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Research Advances in Liposomes for Antitumor Therapy

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Abstract. As a classic nanocarrier delivery system, liposomes significantly enhance drug stability and bioavailability. By prolonging in vivo circulation time and improving tumor-targeting capability, they exhibit unique advantages and considerable value in cancer treatment. This review outlines the basic composition and common preparation methods of liposomes, and systematically introduces their classifications and respective characteristics. It highlights recent advances in liposome applications for treating breast cancer, lung cancer, and glioma, discusses key challenges in clinical translation, and offers perspectives on improving therapeutic efficacy and safety through optimized preparation processes, novel materials, and innovative drug delivery strategies.

Keywords: liposomes, cancer therapy, nanocarrier drug delivery system, targeted therapy

1. Introduction

Malignant tumors pose a serious threat to human health, with high incidence and mortality rates and an increasing trend of occurrence in younger populations [1]. Conventional therapies such as surgery, radiotherapy, and chemotherapy have significant limitations: surgery is mostly applicable to early-stage tumors, while radiotherapy and chemotherapy often damage normal cells, leading to substantial toxicity and side effects that impair patients' quality of life. Therefore, the development of safe and efficient novel therapies is of great importance. Since their discovery in 1965, liposomes have demonstrated considerable potential as a nanocarrier system in oncology [2], with multiple formulations approved by the FDA and EMA. Liposomes exhibit good biocompatibility, biodegradability, and low immunogenicity. They can encapsulate various types of drugs and significantly reduce the systemic toxicity of conventional chemotherapeutic agents. By modulating particle size, surface charge, and polyethylene glycol (PEG) modification, their circulation time can be prolonged, enabling enrichment at tumor sites via the enhanced permeability and retention (EPR) effect [3-5]. This review aims to summarize recent advances in liposome-based antitumor research, analyze existing challenges, and explore future clinical potential to provide a foundational reference for related studies.

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2. Introduction to liposomes

2.1. Structure and composition

Liposomes are microscopic vesicles composed of bilayer phospholipid molecules, with hydrophilic heads facing outward and hydrophobic tails inward, forming a closed structure [2]. Their diameters typically range from 50 to 5000 nm, and they can be classified into unilamellar vesicles (50–250 nm) and multilamellar vesicles (500–5000 nm) based on the number of bilayers [6]. Phospholipids are the main components of liposomes and can be categorized by charge into neutral phospholipids (e.g., phosphatidylcholine), cationic phospholipids (e.g., trimethylammonium derivatives), and anionic phospholipids (e.g., dipalmitoylphosphatidylglycerol and dipalmitoylphosphatidylcholine, DPPC) [7]. The physical properties of the lipid bilayer, such as phase behavior and elasticity, are influenced by the characteristics of the fatty acid residues, particularly the number of double bonds [8]. Phospholipids spontaneously form bilayer structures in aqueous environments. Hydrophilic drugs such as cytarabine and doxorubicin can be encapsulated in the aqueous core, while hydrophobic drugs such as amphotericin B and daunorubicin reside within the lipid bilayer [9]. As simplified models of biological membranes, the rigidity and stability of liposomes can be modulated by cholesterol, conferring low toxicity, biodegradability, and biocompatibility [7,10,11]. These features make liposomes ideal carriers for antitumor drugs, protecting them from rapid dilution or degradation.

2.2. Preparation methods

Advances in liposome research have spurred the development of diverse preparation techniques. mainly including thin film hydration, ultrasonic dispersion, and reverse evaporation method. Table 1 summarizes the advantages and disadvantages of these three preparation methods. The thin-film hydration method is widely used in laboratories due to its simplicity and low equipment requirements. This method involves dissolving phospholipids and cholesterol in organic solvents such as chloroform or methanol, evaporating the solvent to form a thin film, and then hydrating with an aqueous medium above the phase transition temperature (T_m) of the phospholipids. Lipids self-assemble into multilamellar or unilamellar vesicles via their amphiphilic nature. Selecting phospholipids with a T_m higher than body temperature facilitates the preparation of stable drug-loaded liposomes [12]. However, this method often yields large, heterogeneous, and predominantly multilamellar vesicles, usually requiring additional processing such as sonication, homogenization, or extrusion to obtain smaller, more uniform unilamellar vesicles [11].

Sonication dispersion utilizes ultrasonic cavitation to break down large vesicles. Conventional methods include probe sonication and bath sonication [13]. However, traditional sonication suffers from uneven energy distribution and limited parameter control. Liposomes prepared via bath sonication often exhibit less uniform size distributions compared to those prepared by extrusion [14,15]. Improved focused ultrasound technology, which concentrates energy at the sample center and allows precise control of power and frequency, can produce smaller liposomes with lower polydispersity indices and improved stability [14].

