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RECENT ADVANCEMENTS AND CLINICAL APPLICATIONS OF LIPOSOMAL DELIVERY SYSTEMS IN CANCER TREATMENT

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ABSTRACT

The primary objective of this review is to elucidate the benefits of liposomal delivery systems in cancer treatment. The review aims to explore the advantages of targeted drug delivery using liposomal nanomedicine, the spatiotemporal fate of liposomes in the body, different types of liposome-based drug delivery systems, and the potential combination of liposomal agents with other therapeutic modalities. Comprehensive review of existing literature on liposomal nanomedicine for cancer therapy. Gathering recent insights into the spatiotemporal fate of liposomes following various routes of drug administration. Exploration and analysis of different types of liposome-based drug delivery systems and their distinct advantages in cancer therapy. Integration of Combinatorial Therapies: Examination of the combination of liposomal agents with photodynamic therapy and photothermal therapy. Targeted Drug Delivery: Liposomal nanomedicine offers targeted drug delivery, enhancing the efficacy of cancer treatment while minimizing harm to healthy tissues and cells. Spatiotemporal Fate of Liposomes: Insights into the behavior and distribution of liposomes in the body following different routes of drug administration. Types of Liposome-Based Drug Delivery Systems: Identification and analysis of various liposome-based drug delivery systems, each with its unique advantages in cancer therapy. Combination Therapies: The combination of liposomal agents with photodynamic therapy and photothermal therapy has shown improved tumor-targeting efficiency and therapeutic outcomes. Enhanced Therapeutic Efficacy: Highlighting the potential of liposomal nanomedicine to improve the therapeutic efficacy of cancer treatments.

Keywords:- Liposome, Cancer, Delivery system, Combination therapy.

1. INTRODUCTION

Cancer, a malignant disease, poses a significant threat to human health and ranks as the second leading cause of death globally[1]. Addressing the challenge of cancer therapy involves not only discovering drugs that are harmful to cancer cells but also identifying ones capable of selectively targeting cancer cells while preserving the integrity of normal cells. Currently, mainstream treatment modalities in clinical practice include chemotherapy, radiotherapy, and surgery [2]. However, the limitations associated with conventional cancer treatments have spurred the development of various nanotechnologies aimed at enhancing the effectiveness and safety of cancer treatment[3-6]. Bangham's exploration of liposomes dates back to 1961, with the first formal article on the subject published in 1965[7]. Since then, liposomes have emerged as prevalent carriers for a diverse range of molecules, including small molecule drugs, proteins, nucleotides, and even plasmids[8-9]. They are notably prominent in anticancer therapy. Liposomes, characterized by bilayer structures, possess physiological compatibility akin to human cell membranes, rendering them compatible with cell membranes. Their size varies depending on lipid compositions and preparation methods, spanning from about 20 nm to over 1 μm[10].

Among all nanomedicine utilized clinically, liposomes stand out as one of the most mature platforms, with several FDA approvals for cancer treatment attributed to their favorable attributes such as appropriate size, biocompatibility, biodegradability, low toxicity, and immunogenicity [11]. Furthermore, liposomal encapsulation offers a protective shield, reducing adverse reactions and enhancing drug absorption, thereby improving therapeutic outcomes. This review delves into the interactions between tumors and liposomes, outlining the advancements, opportunities, and challenges associated with liposomal applications in clinical cancer treatment.

2. The evolution of liposomes

Bangham's initial exploration of liposomes in 1961 focused on investigating the interaction between phospholipids and water. Under certain conditions, they observed the spontaneous formation of bilayered structures consisting of small vesicles, which they termed liposomes. Subsequently, they systematically studied the mechanism of liposome formation, along with their physical and chemical properties. Concurrently, they investigated the size, morphology, and stability of liposomes [12]. By 1968, liposomes began to serve as a model system for studying the properties and functions of cell membranes due to their structural similarity.

In the 1970s, scientists explored various applications of liposomes. They found that liposomes were biocompatible and could encapsulate and deliver drugs and biomolecules such as proteins, enzymes, and nucleic acids [13]. Additionally, studies on loading antibiotics into liposomes were proposed during this period [14]. Methods and compositions for liposome preparation tailored to specific delivery needs emerged between 1976 and 1979, allowing control over the size and stability of liposomes by adjusting phospholipid types and concentrations [15-16].

