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Liposomes in Panoramic View: From Structural Engineering to Clinical Translation in Advanced Therapeutics

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Abstract. Liposomes, as biosimilary stealth nanocarriers composed of phospholipid bilayers, have become a core technological platform for breaking through traditional drug delivery bottlenecks due to their unique structural features (ability to encapsulate both hydrophilic and hydrophobic drugs), excellent biocompatibility, and high functional designability. This review systematically summarizes the current research progress of liposomes. First, the composition and classification of liposomes are analyzed and summarized based on particle size and vesicle structure, clarifying the intrinsic link between structural characteristics and application requirements. Second, the main preparation strategies such as Thin-Film Hydration Method, Reverse phase evaporation technique, Ether injection method, and Microfluidic method are evaluated and compared. Third, the research progress of liposome delivery systems is described in detail, including conventional liposomes, targeted liposomes, long-circulating liposomes, and stimuli-responsive liposomes. Fourth, the research progress and clinical applications of liposomes are elaborated in detail, including their transformation achievements and key milestones in fields such as anti-tumor, anti-infection, anti-fungal, gene therapy, and vaccine delivery. The challenges and development trends faced by current research frontiers are also analyzed.

Keywords: Liposome, classification, preparation method, delivery system, clinical application

1. Introduction

Drug delivery technology is one of the core driving forces in the advancement of modern medicine. Its goal is to deliver therapeutic agents (including drugs, genes, vaccines, etc.) to specific targets within the body in a safer, more effective, and precise manner. However, many promising molecules (such as nucleic acid-based drugs, drugs with poor water or lipid solubility, and unstable large biologic drugs) often face challenges due to their physicochemical properties (e.g., poor solubility, low stability) or in vivo physiological barriers (e.g., enzymatic degradation, non-specific distribution, biological membrane barriers, and immune clearance). These challenges frequently result in suboptimal delivery efficiency and therapeutic outcomes.

Liposomes, as one of the earliest discovered and most extensively studied biomimetic nanomedicine carriers, have provided an attractive solution to overcome the limitations of conventional drug delivery since they were first reported by Alec D. Bangham in the 1960s [1].

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Their unique bilayer structure and high designability make them particularly appealing. Structurally, liposomes are closed vesicles formed by the self-assembly of amphiphilic phospholipid molecules (such as phosphatidylcholine) in an aqueous environment, with water phases inside and outside and a lipid bilayer in between. This sophisticated structure grants them the following properties: (1) the ability to efficiently encapsulate hydrophilic drugs in the inner aqueous compartment and lipophilic drugs within the lipid bilayer; (2) excellent biocompatibility and biodegradability, stemming from their major components being similar to cell membrane constituents; (3) through surface modifications (such as PEGylation), their in vivo pharmacokinetic properties can be significantly improved, achieving long circulation; (4) by incorporating specific targeting ligands (such as antibodies, peptides, or aptamers), they can actively target and deliver drugs to specific cells or tissues; (5) through the design of stimulus-responsive properties (such as pH sensitivity, temperature sensitivity, or enzyme sensitivity), liposomes can achieve spatiotemporal-controlled drug release at disease sites.

After more than half a century of in-depth research and engineering modifications, liposomes have evolved from their initial basic models into an extremely diverse classification system. For example, based on particle size, layers, and surface properties, they can be categorized into Multilamellar Vesicles, Large Unilamellar Vesicles, Small Unilamellar Vesicles, LNP (Lipid Nanoparticles), surfactant-based liposomes, PEGylated liposomes, immunoliposomes, and others [2]. Additionally, liposome preparation involves a variety of precise techniques, such as the lipid film hydration method, reverse evaporation method, extrusion method, and microfluidics method [3], to meet the requirements of different application scenarios and to precisely control drug encapsulation efficiency, particle size, stability, and release behavior.

Liposome technology has achieved remarkable success in the field of clinical applications. Since the first liposomal anticancer drug, Doxil® (liposomal doxorubicin hydrochloride) [4], was approved by the FDA in 1995, more than a dozen liposome-based drug formulations have been globally approved for clinical use, including Ambisome® for fungal infections [5], COVID-19 mRNA vaccines [6], and Onpattro® for small interfering RNA (siRNA) delivery to treat transthyretin amyloidosis. These formulations cover multiple therapeutic areas such as anti-tumor, anti-infective, anti-fungal, vaccine delivery, and gene therapy, fully demonstrating the immense clinical value and translational potential of liposomes as a mature nanotechnology platform. At the same time, in response to more complex physiological and pathological scenarios, such as tumor microenvironment targeting, crossing the blood-brain barrier, organelle-specific delivery, and integrated diagnosis and therapy, liposome research remains at the forefront of high-speed innovation, with novel design strategies continuously pushing the boundaries of their clinical applications.

