JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

Descriptive Review on Liposomal Drug Delivery System

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Publication history: Received on 7th June; Revised on 18th June; Accepted on 2nd July 2024

Article DOI: 10.69613/93vtyy97

Abstract: Liposomal drug delivery systems have transformed pharmaceutical science, offering a versatile platform for enhancing drug efficacy and reducing toxicity. These microscopic vesicles, composed of lipid bilayers, can encapsulate both hydrophilic and lipophilic drugs, significantly improving their pharmacokinetic profiles. Recent advancements include the development of stimuli-responsive and targeted liposomes, expanding their therapeutic potential across various medical fields. The unique pharmacokinetics and biodistribution of liposomal formulations contribute to their improved drug delivery capabilities. However, challenges persist in liposome stability, drug loading efficiency, and large-scale production. Innovative solutions are being developed to address these issues, including novel lipid compositions and manufacturing techniques. Liposomes have shown remarkable potential in cancer therapy, gene delivery, vaccine development, and diagnostic imaging. The integration of liposomes with nanotechnology has opened new avenues for targeted drug delivery and theranostic applications. Emerging trends also highlight their role in personalized medicine. Despite challenges, liposomal drug delivery systems continue to evolve, promising significant advancements in therapeutic interventions and paving the way for more effective and tailored treatment strategies in modern medicine.

Keywords: Liposomes; Drug Delivery; Targeted Therapy; Nanocarriers; Pharmacokinetics.

1. Introduction

1.1. Historical perspective

The discovery of liposomes marks a significant milestone in the field of drug delivery systems. In 1961, Alec D. Bangham and his colleagues at the Babraham Institute in Cambridge, England, accidentally observed that phospholipids in aqueous solutions formed closed bilayer structures [1]. This serendipitous finding laid the foundation for liposome research and development. Initially, liposomes were primarily used as model membrane systems to study biological membranes. However, their potential as drug carriers was quickly recognized. In 1971, Gregoriadis and Ryman first proposed using liposomes for drug delivery [2]. This concept revolutionized the pharmaceutical industry, offering a way to improve drug efficacy and reduce toxicity.

The 1970s and 1980s saw rapid advancements in liposome technology. Researchers developed various methods for liposome preparation, including sonication, extrusion, and reverse-phase evaporation [3]. These techniques allowed for better control over liposome size and lamellarity, crucial factors in drug delivery applications. A major breakthrough came in the 1990s with the approval of the first liposomal drug formulation, Doxil®, for the treatment of AIDS-related Kaposi's sarcoma [4]. This success spurred further research and development of liposomal drug delivery systems. In recent years, the field has expanded to include stimuli-responsive liposomes, targeted liposomes, and their integration with nanotechnology, opening new avenues for personalized medicine and advanced therapeutic strategies [5].

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1.2. Fundamentals of liposomes

Liposomes are microscopic vesicles composed of one or more lipid bilayers enclosing an aqueous core (shown in Figure 1). Their structure mimics that of cellular membranes, making them biocompatible and biodegradable [6]. The unique architecture of liposomes allows them to encapsulate both hydrophilic and hydrophobic drugs, with hydrophilic drugs residing in the aqueous core and hydrophobic drugs inserted within the lipid bilayers [7].

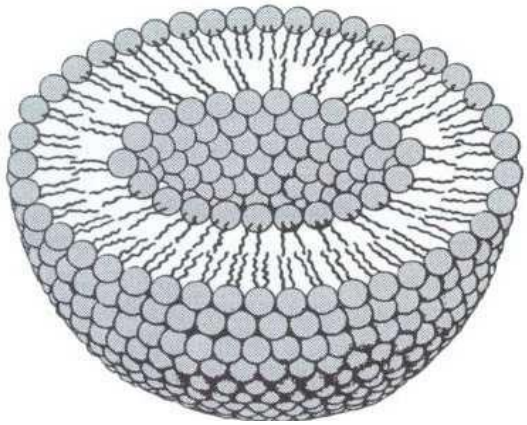

Figure 1. Illustration of structure of liposomes

The size of liposomes can range from 20 nm to several micrometers, depending on the preparation method and composition. This versatility in size allows for tailored drug delivery to different tissues and cellular compartments [8].