The reverse-phase evaporation (RPE) method involves forming an emulsion in an organic/aqueous system and then removing the organic solvent to induce lipid assembly into vesicles [12]. This technique has shown good applicability and structural stability for encapsulating chemotherapeutic agents such as paclitaxel and cisplatin, active components of traditional Chinese

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medicine such as ursolic acid and ginsenosides, and peptides [16-19]. However, it carries a risk of organic solvent residue and challenges in controlling size distribution. Studies indicate that high-polarity solvents can cause phase separation, while low-polarity solvents tend to yield more homogeneous liposomes. High-boiling-point solvents often produce larger liposomes. The addition of cholesterol can reduce size but affects the correlation between reverse micelle and liposome size and the phase behavior of intermediate products [20]. Developing low-toxicity, low-polarity solvents such as Transcutol® may replace traditional alcohols, improving the safety and efficiency of RPE-prepared liposomal drugs [21]. Other feasible techniques include ethanol injection, drying-rehydration, and 3D-printed microcapillary devices [12,22].

Table 1. Advantages and disadvantages of different preparation methods

Preparation methods	Advantages	Disadvantages
Thin-film hydration	Simplicity; Low equipment requirements.	Yields large, heterogeneous, and predominantly Multilamellar vesicles; Low EE for hydrophilic drugs.
Sonication dispersion	Rapid downsizing to small unilamellar vesicles; Reproducible.	Heat may degrade drug/lipid; High energy bursts rupture vesicles; Requires tight control of power/time/temp.
Reverse-phase evaporation	High EE for hydrophilic/ macromolecular drugs; scalable; Forms large unilamellar vesicles.	High organic solvent load, residue risk; Proteins may denature; Yields large, polydisperse vesicles.

3. Classification of liposomes

3.1. Conventional liposomes

Conventional liposomes consist of a lipid bilayer similar to biological membranes and exhibit good biocompatibility, biodegradability, and low immunogenicity. However, their short in vivo half-life, due to rapid clearance by the mononuclear phagocyte system (MPS) and circulating neutrophils, significantly hinders effective drug delivery to target sites [3]. Overcoming this limitation and prolonging circulation time are key research directions for enhancing the clinical utility of conventional liposomes.

3.2. Long-circulating liposomes

Long-circulating liposomes significantly extend in vivo circulation time and improve bioavailability through surface modification, with PEGylation being the most common strategy. PEG demonstrates good biocompatibility, low toxicity, and a broad range of molecular weights. PEG modification reduces nonspecific binding to plasma proteins, enhances stability, and prolongs circulation half-life [23,24]. Further modification with targeting peptides can improve specificity [25-27]. However, traditional PEGylation may hinder tumor cell uptake and intratumoral penetration. Novel smart-responsive liposomes can shed PEG in the hypoxic tumor microenvironment, maintaining long-circulation advantages while enhancing drug release efficiency [28]. Notably, PEG is not entirely non-immunogenic; anti-PEG antibodies may develop in humans, leading to accelerated blood clearance (ABC) upon repeated dosing and even hypersensitivity reactions [5]. Therefore, exploring alternative materials such as N-(2-hydroxypropyl)methacrylamide copolymer, which exhibits good

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biocompatibility and non-immunogenicity, represents an important direction for overcoming PEG-related limitations [29].

3.3. Functional liposomes

3.3.1. Thermosensitive liposomes

Thermosensitive liposomes release drugs in response to temperature changes. Conventional thermosensitive liposomes are mainly composed of DPPC and distearoylphosphatidylcholine, with a T_m of 42–44°C, which is ideal for hyperthermia (HT) but may face stability and release rate issues. Incorporating lysophospholipids can lower T_m and enable rapid drug release [30]. The first thermosensitive liposome to enter human clinical trials, lyso-thermosensitive liposomal doxorubicin, offers important insights for combination therapy [31]. Studies show that combining thermosensitive liposomal doxorubicin with mild HT and low-dose radiotherapy produces synergistic antitumor effects, significantly inhibiting primary tumors and reducing distant metastasis while lowering toxicity [32]. Novel multifunctional designs, such as the betulinic acid-magnetic liposome developed by Farcas et al., integrate magnetic hyperthermia with thermosensitive drug release, demonstrating high efficacy, targeting capability, and EPR compatibility against triple-negative breast cancer (TNBC) cells. Additionally, modifying liposomes with temperature-sensitive polymers can circumvent EPR limitations, and further optimizing polymer structure and lipid composition can enhance carrier stability and release precision [33].