In the 1980s, researchers explored liposomes as potential drug delivery systems (DDS). Liposomes were identified as promising DDSs capable of enhancing drug bioavailability and reducing toxicity [17]. The first preclinical studies involving liposomes encapsulating chemotherapeutic drugs for cancer therapy emerged during this time [18]. Research efforts in the 1980s primarily focused on improving liposome stability and drug loading efficiency due to their susceptibility to enzymatic breakdown in the body [19].

During the 1990s, liposomes transitioned towards clinical applications and commercialization. Several liposomal drugs entered clinical trials, including liposome-based doxorubicin, which gained attention as a chemotherapeutic agent. In 1995, Doxil became the first liposomal drug approved by the FDA. This success spurred further research into liposomal DDSs, both in basic science and applied research. Strategies such as surface modification were employed to facilitate translation from bench to bedside.

In the 21st century, with advancements in nanotechnology, novel liposomes were designed and optimized. Innovative lipids and surface modifications, such as PEGylation and pH-responsive materials, were introduced to enhance liposome delivery capabilities (Immordino et al., 2006). Liposomes with improved targeted delivery capabilities were developed, enabling precise drug delivery to lesion sites [20]. Furthermore, the scope of payloads for liposomal DDSs expanded to include radionuclides, gene drugs, and protein drugs[21].

Integration with emerging technologies like gene editing and biosensors broadened the applications of liposomes, leading to significant advances in vaccine and immunotherapy [22-23]. For instance, liposomes played a crucial role in the development of mRNA vaccines for COVID-19, attracting global attention [24-25]. Therefore, it is anticipated that liposomes will continue to play pivotal roles in cutting-edge medical fields such as gene therapy, immunomodulation, and personalized therapy.

3. Liposome-biological interaction

3.1. Systemic circulation

The absorption pathways of liposomes vary significantly depending on the route of administration. When administered orally, liposomes can be destabilized by enzymes in gastric acid, bile salts, intestinal surfactants, and pancreatic secretions, leading to drug release. Over recent years, modifications have been made to liposomes to enhance their stability and bioavailability for oral administration. For instance, the incorporation of hydrogenated long-chain phospholipids with higher phase transition temperatures has been utilized to protect liposomes from bile salts and adverse conditions in the gastrointestinal tract, thus improving their stability[26].

Intranasal administration, characterized by high permeability and vascularity, is suitable for both local and systemic drug delivery. It bypasses the first-pass effect and enzymatic degradation in the gastrointestinal tract associated with oral administration. Liposomes administered intranasally adhere to the olfactory epithelium, prolonging their residence time and bypassing rapid mucociliary clearance. They also offer a pathway for direct delivery of molecular drugs to the brain through the olfactory bulb or trigeminal pathways, as demonstrated in the intranasal delivery of therapeutic agents for glioblastoma [27].

Similarly advantageous, transdermal drug delivery bypasses the first-pass effect and gastrointestinal drug instability. Liposomes interact with phospholipids in the skin's stratum corneum, affecting its barrier function and enabling successful passage of payloads. Transdermal administration has shown benefits in treating certain skin and breast cancers, serving as a delivery vehicle for drugs with large molecular weights, as exemplified by the successful co-delivery of curcumin and STAT3 siRNA for skin cancer treatment using deformable cationic liposomes combined with iontophoresis [28].

For drugs with low oral absorption, the pulmonary route offers an alternative systemic delivery route. The lung's large surface area, thin epithelial barrier, high vascularity, avoidance of first-pass metabolism, and low enzymatic activity make it a favorable drug delivery target compared to the gastrointestinal system. For instance, sustained-release lipid inhalation using cisplatin (liposome) has been clinically evaluated for treating osteosarcoma metastasis to the lung (ClinicalTrials.gov Identifier: NCT00102531). Liposomes increase residence time in the lungs, enhancing their efficacy in treating respiratory diseases[29-30].