Liposomes possess several key features that make them excellent drug carriers:

- Biocompatibility: Being composed of natural or synthetic lipids, liposomes are generally non-toxic and well-tolerated by the body [9].
- Versatility: They can encapsulate a wide range of therapeutic agents, from small molecules to macromolecules like proteins and nucleic acids [10].
- Protection of cargo: Liposomes shield their encapsulated drugs from degradation and premature clearance, potentially improving the drug's pharmacokinetic profile [11].
- Targeted delivery: The surface of liposomes can be modified with targeting ligands to enhance their specificity for certain tissues or cell types [12].
- Controlled release: The release of drugs from liposomes can be controlled by manipulating the lipid composition and environmental responsiveness [13].

2. Composition and Structure of Liposomes

2.1. Phospholipids

Phospholipids are the primary structural components of liposomes, forming the bilayer that encapsulates the aqueous core. These amphiphilic molecules consist of a hydrophilic head group and two hydrophobic fatty acid tails [14].

The most commonly used phospholipids in liposome preparation include:

- Phosphatidylcholine (PC): Derived from natural sources like egg or soy, or synthesized, PC is the most frequently used phospholipid due to its stability and biocompatibility [15].
- Phosphatidylethanolamine (PE): Often used in combination with PC, PE can enhance the fusion of liposomes with cell membranes [16].
- Phosphatidylserine (PS): Negatively charged PS can be used to create anionic liposomes, which have specific interactions with certain cell types [17].
- Phosphatidylglycerol (PG) and Phosphatidylinositol (PI): These negatively charged phospholipids are used to modulate the surface charge of liposomes [18].

- The choice of phospholipids significantly influences the liposome's properties, including stability, size, charge, and drug release characteristics. For instance, saturated phospholipids with long acyl chains (e.g., dipalmitoylphosphatidylcholine) form more rigid and stable bilayers, while unsaturated phospholipids (e.g., dioleoylphosphatidylcholine) create more fluid and permeable membranes [19].

2.2. Cholesterol

Cholesterol is a crucial component in many liposomal formulations, playing a vital role in modulating membrane (Figure 2) properties:

- Membrane fluidity: Cholesterol reduces the fluidity of the lipid bilayer above the phase transition temperature and increases it below this temperature, leading to a more stable membrane over a broader temperature range [20].
- Permeability: By filling gaps between phospholipid molecules, cholesterol decreases membrane permeability, reducing drug leakage [21].
- Stability: Cholesterol enhances the mechanical strength of the lipid bilayer, improving liposome stability in biological fluids [22].
- Phase transition: It eliminates the sharp phase transition of phospholipids, which can be beneficial for maintaining liposome integrity during storage and administration [23].
- The molar ratio of cholesterol to phospholipids typically ranges from 1:4 to 1:1, depending on the desired liposome properties and the encapsulated drug [24].

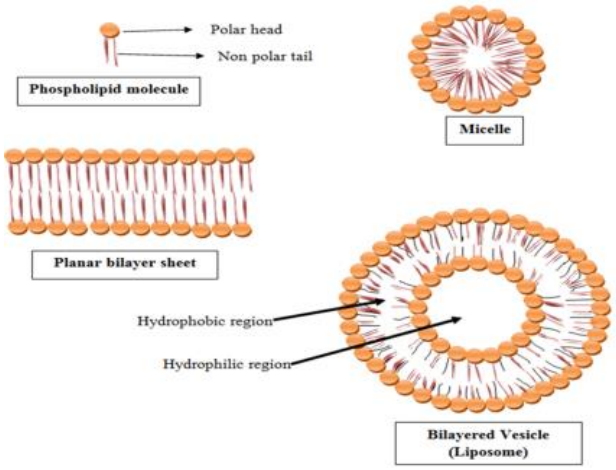

Figure 2. Phospholipid bilayer liposomes

2.3. Other components

While phospholipids and cholesterol form the basic structure of liposomes, various other components can be incorporated to enhance functionality:

- PEGylated lipids: Polyethylene glycol (PEG)-modified lipids are used to create "stealth" liposomes with prolonged circulation times by reducing opsonization and clearance by the reticuloendothelial system [25].
- Cationic lipids: Lipids like DOTAP (1,2-dioleoyl-3-trimethylammonium-propane) are used in gene delivery applications, facilitating the complexation with negatively charged nucleic acids [26].
- pH-sensitive lipids: Lipids that undergo conformational changes in response to pH variations can be used to create pH-responsive liposomes for targeted drug release [27].
- Targeting ligands: Various molecules, including antibodies, peptides, and small molecules, can be conjugated to the liposome surface to enhance targeting to specific tissues or cell types [28].
- Antioxidants: Compounds like α-tocopherol can be incorporated to prevent lipid peroxidation and improve liposome stability [29].
- Charged lipids: The inclusion of charged lipids (positive or negative) can alter the surface charge of liposomes, affecting their interactions with biological membranes and drug loading efficiency [30].

3. Classification of Liposomes

3.1. Based on size and lamellarity

Liposomes are classified based on their size and the number of lipid bilayers they possess (Figure 3). Small Unilamellar Vesicles (SUVs) range from 20-100 nm in size and consist of a single lipid bilayer. They are typically prepared by sonication or extrusion methods. SUVs offer advantages such as long circulation time and high curvature for certain applications, but their small size limits their encapsulation volume [31]. Large Unilamellar Vesicles (LUVs) are larger than 100 nm, usually between 100-1000 nm, and also have a single lipid bilayer. LUVs are prepared by extrusion, reverse-phase evaporation, or detergent dialysis. They offer high encapsulation efficiency and stability, making them ideal for encapsulating large macromolecules [32].

Multilamellar Vesicles (MLVs) are larger than 500 nm and consist of multiple concentric lipid bilayers. They are easily prepared by simple hydration of lipid films. MLVs excel at encapsulating lipophilic compounds but have limitations in encapsulating hydrophilic compounds and tend to be cleared from circulation more quickly [33]. Oligolamellar Vesicles (OLVs) fall between LUVs and MLVs in terms of properties, with sizes ranging from 100-1000 nm and containing a few concentric bilayers, usually 2-5. OLVs are typically prepared by reverse-phase evaporation or detergent removal methods [34].

Giant Unilamellar Vesicles (GUVs) are the largest class, with sizes exceeding 1000 nm and reaching up to 100 µm. These vesicles consist of a single lipid bilayer and are primarily used for studying membrane properties and as cell membrane models. GUVs are prepared using specialized techniques such as electroformation or gentle hydration methods [35].

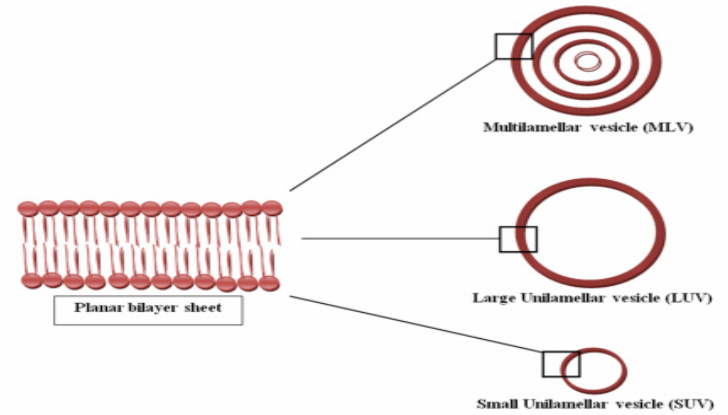

Figure 3. Liposomes classification based on lamellarity

3.2. Based on composition and functionality

Liposomes can also be classified based on their lipid composition and functional characteristics. Conventional liposomes, the first generation, are composed of neutral or negatively charged phospholipids and cholesterol. These liposomes are rapidly cleared by the reticuloendothelial system (RES) [36]. Stealth liposomes incorporate PEGylated lipids, which allow them to evade RES uptake, resulting in longer circulation times. This property enhances their pharmacokinetics and takes advantage of the enhanced permeability and retention (EPR) effect in certain disease states [37].