3.3.2. pH-sensitive liposomes

pH-sensitive liposomes regulate drug release in response to changes in environmental acidity. The tumor microenvironment is weakly acidic (pH 6.5–6.8) due to lactic acid accumulation from hypoxia [34]. Incorporating pH-responsive components such as 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) and cholesteryl hemisuccinate (CHEMS) can stabilize liposomes at physiological pH while promoting destabilization and fusion in acidic environments, enabling precise drug release at tumor sites. DOPE, composed of a small phosphoethanolamine head and two large unsaturated oleoyl chains, is often used as a fusogenic lipid. CHEMS, a cholesterol derivative, stabilizes the DOPE bilayer via negatively charged carboxyl groups under physiological conditions; protonation at lower pH induces membrane fusion [35]. pH-sensitive liposomes can effectively encapsulate doxorubicin, oncolytic adenoviruses, and other agents for targeted therapy of various cancers [36,37]. Ting Zhao et al. developed a multi-stage pH-responsive co-delivery liposome that sequentially responds to the acidic tumor microenvironment and lysosomal environment, achieving deep intratumoral penetration and efficient intracellular release [38].

3.3.3. Ligand-targeted liposomes

Ligand-targeted liposomes achieve active targeting through surface-conjugated specific targeting ligands. For example, EGFR-targeting peptide-modified liposomes can target tumor cells overexpressing EGFR [37]. Optimized peptide ligands such as DSP and Aβ-CN peptides, which resist aggregation and enzymatic degradation, can enhance blood–brain barrier (BBB) penetration [26,27]. Innovative strategies, such as using ginsenosides to replace cholesterol for paclitaxel encapsulation, leverage surface carbonyl groups to target glucose transporters Glut1 and Glut3, enhancing tumor uptake and inhibiting myeloid-derived suppressor cell function, thereby improving efficacy [39]. Ligand-targeted liposomes significantly improve drug distribution specificity,

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therapeutic efficacy, and reduce damage to normal tissues. Combining them with pH-sensitive liposomes enables simultaneous active targeting and environment-responsive release, enhancing antitumor effects while reducing toxicity, showcasing broad application prospects. In Table 2, the structural characteristics, advantages, and limitations of different liposomes are summarized.

Table 2. Comparison of different liposomes

Category	Structural Characteristics	Advantages	Limitations
Conventional Liposomes	Phospholipid bilayer vesicles.	1.Simple preparation; Good biocompatibility; 2.Co-load water/lipid.	1.Rapid RES clearance; 2.Poor targeting; 3.Easy drug leakage.
Long-Circulating liposomes	Surface-modified with PEG/ hydrophilic polymers.	1.Prolonged circulation; 2.Reduced RES phagocytosis; 3.Increased target tissue accumulation.	Risk of ABC effect.
Thermosensitive liposomes	1.Uses phospholipids with defined phase transition temp; 2.Sharp membrane permeability increase at Tm.	1.Strong temperature responsiveness; 2.High target [drug] and low normal toxicity.	1.Relies on precise heating equipment; 2.Risk of off-target drug leakage.
pH-Sensitive liposomes	1.Membrane with pH-sensitive groups; 2.Destabilized at pH≈5.5-6.5 (tumor).	1.Acidic target environment; 2.Increased intracellular [drug] and reduced blood leakage.	Non-specific release at blood acidic sites.
Ligand-Modified liposomes	Surface-conjugated with specific ligands.	1.Active targeting; 2.Reduced normal cell toxicity.	1.Complex ligand conjugation; 2.Risk of ligand-induced immune response.

4. Applications of liposomes in antitumor therapy

4.1. Breast cancer

Liposomes demonstrate broad application value in breast cancer therapy, significantly improving drug efficacy and safety. Targeting tumor cell metabolism, researchers constructed liposomes co-loading glucose oxidase(COx) and telaglenastat to block metabolic compensation mechanisms in breast cancer cells via dual intervention, achieving potent antitumor and antimetastatic effects [40]. In TNBC treatment, liposomes show unique advantages due to their excellent delivery capacity. For instance, encapsulating the anthraquinone derivative RV-59 in PEGylated liposomes significantly enhanced efficacy [41]. Another study developed a liposome co-loading paclitaxel and carboxymethyl chitosan (CTS), modified with LyP-1 and chondroitin sulfate(CS) to simultaneously target p53 and CD44. This approach achieved chemotherapy sensitization, immunogenic cell death induction, STAT3 signaling inhibition, and remodeling of the immunosuppressive tumor microenvironment, effectively suppressing TNBC primary tumors and lung metastases [42]. These studies highlight how liposomes enhance the precision and effectiveness of breast cancer therapy through diverse mechanisms.