By integrating the three dimensions of classification, preparation and clinical application, this paper aims to provide clear guidance for researchers entering this field, and at the same time offer valuable references for researchers within the field to optimize design ideas, overcome key obstacles, and promote broader clinical transformation and application.

2. Composition and classification of liposomes

Liposomes are man-made spherical vesicles composed mainly of phospholipids [7]. It has been shown that when phospholipids are hydrated in aqueous solutions, they impulsively form closed structures driven by hydrophobic interactions and other intermolecular interactions. This is because phospholipids are amphiphilic molecules with a hydrophobic tail group and a hydrophilic head

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group. Such vesicles with one or more phospholipid bilayers can transport aqueous or lipid drugs [8].

Phospholipids can be synthesized entirely or partially from natural sources. According to the alcohol group present in the structure of the phosphorus root, it can be divided into glycerophospholipid and sphingophospholipid. The most commonly used glycerophospholipids in liposome formation are phosphatidylcholine (PC), phosphatidylethanolamine (PE), phospha tidylseric acid (PS), phosphatidylinositol (PI), and phosphatidyl glyceride (PG). The stability of the lipid body is determined by the degree of insaturation of the phosphate lipid, the side chain of the lipid acid and the temperature of the phase change. One of the important properties of phospholipids is the formation of lipid bodies under phase change temperature (TC). The phase change temperature of the phospholipid is the temperature at which the phospholipid state changes from the gelation phase to the liquid crystal phase. When the phase transition temperature of the lipid reaches, the lipid tightly encapsulated in the bilayer region of the lipid body begins to loosen and become more permeable. This change leads to more voids between the phospholipids, thereby facilitating the membrane formation of the lipid body preparation. Phospholipids with higher phase temperature variability were more stable at room temperature [9].

At the same time, the encapsulation efficiency, toxicity and stability of liposomes are affected by the type of phospholipids used in the preparation. The choice of the composition of the bilayer lipid determines its rigidity (or fluidity) and electrical charge [10]. Natural liposomes prepared from unsaturated phosphatidylcholine substances provide a bilayer structure with high permeability and low stability [7]. However, liposomes made from saturated phospholipids, such as dipalmitoyl phosphatidylcholine, produce a rigid and nearly impenetrable bilayer structure [11]. Introduces positively or negatively charged lipids to provide surface charge for the lipid body.

Cholesterol constitutes a fundamental sterol component in liposomal architectures, serving as the predominant choice in formulation design due to its multifaceted stabilizing functions. It facilitates phospholipid molecular packing and promotes bilayer self-assembly while concurrently reducing membrane fluidity through steric hindrance. Critically, cholesterol attenuates transmembrane permeation of hydrophilic therapeutic agents and enhances bilayer integrity within biological milieus (e.g., blood plasma), achieved by minimizing opsonin adsorption, decreasing phospholipid depletion via high-density lipoproteins, and suppressing macrophage-mediated clearance mechanisms [12]. Structurally, the cholesterol moiety adopts an orientation with its hydroxyl group directed toward the aqueous core and its hydrophobic sterol ring embedded within the bilayer's acyl chain domain. This molecular configuration substantially elevates membrane rigidity and mechanical strength, thereby reducing permeability to hydrophilic compounds. Crucially, cholesterol-deficient systems exhibit compromised lamellar stability due to excessive fluidity and disordered packing, ultimately destabilizing these nanocarriers. Thus, cholesterol integration is indispensable for regulating membrane microviscosity and optimizing colloidal stability [13]. Complementary stabilization approaches include surface functionalization with biopolymers (e.g., oligosaccharides, chitosan, whey proteins) for controlled release modulation [12], and strategic PEGylation via phospholipid-conjugated polyethylene glycol to alter pharmacokinetic profiles and reduce opsonization [13].