Cationic liposomes contain positively charged lipids and are primarily used for gene delivery and nucleic acid therapeutics. Their positive charge enhances cellular uptake due to electrostatic interactions with cell membranes [38]. Fusogenic liposomes contain fusion-promoting lipids like DOPE, designed to fuse with cellular or endosomal membranes, thereby enhancing intracellular delivery of their cargo [39].

pH-sensitive liposomes incorporate pH-sensitive lipids or polymers that respond to acidic environments, such as those found in tumors or endosomes. This property improves targeted drug delivery and intracellular release [40]. Thermosensitive liposomes contain temperature-sensitive lipids that release their drug cargo at specific temperatures, often used in combination with localized hyperthermia for targeted release [41].

Immunoliposomes are surface-modified with antibodies or antibody fragments, enhancing their targeting to specific cell types or tissues. This modification significantly improves therapeutic efficacy in various diseases, especially cancer [42].

4. Methods of Liposome Preparation

4.1. Passive loading techniques

Passive loading techniques involve encapsulating drugs during the liposome formation process. The thin-film hydration method is a simple technique where lipids are dissolved in an organic solvent, dried to form a thin film, and then hydrated with an aqueous drug solution. While straightforward, this method often results in low encapsulation efficiency for hydrophilic drugs [43]. The reverse-phase evaporation method offers higher encapsulation efficiency for hydrophilic drugs. In this technique, lipids and the aqueous drug solution form a water-in-oil emulsion, followed by the removal of the organic solvent under vacuum [44].

The freeze-thaw method involves rapid freezing and thawing of MLVs containing the drug, which improves the encapsulation of macromolecules. This technique is often combined with other methods to enhance overall efficiency [45]. Sonication uses sound waves to disrupt MLVs into SUVs, producing small, homogeneous liposomes. However, this method carries the risk of drug degradation due to heat generation [46]. Extrusion is a technique that forces liposomes through polycarbonate membranes to produce uniform-sized liposomes while maintaining the integrity of sensitive compounds [47].

4.2. Active loading techniques

Active loading techniques involve creating a gradient to drive drug encapsulation after liposome formation. The pH gradient method creates a pH difference between the liposome interior and exterior, which is effective for weak bases or acids. This method can achieve high encapsulation efficiency, often exceeding 90% for some drugs [48]. The ammonium sulfate gradient technique uses an ammonium sulfate gradient to load amphipathic weak bases. It is highly efficient for drugs like doxorubicin and provides stable drug retention [49]. The ion gradient method employs ion gradients, such as calcium acetate, for loading. This approach is particularly useful for drugs that form insoluble calcium complexes, offering high loading efficiency and improved stability [50].

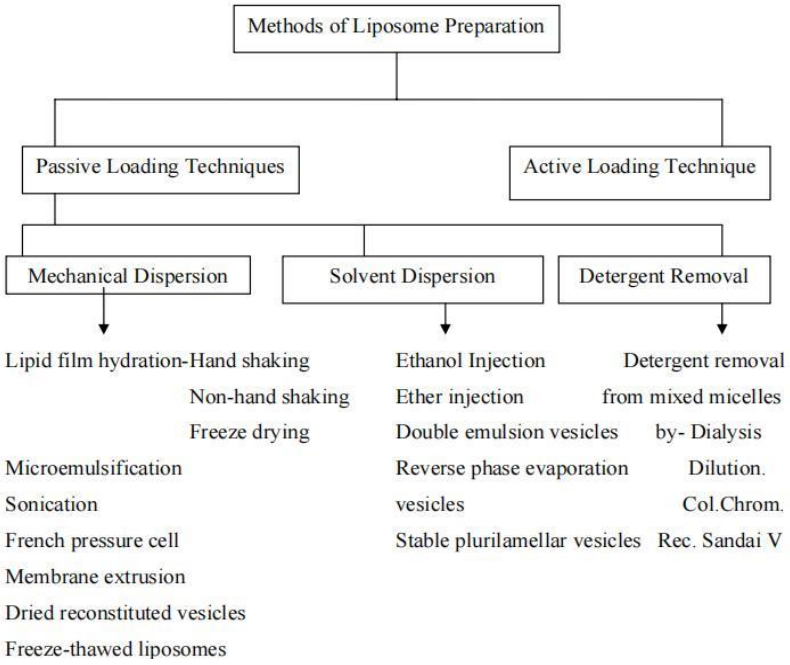

Figure 4. Methods for liposome preparation

4.3. Recent advancements in preparation methods

Recent innovations aim to improve liposome preparation efficiency and scalability. Microfluidic techniques offer precise control over liposome size and lamellarity, with the potential for continuous production and large-scale manufacturing [51]. Supercritical fluid methods use supercritical CO2 as a solvent, providing an environmentally friendly, residual solvent-free approach suitable for thermolabile compounds [52].