In cancer therapy, liposomes are of particular interest for their ability to deliver drugs to cancer cells. However, their spatiotemporal fate in vivo is influenced by various factors, including anatomical and physiological properties of the body, such as mechanical filtration, membrane fusion events, and interactions with serum proteins and cellular receptors. Liposomes are administered through different routes, including intravenous injection, intraperitoneal injection, and intramuscular injection, depending on the characteristics of the drugs and the desired target site. However, challenges such as rapid clearance, limited circulation time, and infusion reactions must be addressed to optimize their therapeutic efficacy.

3.2. Enhanced permeability and retention effect

The enhanced permeability and retention (EPR) effect is a well-known phenomenon observed in tumors, characterized by their heightened permeability and retention in solid tumor tissues [31]. Compared to normal tissues, the newly formed blood vessels in tumor tissues exhibit structural and morphological differences[32]. While microvascular endothelial gaps in normal tissues are dense and structurally intact, tumor cells undergo abnormal vascular proliferation to meet the increased demand for oxygen and nutrients during rapid proliferation. Consequently, the gaps between capillary endothelial cells in tumor tissues are larger than those in normal vessels, allowing particles smaller than 200 nm to penetrate the tissue gap through the vessel wall. Moreover, the absence of lymphatic vessels in tumor tissues hinders the return of lymphatic fluid, facilitating the accumulation of macromolecules within tumor tissues without being carried away by lymphatic fluid. This results in prolonged retention of these molecules within tumor tissues.

Since its discovery by Maeda et al. in 1986 [33], the EPR effect has been recognized as a crucial factor contributing to the enrichment of nanoparticles at tumor sites. For instance, studies have shown that encapsulating chemotherapeutic drugs such as paclitaxel and camptothecin into liposomes enables the drugs to accumulate at the tumor site, with the EPR effect playing a pivotal role in this process [34]. Hence, leveraging the EPR effect can be a promising strategy to enhance tumor treatment.

3.3. Cellular uptake and intracellular transport

The mechanisms governing the cellular uptake of liposomal drug delivery systems (DDS) can be categorized into passive and active transport pathways. The properties of the cell membrane and the physicochemical characteristics of liposomes play crucial roles in this process [35]. The uptake of uncharged liposomes primarily occurs through passive diffusion across the cell membrane. Conversely, large DDSs are predominantly internalized through active transport mechanisms, such as macropinocytosis, caveolae-mediated endocytosis, clathrin-mediated endocytosis, or clathrin/caveolae-independent endocytosis.

Macropinocytosis involves cells engulfing liposomes into large vesicles called macropinosomes[36]. This process is typically initiated by the extension of plasma membrane ruffles or protrusions induced by various stimuli such as growth factors or nutrients. The dynamic changes in the cell membrane lead to the formation of cup-shaped structures, eventually sealing off liposomes into macropinosomes. These macropinosomes can either recycle to the plasma membrane, release liposomes into the extracellular space, or enter the lysosomal pathway [37].

In clathrin-mediated endocytosis, clathrin-coated pits form around the curved membrane through the assembly of protein components such as the AP2 complex, AP180, and epsins[38]. These protein components recruit other molecules to create a protein coat, leading to the formation of clathrin-coated vesicles. These vesicles detach from the plasma membrane and are transported to early endosomes, followed by transport along the endo-lysosomal pathway[39]. During this process, payloads within liposomes are released or degraded by hydrolytic enzymes.

Caveolae-mediated endocytosis begins in membrane domains rich in glycolipids, sphingolipids, and cholesterol, where caveolins anchor to the cytosolic side of the plasma membrane and bind to actin filaments[40]. This interaction leads to the formation of caveolae, which encapsulate liposomes. With the assistance of dynamin's GTPase activity, the membrane is pinched off to generate caveosomes[41]. These liposome-containing caveosomes may either enter the endo-lysosomal pathway or avoid degradation by transporting their cargo to organelles such as the endoplasmic reticulum or mitochondria.

In many instances, liposomes can fuse with the cell membrane and be internalized through endocytosis. The efficiency of liposomal DDS and membrane fusion can be enhanced by incorporating cationic or aromatic molecules into lipids to form cationic liposomes[42]. Additionally, the surface charge of liposomes influences their interactions with cells[43]. Generally, cationic liposomes exhibit higher uptake in macrophages due to their interaction with negatively charged cell membranes. Moreover, the process of liposome uptake by cells may also depend on the flexibility of the lipid bilayer, as observed with unsaturated lipid 1,2-dioleoyl-sn-glycero-3-phosphocholineThe incorporation of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) enhances the flexibility of liposomes and promotes their uptake by dendritic cells[44]. In addition to the factors mentioned earlier, cellular uptake is further influenced by the interplay between liposomes and plasma proteins. This interaction results in the formation of protein crowns, altering surface properties and thereby impacting cellular uptake mechanisms[45].