Liposomes are vesicles ranging in size from 20 nm to 2.5 μm. They can consist of one or several concentric or nonconcentric membranes. The classification of lipid bodies is mainly based on two genera: lamellar (number of double layers) and size. The roots are stratified, and the lipid bodies are divided into single-layered vesicles, multi-layered vesicles, and oligometahedral vesicles. If a bilayer membrane separates the inner and outer water phases, they are called unilaminar

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vesicles.Liposomes are categorized by lamellarity and size into: (1) Unilamellar vesicles (ULV) with a single phospholipid bilayer, Small Unilamolar Vesicles(SUV， 20~100 nm), Large Unilamolar Vesicles (LUV， 100~1000 nm), and Giant unilamellar vesicles (GUV, >1 μm); (2) Multilamellar systems including Oligolamellar vesicles (OLV, 2~5 bilayers, 0.1~1 μm), Multilamellar vesicles (MLV，>5 concentric bilayers, typically >500 nm), and Multivesicular vesicles (MVV, >1 μm with encapsulated non-concentric vesicles) [14].where vesicle dimensions and lamellar complexity critically govern drug encapsulation efficiency, systemic clearance, and circulation kinetics [15].

3. Methods for the preparation of liposomes

The critical prerequisite for liposome self-assembly involves maintaining processing temperatures above the transition temperature (Tm) of constituent lipids. Liposomal physicochemical characteristics—including mean particle diameter, polydispersity index, and lamellarity—are intrinsically governed by multiple formulation parameters: (i) preparation methodology, (ii) lipid chemical identity (e.g., anionic, cationic, or zwitterionic headgroups), (iii) compositional ratios of membrane constituents, (iv) surfactant additives, (v) organic solvent selection, and (vi) ionic strength of the hydration medium. This section comprehensively evaluates emerging nanofabrication platforms while contextualizing established conventional techniques within the framework of modern drug delivery optimization.

3.1. Thin-Film Hydration (TFH) method

Bangham and colleagues pioneered the thin-film hydration (TFH) technique as the foundational methodology for liposome fabrication [16]. This widely adopted procedure begins by co-dissolving surfactants and cholesterol in volatile organic solvents (e.g., diethyl ether, chloroform, or methanol), followed by solvent volatilization under reduced pressure using rotary evaporation. This process generates a uniform thin lipid film adhering to the flask interior [17]. Subsequent hydration with drug-containing aqueous media—conducted at temperatures exceeding the surfactants' phase transition temperature (Tm)—combined with controlled agitation facilitates self-assembly into multilamellar vesicles (MLVs) with heterogeneous size distribution after defined incubation periods [18]. Despite its operational simplicity and widespread utility, intrinsic limitations of the TFH method include potential drug degradation under thermal stress and the formation of poorly homogenized vesicle populations exhibiting suboptimal colloidal homogeneity.

3.2. Reverse phase evaporation technique (REV)

Reverse evaporation liposome synthesis was initiated by co-dissolving surfactants and cholesterol at equimolar ratios in a chloroform-diethyl ether binary solvent system [18]. To this organic phase—containing membrane-forming surfactants and structural additives—an aqueous drug solution was introduced, forming a biphasic mixture subsequently sonicated at 4~5°C under controlled thermostatic conditions [19]. The mixture underwent vigorous mechanical homogenization through high-frequency sonication to produce a metastable water-in-oil emulsion. This emulsion system was subjected to progressive solvent removal via rotary vacuum evaporation at constant 40°C, wherein continuous membrane reorganization generated LUVs. Complete particle maturation occurred concomitantly with organic phase elimination and full phospholipid hydration. The resultant suspension was diluted in phosphate-buffered saline (PBS) followed by thermal annealing in a 60°C water bath for precisely 10 min to achieve final vesicle stabilization [20]. Critical advantages

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include elevated aqueous-to-lipid mass ratios enabling expanded hydrophilic core volumes (>85% encapsulation efficiency for biomacromolecules), particularly advantageous for proteins and nucleic acid payloads (DNA/RNA). Fundamental methodological constraints involve unavoidable organic solvent residues requiring stringent elimination protocols and potential structural degradation of thermolabile compounds during high-energy emulsification steps.