Dual asymmetric centrifugation combines mixing and homogenization in one step, useful for preparing small-scale, highly concentrated liposomes, and is applicable for semisolid formulations [53]. The membrane contactor method pushes the organic lipid phase through a membrane into an aqueous phase, offering a continuous, scalable process with good control over size

distribution [54]. Modifications to the ethanol injection method, such as cross-flow injection techniques, have improved control over liposome characteristics and show potential for continuous, large-scale production [55].

5. Drug Loading and Release Mechanisms

5.1. Strategies for drug incorporation

Drug incorporation into liposomes is a critical aspect of liposomal drug delivery systems, significantly influencing the formulation's efficacy and pharmacokinetics. The choice of drug loading strategy depends on the physicochemical properties of the drug, the liposome composition, and the desired release profile. Passive loading methods involve incorporating the drug during liposome formation. For hydrophilic drugs, this typically occurs in the aqueous core of the liposome, while lipophilic drugs tend to partition into the lipid bilayer [56]. However, passive loading often results in low encapsulation efficiency for hydrophilic drugs.

Active loading techniques have been developed to improve encapsulation efficiency, particularly for weakly basic or acidic drugs. These methods exploit pH or ion gradients across the liposomal membrane to drive drug accumulation within the liposomes. For instance, the remote loading technique using an ammonium sulfate gradient has been successfully employed for amphipathic weak bases like doxorubicin, achieving encapsulation efficiencies exceeding 95% [57]. Another approach involves the use of cyclodextrins as drug-complexing agents, which can enhance the loading of poorly water-soluble drugs [58].

Recent advancements in drug loading strategies include the development of dual-drug loading techniques, where two drugs with different physicochemical properties are simultaneously loaded into a single liposome. This approach has shown promise in combination therapy, particularly in cancer treatment, where it can help overcome drug resistance and enhance therapeutic efficacy [59].

5.2. Factors affecting drug release

The release of drugs from liposomes is a complex process influenced by various factors related to the liposome composition, the encapsulated drug, and the surrounding environment. The lipid composition plays a crucial role in determining membrane permeability and stability. Saturated lipids with longer acyl chains generally form more rigid membranes, resulting in slower drug release, while unsaturated lipids increase membrane fluidity and may accelerate release [60]. The inclusion of cholesterol in the lipid bilayer can modulate membrane permeability, often leading to reduced drug leakage.

The physicochemical properties of the encapsulated drug, including its molecular weight, charge, and lipophilicity, significantly affect its release profile. Larger molecules typically exhibit slower release rates compared to smaller ones. The interaction between the drug and lipid components can also influence release kinetics, with stronger interactions generally resulting in slower release [61]. Environmental factors such as temperature, pH, and the presence of serum proteins can dramatically affect drug release from liposomes.

Elevated temperatures increase membrane fluidity and may accelerate drug release, a principle exploited in thermosensitive liposomal formulations. Changes in pH can alter the ionization state of both the drug and lipid components, potentially triggering release in specific physiological environments, such as the acidic milieu of tumors or endosomes [62].

5.3. Controlled release systems

Controlled release systems aim to optimize the therapeutic efficacy of liposomal drugs by maintaining drug concentrations within the therapeutic window over an extended period. Various strategies have been developed to achieve controlled release from liposomes. One approach involves the use of polymer-coated liposomes, where the polymer coating acts as an additional diffusion barrier, slowing drug release [63]. Another strategy employs pH-sensitive lipids or polymers that destabilize the liposome structure in response to acidic environments, triggering rapid drug release in target tissues or intracellular compartments. Stimuli-responsive liposomes represent an advanced approach to controlled release.

