDA-approved liposome drugs such as Doxil®, for example, have proven to be effective in treating cancers, and other liposome drugs are being researched for neurological and infectious disorders. Despite all such advances, biological barriers and immune interactions and scale-up manufacturing constraints remain significant hurdles. Techniques like PEGylation, ligand-functionalized liposomes, and hybrid nanocarrier integration have been suggested to address such constraints. All such newer innovations such as AI-based patient-specific liposomal formulation and BBB-penetrating liposomes are where drug delivery will head in the future, with even more targeted and patient-specific therapies. This review provides a detailed overview of liposomal strategy, challenge, and the future aimed at addressing biologic and manufacturability hurdles. The introduction of stimulus-responsive liposomes, hybrid carriers, and second-generation target mechanisms will shape future nanomedicine, and liposomal drugs will be the basis for next-generation drug delivery systems.

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1. Introduction to Liposomal Drug Delivery

1.1. Historical Evolution and Advancements in Liposomal Formulations

Liposomal drug delivery systems have experienced monumental growth since the 1960s when they were discovered. Initially, they were thought to be phospholipid vesicles, but subsequent studies in bilayer structure and encapsulation character started formulating possibilities of increased application towards drug delivery [1]. Various modifications were performed over time in liposome stability, targeting efficacy, and release of the drug. Early liposome formulations were hampered by the problem of rapid clearance through the MPS, and this opened the door to stealth liposomes with PEGylated surfaces, significantly prolonging circulation times [2]. These developments translated into clinical use, and liposomes are now a new drug delivery platform of choice for modern medicine.

1.2. Key Mechanisms and Benefits of Liposomal Drug Delivery

Liposomal drug delivery is obtained from phospholipid bilayers encapsulating hydrophobic and hydrophilic drugs for controlled targeted delivery [3]. The versatility of liposomes to increase drug solubility, protect active pharmaceutical ingredient from degradation, and site-specific delivery of drugs has made them most beneficial in oncology, infection, and gene therapy [4]. Apart from this, the developments like ligand-targeting and pH-sensitive liposomes have maximized their therapeutic index with effective cellular uptake and low off-targeting. These developments also provide impetus to the development of liposomal nanocarriers in drug discovery.

2. Liposomal Formulation Strategies and Composition

2.1. Role of Lipid Polymorphism and Cholesterol in Liposomal Stability

Lipid polymorphism is the cause of regulating structural and functional characteristics of liposomes. Lipid phases, i.e., hexagonal, lamellar, and cubic phases, regulate membrane permeability, fusion, and drug entrapment efficiency [5]. Structural mobility of lipids to transform from one phase to another at physiological condition regulates drug release kinetic and stability. Among all the lipids, phosphatidylcholine-derived liposomes are most common due to compatibility as well as the potential to form stable bilayer structure [5].

Cholesterol is also an essential element that supports liposomal stability by way of membrane rigidity and control over permeability. Cholesterol gets incorporated into the phospholipid bilayer, lowering membrane fluidity and also drug leakage too early [6]. Resistant to destabilization by serum and enhancing in vivo circulation time enables liposomes as potential drug carriers [6].

2.2. Pharmacokinetics and Drug Retention in Liposomal Carriers

Pharmacokinetics of drug delivery via liposomes is controlled by particle size, charge, and lipid structure. PEGylation is most effective with long-circulation liposomes, which decreases opsonization and phagocytosis by the mononuclear phagocyte system and increases bioavailability [7]. Drug release profile also depends on physicochemical properties of liposomal formulation, which can be designed to deliver drugs in sustained and controlled fashion [7].

Furthermore, lipid composition determines drug retention, and dihydrosphingomyelin-based liposomes are reported to retain more drug than normal phospholipid-based formulations [8]. Encapsulated drug stability discourages premature leakage and ensures high site-specific targeting at the site of targeting [8]. Modulation of lipid composition and modification of the surface continue to be of utmost importance in current efforts to maximize therapeutic efficacy and patient care.

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Table 1. Liposomal Formulation Strategies and Composition.