3.3. Ether injection method

The ether injection technique employed controlled infusion of lipid solutions via Hamilton microliter syringe into 10 mL of thermostated PBS（pH 7.4) maintained at 60~65°C, with precise flow modulation at 1 mL/min under constant magnetic agitation (500 rpm) [21]. Subsequent rotary evaporation (40°C, 15 kPa) facilitated organic solvent elimination while simultaneously driving monolayer vesicle self-assembly via interfacial film hydration. Resultant liposomal populations demonstrated predominantly unilamellar morphologies with Z-average diameters <2 μm as confirmed by dynamic light scattering [19]. Characteristic low operational temperatures (~40°C) render this methodology particularly suitable for thermally labile compounds exhibiting adequate ether solubility. Particle size modulation was achievable through strategic variation of phospholipid concentration in the organic phase, enabling production of monodisperse suspensions with tunable hydrodynamic diameters [22]. While advantageous for scalable batch production, the technique inherently generates liposomes with polydisperse size distributions (PDI >0.2) due to uncontrolled hydrodynamic shearing during injection.

3.4. Microfluidic method

Microfluidic preparation of liposomes is a relatively new technology, which uses microfluidic chips to precisely control the flow and mixing of fluids to prepare liposomes with specific properties [23]. Isopropyl alcohol solution containing dimyristoylphosphatidylcholine and cholesterol was introduced as organic phase in the middle channel of the chip, and PBS solution was introduced into the two channels. When the three streams of fluid are focused in the main channel, the lipid-alcohol solution is squeezed by the water phase on both sides and diffused into the water phase to form a narrow-mixed solvent region. When the alcohol content in the mixed solvent region is lower than that required for lipid dissolution, phospholipids will self-assemble to form a single layer of small size spherical liposomes [24]. The size of the liposomes can be controlled by the flow rate of organic phase or aqueous phase at 100~300 nm, and the monodispersing is good. Compared with the traditional preparation methods of liposomes (such as film hydration, reverse evaporation, ether injection, etc.), microfluidic method shows better control effect, and can achieve the preparation of liposomes with smaller particle size and higher drug loading [25].

4. Liposome drug delivery systems

According to the formulation and mode of action of the liposomes, it can be divided into Conventional Liposomes, Active Targeting Liposomes and Environment-Responsive Liposomes, Long-Circulating Liposome, and so on. The traditional liposomes are comprised of natural phospholipids and cholesterol, exhibiting inherent negative charges that typically adopt a negative or neutral electrostatic state. Negative charged liposomes can enhance the stability of drugs, ensure sustained drug release and reduce the recognition potential of the mononuclear phagocyte system (MPS) [26]. Compared to free drugs, conventional liposomes demonstrate enhanced therapeutic

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efficacy while significantly reducing the systemic toxicity associated with encapsulated drugs [27]. For example, in the treatment of tumors, traditional chemotherapy drugs will not only kill diseased cells, but also kill rapidly growing healthy cells, which has serious side effects on blood cells, hair follicles and other tissues and intestinal mucosal cells, and limits the dose and frequency of clinical drugs. The encapsulated liposomes can change the pharmacokinetics of the drug, which can prolong the blood circulation of the drug, improve the bioavailability of the drug, and preferentially accumulate in the disease site [28]. Additionally, due to the pathophysiological condition of tumor vascular leakage in tumor tissue, traditional liposomes can preferentially accumulate the encapsulated drug into tumor tissue through the EPR effect-mediated passive targeting strategy, thereby achieving effective accumulation at the disease site.