These systems are designed to release their cargo in response to specific stimuli such as temperature, light, ultrasound, or magnetic fields. For example, thermosensitive liposomes incorporating temperature-sensitive lipids undergo a phase transition at specific temperatures, leading to rapid drug release. This property has been exploited in combination with local hyperthermia for targeted drug delivery in cancer therapy [64]. Another innovative approach involves the use of enzyme-sensitive liposomes, where the liposome structure is destabilized by specific enzymes overexpressed in diseased tissues. This strategy offers a high degree of specificity in drug release, potentially improving therapeutic efficacy while minimizing systemic side effects [65].

6. Pharmacokinetics and Biodistribution of Liposomal Formulations

6.1. Absorption and distribution

The pharmacokinetics and biodistribution of liposomal formulations differ significantly from those of free drugs, largely due to the unique properties of the liposomal carrier. When administered intravenously, liposomes primarily remain within the vascular compartment, with their size preventing immediate extravasation into tissues. This confinement to the bloodstream can dramatically alter the volume of distribution compared to free drugs [66].

The distribution of liposomes is largely governed by their physicochemical properties, particularly size and surface characteristics. Conventional liposomes are rapidly recognized and cleared by the mononuclear phagocyte system (MPS), leading to accumulation in organs rich in these cells, such as the liver and spleen. This phenomenon can be exploited for passive targeting of drugs to these organs but may limit the therapeutic efficacy for other target sites [67]. PEGylated or "stealth" liposomes exhibit prolonged circulation times due to reduced MPS uptake. This extended circulation allows for greater accumulation in tissues with increased vascular permeability, such as tumors and sites of inflammation, through the enhanced permeability and retention (EPR) effect [68]. The size of liposomes also plays a crucial role in their distribution, with smaller liposomes (<100 nm) generally exhibiting better extravasation and tissue penetration compared to larger ones.

6.2. Metabolism and excretion

The metabolism and excretion of liposomal formulations involve complex processes that depend on both the liposomal carrier and the encapsulated drug. Liposomes themselves are metabolized primarily by the action of phospholipases in the liver and other tissues. The lipid components are typically broken down and either excreted or reused in cellular metabolism [69].

The fate of the encapsulated drug depends on its release from the liposome and its inherent pharmacokinetic properties. Drugs released from liposomes in the circulation undergo metabolism and excretion similar to their free form. However, the rate and extent of drug metabolism can be significantly altered when the drug remains encapsulated, potentially leading to prolonged half-lives and altered metabolite profiles [70]. Excretion of intact liposomes is minimal due to their size, which exceeds the renal filtration threshold. However, as liposomes break down, their components and the released drug may be excreted through renal or hepatobiliary pathways, depending on their molecular properties [71].

6.3. Factors influencing in vivo behavior

Several factors influence the in vivo behavior of liposomal formulations. Liposome size is a critical determinant, affecting circulation time, tissue distribution, and cellular uptake. Generally, liposomes in the range of 50-200 nm exhibit optimal pharmacokinetic properties, balancing extended circulation with effective tissue penetration [72]. Surface charge plays a significant role in liposome-protein interactions and cellular uptake. Neutral and slightly negative liposomes typically exhibit longer circulation times compared to highly charged ones. Positive charge can enhance cellular uptake but may also lead to increased clearance and potential toxicity [73].

The lipid composition affects liposome stability, drug retention, and interaction with biological membranes. The inclusion of cholesterol, for instance, can enhance stability in the bloodstream, leading to prolonged circulation times. The degree of saturation of phospholipids influences membrane fluidity and drug retention, with more saturated lipids generally providing better drug retention [74]. Protein corona formation, where plasma proteins adsorb onto the liposome surface, significantly impacts the in vivo fate of liposomes. This protein layer can affect circulation time, cellular uptake, and biodistribution. PEGylation reduces protein adsorption, contributing to the "stealth" properties of these liposomes [75].

7. Targeting Strategies for Liposomes

7.1. Passive targeting

Passive targeting relies on the inherent properties of liposomes and the pathophysiological features of diseased tissues to achieve preferential accumulation at target sites. The most well-known mechanism of passive targeting is the enhanced permeability and retention (EPR) effect, prevalent in solid tumors and inflammatory sites. This effect arises from the leaky vasculature and impaired lymphatic drainage in these tissues, allowing preferential accumulation of nanoparticles, including liposomes [76]. To exploit the EPR effect, liposomes must maintain prolonged circulation times, typically achieved through PEGylation. The optimal size range for EPR-mediated accumulation is generally considered to be 50-200 nm, balancing long circulation with effective extravasation [77]. While passive targeting has shown considerable success, particularly in cancer therapy, its efficacy can be limited by tumor heterogeneity and barriers to deep tissue penetration.