Aspect	Key Role in Liposomal Stability and Drug Delivery	Reference
Lipid Polymorphism	Determines liposome structure, permeability, and drug encapsulation efficiency	[5]
Lipid Phases	Includes lamellar, hexagonal, and cubic phases that affect membrane fusion and release kinetics	[5]
Phosphatidylcholine (PC)	Ensures bilayer stability and biocompatibility	[5]
Cholesterol	Modulates membrane rigidity, reduces fluidity, and prevents premature drug leakage	[6]
Serum Stability	Cholesterol enhances resistance to serum-induced destabilization, improving circulation time	[6]
PEGylation	Reduces opsonization and clearance, prolonging circulation time	[7]
Particle Size & Surface Charge	Influence pharmacokinetics, bioavailability, and cellular uptake	[7]
Dihydrosphingomyelin-Based Liposomes	Improve drug retention and reduce premature leakage	[8]
Controlled Drug Release	Achieved through lipid composition and surface modifications	[7], [8]

3. Clinical Applications and FDA-Approved Liposomal Drugs

3.1. Doxil® and Other Approved Liposomal Formulations in Cancer Therapy

The first FDA-approved nanodrug, Doxil® (liposomal doxorubicin), transformed liposomal drug delivery [9]. By encapsulating doxorubicin within PEGylated liposomes, Doxil® maximizes prevention of cardiotoxicity and maximal drug concentration within tumor tissues by the EPR effect [9]. Other FDA-approved liposomal oncology drugs include Myocet® (non-PEGylated liposomal doxorubicin) and Marqibo® (liposomal vincristine) for best therapeutic index and safety in patients [10]. These formulations reveal the therapeutic possibilities of liposomes in reducing off-target toxicity and maximizing drug effect in cancer therapy [10].

3.2. Emerging Clinical Applications in Targeted Drug Delivery

Other than in oncology, target delivery by liposomes is aimed at infectious disease, gene therapy, and inflammatory disease. The Liposomal amphotericin B (Ambisome®) with lower nephrotoxicity than native formulations is a prime example of an antifungal [11]. Blood-brain barrier penetration has been bypassed by utilizing the use of liposomal formulation such that central nervous system (neurologic) diseases, i.e., glioblastoma and Alzheimer's, become amenable to therapeutic levels [11].

Ligand-directed innovation, including receptor-directed and antibody-conjugated liposomes, is continually improving the efficacy of site-specific drug targeting. Transferrin or folate ligand-coated liposomes, for instance, push drug targeting into cancer cells of cancer cell cells for enhanced therapeutic effect [12]. The innovation is shifting towards increased dependence on liposomal carriers in precision medicine formulation [12].

Table 2. Clinical Applications and FDA-Approved Liposomal Drugs.

Category	Liposomal Drug/Formulation	Key Advantages	Reference
Oncology (Cancer Therapy)	Doxil® (Pegylated Liposomal Doxorubicin)	Reduces cardiotoxicity, enhances tumor targeting via EPR effect	[9]
	Myocet® (Non-PEGylated Liposomal Doxorubicin)	Improves therapeutic index and patient safety	[10]

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	Marqibo® (Liposomal Vincristine)	Increases drug accumulation in cancer cells	[10]
Infectious Diseases	Ambisome® (Liposomal Amphotericin B)	Lower nephrotoxicity in antifungal therapy	[11]
Neurological Disorders	Liposomal BBB-Penetrating Formulations	Enables drug delivery for glioblastoma, Alzheimer's	[11]
Targeted Drug Delivery	Ligand-Based Liposomes (Transferrin/Folate-Conjugated)	Enhances intracellular uptake in tumor cells	[12]

4. Challenges in Liposomal Drug Delivery

4.1. Overcoming Biological Barriers and Immune System Interactions

Prevention of the premature clearance of MPS is one of the important challenges of liposomal drug delivery because the MPS identifies liposomes as a foreign particle and removes them from the circulation [13]. For its prevention, PEGylation (polyethylene glycol coating on liposomes) has been performed on a regular basis, which prolongs circulation time and drug bioavailability [13]. Redosing with extended PEGylation results in the formation of anti-PEG antibodies, which lowers efficacy [14].

Also, drug delivery through biological barriers like blood-brain barrier (BBB) and tumor microenvironment is still an unresolved challenge. Ligand-induced active targeting (e.g., by transferrin, folate) and pH-sensitive liposomes have been made to deliver intracellularly for enhanced therapeutic effect [14].

Table 3. Strategies to Overcome Biological Barriers in Liposomal Drug Delivery [13,14].