Although Conventional Liposomes can lower the recognition rate of MPS, compared to Active Targeting Liposomes, they are still relatively easy to be captured by MPS after entering the body, leading to their short circulation times in the body (or rapid clearance of blood). In addition, the non-specific targeting capability and ease of aggregation in vivo of conventional liposomes are increasingly being superseded by other types of active-targeting liposomes. These advanced liposomes enable specific recognition and binding to target cells or tissues through the attachment of tailored ligands or antibodies to their surfaces, thereby achieving precise and active targeted drug delivery. For example, several receptors such as the folate receptor (FAR), human epidermal growth factor receptor (EGFR), and transferrin receptor, are expressed on the surface of tumor cells or in blood vessels. These receptors play a critical role in tumor growth and proliferation. By incorporating folate, human epidermal growth factor 2, and transferrin as ligands, the lipid nanoparticles can actively target tumor cells for therapeutic delivery. Dinakar et al [29] successfully engineered a folate- and poly-L-lysine-coupled liposome system for the targeted delivery of anticancer drugs in breast cancer cells. Tie et al [30] successfully designed a folate-modified liposomal platform to deliver BIM-S, a biogenic amine, for the treatment of lung cancer. Their findings revealed that this system could specifically inhibit lung cancer cell proliferation and effectively reduce tumor weight. The EGFR plays a critical role in regulating cell proliferation and differentiation. Upon cancer cell transformation, EGFR expression is significantly elevated, making it an ideal target for therapeutic intervention. Thomas et al [31] developed a liposomal platform with EGFR-targeting specificity, comparing the uptake efficiency between MDA-MB-468 cells (high EGFR expression) and MCF-7 cells (low EGFR expression). The uptake of liposomes in MDA-MB-468 cells was significantly higher than that in MCF7 cells. Notably, the liposome exhibited enhanced efficacy in combination therapy regimens, demonstrating its potential as a promising therapeutic modality for cancer treatment. The transferrin receptor is constitutively and inducibly highly expressed in tumor cells and endothelial cells of the blood-brain barrier (BBB). The development of targeted drug delivery systems can be significantly enhanced by rationally designing active lipid nanoparticles through chemical modification of transprotein ligands and targeting molecules. Experimental evidence has demonstrated that immunoliposomes bearing monoclonal antibodies against the human transferrin receptor exhibit remarkable enhancement of BBB permeability (4-fold increase) relative to conventional IgG immunoliposomes. These findings suggest that this innovative therapeutic strategy represents a pivotal approach for the treatment of brain cancer [32].

In comparison with active-targeting liposomes, environmentally sensitive liposomes provide enhanced local precise control of drug release. These liposomes are capable of sensing changes in various environmental parameters such as pH, temperature, and enzymatic activity, and release drugs under specific conditions, thereby improving therapeutic efficacy and minimizing adverse

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effects. Yuba et al [33] made ph-sensitive liposomes by exploiting unstable membrane disintegration caused by the protonation of phospholipids in the tumor environment. Their study showed that a pH-sensitive liposome containing bleomycin can increase the absorption rate of bleomycin by tumor cells by 2.5 times. Jose A. et al [34] take advantage of the fact that local heating induces the transformation of phospholipids from solid to liquid crystalline state, liposomes were prepared using 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, monopalmitoyl-2-hydroxy-sn-glycero-3-phosphocholine, and different surface active agents. Over 80% of the drug exhibited release within 30 minutes upon transitioning above the activation temperature. Within the tumor microenvironment, significant elevation in the expression of protease, phospholipase, and glycosidase enzymes was observed. LiuD. et al [35] research findings indicate that phospholipase A2-containing lipid nanoparticles encapsulating cisplatin or doxorubicin can selectively release these drugs at the tumor site, demonstrating superior in vivo tumor growth inhibition compared to conventional formulations.

Long-circulating liposomes can reduce the clearance rate of the immune system by surface functionalization such as polyethylene glycol (PEG), significantly prolonging the retention time in the blood, and enhancing the ability of drug targeting accumulation [7]. The particle size of PEGylated liposomes is typically controlled within the range of 80 to 150 nm, mitigating both renal clearance of particles that are too small and uptake by the reticuloendothelial system (RES) for particles that are too large. The particle size of PEGylated liposomes is typically controlled within the range of 80 to 150 nm, mitigating both renal clearance of particles that are too small and uptake by the reticuloendothelial system (RES) for particles that are too large. This optimized design significantly enhances EPR effect-dependent passive targeting efficacy in solid tumors. An excellent example is the clinical use of Doxil®, a PEGylated liposomal formulation of doxorubicin [36]. Liposomal encapsulation of doxorubicin has been reported to improve therapeutic efficacy while significantly reducing the risk of cardiotoxicity associated with anthracycline administration [37]. The stereostable liposomes developed by Yadav et al [38] achieve enhanced drug delivery stability through the strategic intercalation of PEG onto the surface of liposomes, creating a dense conformational cloud that generates spatial steric anchoring. This mechanism significantly increases the molecular interactions between liposomes, effectively reducing their intermolecular interactions with MPS and thereby prolonging their circulation half-life. Additionally, Zhu et al [39] have demonstrated that by leveraging elevated levels of matrix metalloproteinase 2 (MMP-2) within the tumor microenvironment, it is possible to enhance cancer-specific drug delivery. This is accomplished through the conjugation of an antibody-drug targeting ribosomal RNA (mAb 2C5) to PEGylated liposomes, resulting in improved cancer-cell-specific delivery of drug-loaded therapeutic agents.