Another form of passive targeting involves the natural tropism of liposomes for certain organs, particularly those of the mononuclear phagocyte system (MPS). This property can be exploited for delivering drugs to the liver, spleen, and lungs, which are rich in phagocytic cells [78].

7.2. Active targeting

Active targeting involves the modification of liposome surfaces with specific ligands that can recognize and bind to target cells or tissues. This approach aims to enhance the specificity and efficacy of drug delivery, potentially reducing off-target effects. Common targeting moieties include antibodies, antibody fragments, peptides, aptamers, and small molecules [79]. The choice of targeting ligand depends on the specific target and the desired pharmacokinetic profile. For instance, whole antibodies provide high specificity but may lead to increased immunogenicity and faster clearance. In contrast, smaller targeting moieties like peptides or aptamers may offer better tissue penetration and reduced immunogenicity [80]. Active targeting can significantly enhance cellular uptake and internalization of liposomes, particularly when combined with cell-penetrating peptides or ligands that trigger receptor-mediated endocytosis. This approach has shown promise in overcoming drug resistance mechanisms and improving intracellular drug delivery [81].

Recent advancements in active targeting include the development of dual-targeting strategies, where two different ligands are incorporated onto the liposome surface. This approach can enhance targeting specificity and efficiency, particularly in heterogeneous tissues like tumors [82].

7.3. Stimuli-responsive liposomes

Stimuli-responsive liposomes represent an advanced targeting strategy that combines elements of both passive and active targeting with controlled release mechanisms. These "smart" liposomes are designed to release their cargo in response to specific stimuli, which can be either endogenous (e.g., pH, enzymes, redox potential) or exogenous (e.g., temperature, light, ultrasound) [83]. pH-responsive liposomes exploit the acidic microenvironment of tumors or the pH gradient in endosomes/lysosomes to trigger drug release. These liposomes typically incorporate pH-sensitive lipids or polymers that undergo conformational changes or hydrolysis in acidic conditions, leading to liposome destabilization and drug release [84].

Thermosensitive liposomes, composed of lipids with a phase transition temperature slightly above physiological temperature, release their contents when exposed to mild hyperthermia. This approach has shown particular promise in combination with local heating techniques for targeted cancer therapy [85]. Enzyme-responsive liposomes are designed to be degraded by specific enzymes overexpressed in diseased tissues. For example, matrix metalloproteinase (MMP)-sensitive liposomes have been developed for targeted drug delivery to tumors with high MMP activity [86].

Magnetically guided liposomes, incorporating superparamagnetic iron oxide nanoparticles, allow for physical targeting using external magnetic fields. These systems can also generate heat when exposed to alternating magnetic fields, combining targeting with thermally triggered release [87]. The development of multi-responsive liposomes, sensitive to two or more stimuli, represents the cutting edge of this field. These systems offer the potential for precise spatiotemporal control over drug release, potentially maximizing therapeutic efficacy while minimizing side effects [88].

8. Applications of Liposomal Drug Delivery Systems

8.1. Cancer therapy

Liposomal drug delivery systems have found extensive application in cancer therapy, with several formulations approved for clinical use. The most well-known example is Doxil®, a PEGylated liposomal formulation of doxorubicin, which has shown improved efficacy and reduced cardiotoxicity compared to free doxorubicin in various cancer types [89]. Liposomal formulations of other anticancer drugs, such as paclitaxel, irinotecan, and cisplatin, have also demonstrated enhanced therapeutic indices. The advantages of liposomal drug delivery in cancer therapy include improved pharmacokinetics, enhanced tumor accumulation via the EPR effect, and reduced systemic toxicity. Recent developments in this field include the design of multifunctional liposomes that combine drug delivery with imaging capabilities (theranostics) and the development of liposomal formulations for combination therapy [90].