Challenge	Solution/Strategy	Key Benefits
Rapid Clearance by Mononuclear Phagocyte System (MPS)	PEGylation (Coating with Polyethylene Glycol)	Extends circulation time, improves drug bioavailability
Anti-PEG Antibody Formation	Alternative Surface Modifications (e.g., zwitterionic lipids, stealth coatings)	Reduces immune recognition, minimizes loss of efficacy
Limited Blood-Brain Barrier (BBB) Penetration	Ligand-Based Targeting (e.g., Transferrin, Folate Conjugation)	Enhances receptor-mediated endocytosis for brain delivery
Tumour Microenvironment Resistance	pH-Sensitive and Stimuli-Responsive Liposomes	Promotes site-specific drug release in acidic tumor environments

4.2. Limitations in Large-Scale Manufacturing and Stability Concerns

Even with their drug benefits, liposomal drugs are met with manufacturing and stability problems that make mass production a challenge. Heterogeneity in size, charge, and drug entrapment efficiency of the liposomes from batch to batch poses regulatory clearance and quality control challenges [15]. Moreover, long-term physical and chemical stability is not easily attained since liposomal products during storage aggregate, leak, and oxidize easily [15].

As part of the drive to increase scalability, there has been reported improvement in microfluidics and extrusion-based processes, with greater accuracy in controlling liposome size and drug loading efficiency [16]. Furthermore, freeze-dried (lyophilized) liposomal products are more stable and have a longer shelf life, and are less difficult to commercialize [16]. Such issues of manufacturing and stability remain yet to be the key to widespread application of liposomal therapies.

5. Innovations and Future Directions in Liposomal Nanocarriers

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5.1. Advanced Targeting Strategies and Personalized Liposomal Therapeutics

More recent developments in liposomal drug delivery aim precision-targeting systems to maximize therapeutic effect at minimal cost of side effects. Ligand-modified liposomes that will selectively bind to specific receptors on disease cells improve drug delivery to the target tissue [17]. Folate, transferrin, and antibody-targeted liposomes, for example, have delivered improved delivery to cancer cells and intracellular release of drugs [17].

Further, patient-specific liposomal drugs are also being engineered in which drugs are formulated according to patient-specific biomarkers and disease profiles. This maximizes drug efficacy via the potential of liposomal carriers to target specific molecular targets, maximizing clinical outcomes in cancer, neurodegenerative diseases, and infection [18]. Aside from AI-formulation development, liposomes could also be customized for personalized therapy protocols [18].

5.2. Integration with Other Nanocarriers and Hybrid Drug Delivery Systems

Scientists are preparing hybrid drug delivery systems by combining liposomes with other nanocarriers such as polymeric nanoparticles, micelles, and dendrimers to overcome the limitations of conventional liposomes [19]. Hybrid systems are more stable to drugs, exhibit sustained release of drugs, and have enhanced cellular uptake, which makes them suitable for challenging drug delivery conditions [19].

One of such possible research areas includes the use of liposomal nanocarriers in crossing the blood-brain barrier (BBB). Surface modification using BBB-penetrating ligands and nanoparticle-liposome hybrid systems are being created to improve drug delivery in neurological diseases [20]. Additionally, pH-, temperature-, or enzyme-stimuli-sensitive liposomes for stimulus-induced drug delivery is also being researched for targeted drug delivery [21]. The continuous development of hybrid and smart liposomal systems is bound to revolutionize future drug delivery systems [21].

6. Conclusion

Liposomal drug delivery has revolutionized today's pharmacology with enhanced therapeutic efficacy and safety of drugs. The process of developing liposomal formulation during the last decades helped liposomes attain widespread clinical application in cancer and infectious disease. Exploiting the primary mechanisms including passive and active targeting, liposomes have maximized the bioavailability of drugs and reduced systemic toxicity.

Although effective, there are some problems that need to be overcome, e.g., immune clearance, stability, and scale-up problems in production. Methods like PEGylation, ligand targeting, and complex lipid formulation have improved circulation time and site-specific targeting to a large extent. Biological barriers such as the blood-brain barrier (BBB) are still not so easily accessible, and further work needs to be done in hybrid and stimulus-responsive liposomal systems.

In the immediate future, new approaches such as individualized liposomal therapy, artificial intelligence-based formulation design, and hybrid nanocarrier platforms will be expected to further optimize liposomal drug delivery. With ongoing advances in target-specific approaches and convergence with other nanotechnologies, liposomal formulations will be poised to revolutionize drug delivery in various therapeutic fields. Bridge building between discovery and clinical translation will be responsible for the overall acceptance of liposomal therapeutics in personalized medicine.

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