The advancement of liposomal nanovehicles as transporters for therapeutic payloads represents a dynamically evolving research domain. Engineered modifiability of their intrinsic physicochemical properties confers remarkable versatility for encapsulating diverse bioactive agents—including small-molecule drugs, proteins, peptides, and nucleic acids—thereby expanding their potential applicability across multiple clinical contexts. Furthermore, liposomes exhibit unique capacity for co-encapsulating diagnostic and therapeutic compounds, enabling their utility as integrated theranostic platforms that merge therapeutic delivery with imaging capabilities. Nevertheless, the rational design of formulation methodologies aligned with specific therapeutic objectives constitutes a critical prerequisite for developing next-generation, multifunctional lipid-based nanomedicines with enhanced complexity and clinical efficacy.

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5. Clinical application of liposomes

In recent years, with the rapid development of precision medicine, liposome technology has been successfully applied to targeted chemotherapy, anti-infection, vaccine development, gene drug delivery and other fields. This section reviews the latest progress, key technologies and challenges of liposomes in clinical therapy.

5.1. Anti-tumor

Different types of liposomes have different applications in anti-tumor therapy. Doxil® can be used to treat advanced AIDS-related Kaposi's sarcoma. Its long circulation can increase the drug accumulation in tumor tissue, significantly improve the efficacy of traditional doxorubicin and reduce drug toxicity [40]. Doxil® was approved in 2007 as a monotherapy for patients with multiple myeloma at elevated cardiac risk. Clinical studies have confirmed that the efficacy of pegylated liposomal doxorubicin in the treatment of multiple myeloma is equivalent to that of free doxorubicin, but its non-targeted toxicity is significantly reduced. This property is related to the reduction of drug accumulation in myocardial tissue by the liposomal delivery system [41]. In addition, The PEGylated structure of Doxil® prolongs its half-life while lowering peak plasma levels, resulting in reduced cardiotoxicity versus conventional doxorubicin. It is an approved therapy for ovarian cancer [42]. Irinotecan liposome Onivyde® combined 5-fluorouracil (5-FU) was used in metastatic pancreatic cancer to prolong median overall survival to 6.1 months and reduce gastrointestinal toxicity by 35% compared with control [43]. It improves the limitations of traditional irinotecan by prolonging drug circulation time, increasing tumor drug accumulation (EPR effect) and reducing gastrointestinal toxicity [44]. AmBisome® (amphotericin B liposome) for invasive fungal infection is less nephrotoxic than traditional preparations, can target the infection site, and the cure rate is significantly higher than other preparations [45].

5.2. Anti-infection

5.2.1. Anti-bacterial

PEGylated liposomes have demonstrated multifaceted advantages in the treatment of bacterial infections, tuberculosis, and skin infections. Their core advantage lies in enhancing the bioavailability, stability, and targeting of antibiotics [46]. Liposomal nanoparticles improve therapeutic outcomes through targeted delivery, membrane penetration, toxicity reduction, and synergistic antibacterial effects, particularly against drug-resistant bacterial infections. Varshosaz et al [47] demonstrated the antibacterial efficacy of amikacin-loaded solid lipid nanoparticles. Clotrimazole lipid gel, with its enhanced adhesive properties, has demonstrated prolonged drug retention time and lowered the minimum inhibitory concentration (MIC) against Candida albicans, thereby exhibiting superior efficacy compared to conventional creams [48].

5.2.2. Anti-fungal

Commonly utilized antifungal liposomal formulations include liposomal amphotericin B (AmBisome®), The optimized cationic elastic liposome(OCEL), and Griseofulvin (GRF) liposomes. AmBisome® have a lower MIC than the free drug and exhibit high permeability and low toxicity in a cutaneous leishmaniasis model [49]. The OCEL in ketoconazole ethanol sol-gel has demonstrated enhanced drug permeation in ex vivo skin models, achieving a permeation rate twice that of

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conventional formulations. Furthermore, OCEL exhibits higher drug retention in deep skin tissues, making it a promising candidate for the treatment of deep fungal infections [50]. The study by Aggarwal, N. et al [51] showed that GRF is an effective alternative to oral drug therapy against dermatophytes when applied topicallybased on antifungal studies and ex vivo penetration studies.

5.2.3. Anti-virus

Tenofovir, an anti-HIV drug, has been used as a cationic liposome delivery system to increase the apparent permeability (Papp) of the drug in Caco-2 cell model by 5-16 times, which significantly enhances the intestinal absorption efficiency. This improvement may improve oral bioavailability and longer-lasting antiviral efficacy of antiviral agents, reducing the dose or frequency of administration [52].