8.2. Gene therapy

Liposomes, particularly cationic liposomes, have shown significant potential as non-viral vectors for gene therapy. These systems can effectively condense and protect nucleic acids (DNA, RNA, siRNA) from degradation while facilitating cellular uptake and endosomal escape [91]. Liposomal gene delivery systems have been investigated for a wide range of genetic disorders, cancers, and infectious diseases. Recent advancements in this field include the development of pH-sensitive and targeting liposomes to enhance gene transfection efficiency and specificity. The use of liposomes for mRNA delivery has gained particular attention, especially in the context of vaccine development [92].

8.3. Vaccine delivery

Liposomes have emerged as promising vaccine delivery systems, capable of enhancing antigen stability, improving antigen presentation, and modulating immune responses. Liposomal vaccines can encapsulate a wide range of antigens, from proteins and peptides to nucleic acids, and can be designed to target specific immune cells [93]. The flexibility of liposomal systems allows for co-delivery of antigens and immunostimulatory molecules, potentially enhancing vaccine efficacy. Notable examples include the liposomal adjuvant systems used in licensed vaccines for hepatitis A and influenza. The recent success of liposome-based mRNA vaccines for COVID-19 has further highlighted the potential of this technology in rapid vaccine development [94].

8.4. Diagnostic imaging

Liposomes have found application in diagnostic imaging as contrast agents for various imaging modalities. Paramagnetic liposomes, incorporating gadolinium or manganese, have been developed as contrast agents for magnetic resonance imaging (MRI). These systems can enhance contrast in specific tissues or organs, potentially improving disease detection and characterization [95]. Radiolabeled liposomes have been investigated for nuclear imaging techniques such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT). These systems can provide information on liposome biodistribution and target site accumulation, aiding in the development and optimization of liposomal drug delivery systems [96]. The concept of theranostic liposomes, combining therapeutic and diagnostic capabilities, has gained significant interest. These multifunctional systems allow for real-time monitoring of drug delivery and therapeutic response, potentially enabling personalized treatment strategies [97].

8.5. Other therapeutic areas

Beyond cancer, gene therapy, and vaccines, liposomal drug delivery systems have shown promise in various other therapeutic areas. In infectious diseases, liposomal formulations of antibiotics have demonstrated enhanced efficacy against intracellular pathogens and biofilm-associated infections. Liposomal amphotericin B, for instance, has become a standard treatment for invasive fungal infections [98]. In the field of pain management, liposomal formulations of local anesthetics, such as liposomal bupivacaine, have shown prolonged analgesic effects compared to conventional formulations [99]. Liposomal drug delivery has also been explored in the treatment of inflammatory disorders, with liposomal corticosteroids showing promise in reducing systemic side effects while maintaining therapeutic efficacy [100]. In ophthalmology, liposomal formulations have been investigated for improving drug retention and penetration in ocular tissues, potentially enhancing the treatment of both anterior and posterior segment diseases [101]. The application of liposomes in dermatology has focused on improving transdermal drug delivery and developing topical formulations with enhanced skin penetration and retention [102].

9. Conclusion

Liposomal drug delivery systems have emerged as a powerful and versatile platform in the field of nanomedicine, offering significant advantages over conventional drug formulations. This comprehensive review has explored the fundamental aspects of liposomes, from their structure and classification to advanced preparation methods, drug loading strategies, and targeting mechanisms. The breadth of applications discussed, spanning cancer therapy, gene delivery, vaccine development, diagnostic imaging, and various other therapeutic areas, underscores the remarkable potential and adaptability of liposomal technology. The evolution of liposomal formulations from conventional liposomes to sophisticated stimuli-responsive and multifunctional systems reflects the rapid advancements in this field. These developments have been driven by a deeper understanding of liposome-biological interactions, improvements in manufacturing techniques, and the integration of novel materials and technologies. The success of liposomal formulations in clinical practice, exemplified by approved drugs like Doxil® and the recent mRNA-based COVID-19 vaccines, demonstrates the translational potential of this technology. Despite these achievements, challenges remain in optimizing liposomal drug delivery systems. Issues such as stability, scale-up production, and cost-effectiveness continue to be areas of active research. Moreover, the complex interplay between liposome properties and biological systems necessitates ongoing investigation to fully harness the potential of these delivery vehicles.

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