3.4. Metabolism and excretion

Following systemic administration of free drug molecules, hydrophilic drugs with particle sizes smaller than 5.5 nm may undergo rapid excretion into the urine via renal filtration or biotransformation into more hydrophilic compounds before being eliminated into bile or urine by the liver (with hydrophobic molecules typically bound to proteins)[46]. However, in liposomal drug delivery systems (DDSs), drugs are encapsulated within a lipid carrier larger than 5.5 nm, thus impeding drug metabolism and excretion until they are released from the liposomes [47].

Additionally, the total clearance of the drug encapsulated in liposomes is contingent upon the rate of elimination of the liposomes, the release rate of the drug from them, and ultimately the intrinsic clearance rate of the drug itself (a combination of metabolism and in vivo excretion). Notably, the elimination rate of liposomes is primarily determined by their interaction with reticuloendothelial system (RES) cells[48]. Post systemic administration, liposomes predominantly accumulate in the RES within the liver. Critically, they are highly susceptible to clearance by macrophages within the RES of the liver and spleen following intravenous administration[49]. This is attributed to the liver and spleen's pivotal role in immune function, possessing a high density of macrophages [50], thereby actively capturing circulating particles, including liposomes.

Moreover, the hydrodynamic diameter significantly influences the half-life of liposomes in circulation and their penetration into tumor tissue. Research indicates that rapid elimination of liposomes can be mitigated when their particle size falls within the range of 20 to 200 nm. Furthermore, liposomes may undergo enzymatic degradation by lipases and phospholipases, particularly when composed of biodegradable lipids. Upon degradation, lipids can be metabolized and eliminated through normal lipid metabolic pathways, contributing to the body's natural lipid turnover [51].

4. Type of liposomes

Traditional liposomes possess favorable biocompatibility and biodegradability; however, they suffer from reduced stability and heightened susceptibility to environmental factors, leading to inconsistent drug release. These drawbacks have prompted the development of modified liposomes, such as polyethylene glycol (PEG)-coated liposomes, which extend their circulation time in vivo. Furthermore, the unique characteristics of the tumor microenvironment (TME) have driven advancements in liposomal design, resulting in the emergence of pH-responsive, thermosensitive, ultrasound-sensitive, enzyme-responsive, ligand-targeted, and magnetic liposomes[52].

4.1. PEG-coated liposomes

Following injection into the body, liposomes encapsulating drugs encounter various barriers that can limit the total drug amount reaching the tumor, thereby affecting therapeutic outcomes. For instance, liposomes may undergo phagocytosis by macrophages distributed in organs such as the liver, spleen, lung, lymph nodes, and skin [53]. Polyethylene glycolization represents a highly successful technique for mitigating immunogenicity, enhancing nanocarrier stability, and prolonging circulation time, thereby finding widespread clinical application**.** To circumvent macrophage uptake in vivo, liposomes are typically coated with

PEG to achieve a "cloaking" effect, thereby increasing liposome concentration in cancerous tissues. Typically, a concentration of 5 mol% of PEG2000 is commonly chosen for preparing PEG-coated liposomes. PEG modification significantly alters protein crown adsorption on liposome surfaces, thereby prolonging circulation time and enhancing drug biodistribution, facilitating tumor accumulation[54] Furthermore, optimizing PEG conformation can enhance tumor-targeting capability and increase internalization into cancer cells[55-56].

Clinically, Doxil was the pioneering PEG-coated liposomal formulation of doxorubicin (DOX), approved for treating AIDS-related Kaposi's sarcoma in 1995, followed by metastatic breast cancer in 2003 and multiple myeloma in 2007[57]. Despite significantly reducing DOX cardiotoxicity, unfortunately, 40–50% of Doxil users developed palmoplantar sensory loss erythema[58-59]. In summary, PEG-coated liposomes offer the advantages of enhancing drug delivery efficiency and reducing immunogenicity in cancer therapy. However, challenges such as the onset of undesirable side effects and antibody production against PEG following liposomal DDS administration necessitate comprehensive consideration of their pros and cons and adjustments based on specific circumstances.