To engineer an efficacious, user-compliant, and stable mucosal vaccine targeting hepatitis B virus (HBV), Wang T. et al [53]. fabricated mannose-functionalized PEG-cholesterol/lipid A liposomes (MLLs) encapsulating HBsAg through sequential emulsification and lyophilization (freeze-drying). This nanoparticulate system was subsequently infused into microneedle array reverse molds followed by controlled desiccation to generate proHBsAg-MLLs-integrated microneedle arrays (proHMAs). The resultant solid-state proHMAs facilitate minimally invasive oral mucosal vaccination, leveraging the dual adjuvant functionality of mannose receptors and lipid A to establish concurrent mucosal and systemic immune defenses against HBV pathogenesis.

5.3. Vaccine delivery

Liposomes have demonstrated significant potential in vaccine delivery systems. By encapsulating vaccine components, such as antigens and immunomodulators, within liposomal carriers, the delivery efficiency and immunogenicity of vaccines can be markedly enhanced. Research has shown that liposome-antigen conjugates exhibit broader tissue distribution in vivo, rather than being limited to target cells alone, thereby improving antigen recognition and immune response [54]. Furthermore, the nanoscale structure of lipid nanoparticles enables their cellular membrane penetration, thereby avoiding the issue of reduced immunogenicity associated with conventional vaccines due to immune system-mediated clearance [55]. The introduction of this technology provides new possibilities for vaccine delivery and lays the foundation for improving the safety and efficacy of vaccines. For example, the Pfizer-BionTech vaccine (COVID-19 mRNA vaccine), approved in 2021, uses LNP to coat mRNA for efficient delivery and activation of an immune response [56].

5.4. Gene therapy

Liposomes, as a class of biological nanomaterials, exhibit extensive application potential in the field of gene therapy due to their unique physicochemical properties. Their lipid bilayer structure enables efficient penetration of cell membranes, making them ideal carriers for delivering siRNA to silence oncogenes, thereby minimizing the systemic toxicity associated with conventional chemotherapeutic agents on healthy cells. Patisiran (Proprietary Name: ONPATTRO), a double-stranded siRNA encapsulated within lipid nanoparticles, is specifically designed to target and deliver therapeutic agents to the liver. Developed and manufactured by Alnylam Pharmaceuticals, it is indicated for the treatment of polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (hATTR). Approved by the FDA in October 2018, Patisiran represents the first FDA-approved RNA interference (RNAi)-based therapeutic [57]. In preclinical studies involving lung cancer models,

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DOTAP (1,2-dioleoyl-3-trimethylammonium-propane) liposomes have been utilized for siRNA delivery, demonstrating significant inhibition of tumor growth and enhanced drug bioavailability and therapeutic efficacy [58]. Research into LNP delivery systems for mRNA vaccines has also revealed that optimization of LNP formulations—such as adjusting the proportion of DOPE lipid—can markedly improve $CD8^+$ T cell proliferation and cytokine secretion [59]. Furthermore, the favorable biocompatibility and biodegradability of liposomes offer a promising technological platform for advancements in gene therapy.

6. Others

DepoDur® is used for postoperative analgesia, with a single dose lasting up to 48 hours and reducing the frequency of opioid use [60]. Marqibo® (liposomal vincristine) enhances intracranial penetration and is indicated for the treatment of relapsed/refractory acute lymphoblastic leukemia in adults.

7. Conclusion

As an important drug delivery system, liposomes play an irreplaceable role in the field of modern medicine. Their unique composition and structure enable them to achieve targeted delivery and sustained release of drugs, thereby significantly improving therapeutic efficacy and reducing side effects.

Although there are many studies on liposome formulations, few liposome formulations can be used clinically. The clinical application of liposomal formulations faces many challenges, such as complex large-scale production process, high quality control requirements, poor storage stability and in vivo stability, limited targeting in vivo delivery, and high cost. In the future, liposome research requires the development of more efficient and stable liposome preparation methods, promoting the translational research of liposomes in clinical application, and exploring their potential in the treatment of more diseases. Through the new design of material science, combination therapy, precision medicine application and production process optimization, liposome technology is expected to become an important tool for precision medicine and personalized treatment in the future, providing patients with safer and more effective treatment options.

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