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4.2. Lung cancer

In lung cancer therapy, liposomes serve as multifunctional carriers for chemotherapeutic drugs, targeted agents, and immunomodulators, significantly improving treatment outcomes and reducing systemic toxicity. To enhance the efficacy of poorly water-soluble chemotherapeutics such as paclitaxel, researchers used chitosan oligosaccharide (CSO) to modify liposomes, markedly improving targeting capability, cellular uptake, and antitumor effects in lung cancer models [43]. In targeted therapy, liposomes modified with split-PROTAC and cyclic RGD peptides enabled in situ self-assembly at tumor sites, improving tumor accumulation and achieving precise, controllable, and hook-effect-free protein degradation in animal models [44]. For immunotherapy, the MUC1-targeting liposomal vaccine BLP25 activates T-cell immunity to eliminate MUC1-positive tumor cells, offering a new maintenance strategy after chemoradiotherapy for stage III non-small cell lung cancer patients [45]. Another study integrated chemotherapy, immunotherapy, and targeting by constructing hybrid nanovesicles from anti-MSLN/PD-L1 bispecific CAR-T cell-derived exosomes fused with lung-targeting liposomes, co-loading paclitaxel. This system induced immunogenic cell death, inhibited autophagy, and blocked PD-L1, significantly enhancing immunochemotherapy efficacy and reducing systemic toxicity [46]. Additionally, nebulized inhalation of liposomes reduces systemic exposure and increases drug accumulation in the lungs [47]. These advances underscore the important role of liposomes in comprehensive lung cancer treatment.

4.3. Glioma

Liposomes show significant potential in glioma therapy, particularly in overcoming the BBB and tumor immune microenvironment barriers. Their good biocompatibility and modifiability allow prolonged circulation via PEGylation and passive targeting via the EPR effect. Modification with specific ligands enables active targeting of the BBB and brain tumor tissue, significantly improving drug delivery efficiency and retention time in the brain [48]. For example, ANGPT2-specific peptides and ApoE can mediate liposome traversal across the BBB via different pathways, enabling efficient drug delivery to glioma [49,50]. Biomimetic strategies, such as coating liposomes with cancer cell membranes or genetically engineered macrophage membranes, also significantly enhance BBB penetration and targeting precision for glioblastoma [49,50]. Furthermore, constructing a pH-responsive bispecific antibody modification system that bridges the transferrin receptor (TfR) and PEGylated nanoparticles at neutral pH promotes BBB transit, with rapid dissociation and drug release in acidic endosomal environments, markedly improving glioma treatment efficacy [51]. Table 3 summarizes the applications and advantages of liposomes in breast cancer, lung cancer, and brain glioma.

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Table 3. Liposome application comparison in breast cancer, lung cancer, and glioma

Cancer Type	Typical Application	Advantages
Breast Cancer	1.Co-loading different drugs [40]; 2.PEGylated liposomal applications [41]; 3.Multiligand modification [42].	1. Reduces systemic toxicity 2. Improves drug accumulation in solid tumors
Lung Cancer	1.Integrating chemotherapy, targeted therapy, and immunotherapy [43-46]; 2.Nebulization treatment [47].	1.Precise controlled release to reduce toxic side effects; 2.Targeted delivery and enhanced penetration
Glioma	Multiligand modification; Bionic strategy [49,50]; pH-responsive liposomal applications [51].	1.Improves BBB penetration 2. Targets BBB and glioma cells

5. Conclusion and perspectives

Liposomes, as efficient nanocarrier systems, demonstrate broad application prospects in cancer therapy. Their lipid bilayer structure effectively encapsulates antitumor drugs with diverse properties, providing protection and sustained release. Passive targeting is achieved via the EPR effect, while active targeting through antibodies, peptides, or other ligands significantly enhances efficacy and safety. Additionally, PEG modification and biomimetic strategies such as immune cell or erythrocyte membrane coating can effectively prolong circulation time and improve tumor drug accumulation and efficacy.

Nevertheless, liposomes face several challenges in cancer therapy. The EPR effect varies significantly across tumor types and individuals, limiting its universal applicability and consistency. PEGylation may extend circulation time but can also induce the ABC phenomenon. Some liposomal formulations may activate the complement system, causing infusion reactions and safety concerns. Moreover, scalable production and batch-to-batch quality control remain major bottlenecks in clinical translation [52]. Future research should leverage humanized tumor models, develop novel nanomaterials, and innovate drug delivery strategies to balance efficacy and safety. Concurrently, further optimization of preparation processes, establishment of quality control standards, and long-term safety and efficacy evaluations are essential to promote the widespread application and clinical translation of liposomes.

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