4.2. pH-sensitive liposomes

Apart from macrophages, liposomes encounter numerous other barriers upon entry into the body. Tumor tissues typically exhibit a lower pH (<7.4) compared to normal tissues (pH 7.4) [60], prompting the development of pH-sensitive liposomes for cancer therapy. The concept of pH-sensitive liposomes traces back to the 1980s when researchers explored biodegradable materials for constructing drug-controlled release systems. Comprising phospholipids and pH-sensitive polymers, pH-sensitive liposomes respond to environmental pH changes. These polymers undergo conformational changes when the pH drops below specific values, leading to liposome disruption and subsequent drug release. Moreover, pH-sensitive liposomes can achieve targeted action on tumor cells by incorporating targeting molecules onto their surface [61].

Doxil®, clinically approved in 1995 as the pioneering pH-sensitive liposome, consists of PEG-based lipids with pH-sensitive properties, enabling drug release in the acidic tumor environment. This characteristic enhances drug concentration within tumor cells while minimizing toxic effects on normal tissues [62]. Several other pH-sensitive liposomes have since gained clinical approval. For instance, DepoCyt®, introduced by Mallinckrodt Pharmaceuticals in 1999 for treating malignant tumors like central nervous system lymphomas and meningeal metastases, releases cytosine in acidic environments through liposomal pH sensitivity. Similarly, Onivyde®, utilized in metastatic pancreatic cancer treatment, responds to the tumor's acidic milieu to release irinotecan. Nonetheless, careful regulation of pH-sensitive liposome stability and drug release rates is imperative to ensure targeted tissue delivery without premature or excessive drug release [63]. Furthermore, precise techniques for pH-sensitive liposome preparation and characterization are essential to guarantee their performance and efficacy.

4.3. Thermosensitive liposomes

Hyperthermia (HT) has traditionally served as a supplementary treatment alongside radiotherapy and chemotherapy [64]. Experimental research has validated the synergistic interplay between HT and chemotherapy, highlighting the enhanced efficacy of tumor

treatment when combining HT with chemotherapy compared to chemotherapy alone[65]. When utilized alongside thermosensitive liposomes, HT holds potential to augment tumor treatment effectiveness by bolstering tumor vascular permeability and facilitating drug release from temperature-sensitive agents into the tumor's vascular system and interstitium[66]. Moreover, beyond its direct cytotoxic impact on cancer cells, HT may potentiate the therapeutic effects of thermosensitive liposomes by boosting local blood flow, thereby improving target cell permeability to free drugs. Although cancer cells aren't inherently more vulnerable to heat effects than healthy cells, they are rendered more susceptible due to factors such as low oxygen levels, heightened acid concentrations, and nutritional deficiencies in the tumor microenvironment (TME) [67].

At lower temperatures, thermosensitive liposomes may adopt a colloidal crystal state characterized by more ordered lipid molecules, resulting in a slower rate of drug release. However, upon reaching their phase transition temperature, thermosensitive liposomes can shift to a liquid crystal state with loosely arranged molecules, allowing for an increased rate of drug release [68]. To expedite drug release, lysolipid—a compound capable of influencing the thermal sensitivity of liposomes, thereby inducing their phase transition within a specific temperature range—was incorporated into conventional heat-sensitive liposomes by Needham and Dewhirst[69]. Subsequently, the lysolipid formulation underwent further optimization by the biopharmaceutical company Celsion and is presently marketed as ThermoDOX®. Furthermore, lyso-thermosensitive liposomal DOX (LTLD, ThermoDox®), currently undergoing clinical phase II trials (ClinicalTrials.gov Identifier: NCT04791228), shows promise for treating conditions such as rhabdomyosarcoma, nephroblastoma, and liver tumors. LTLD represents a heat-activated formulation of liposomal adriamycin that releases the drug upon exposure to hyperthermia conditions (40–45 ◦C). Additionally, there's a phase I trial investigating the optimal LTLD dosage in combination with radiofrequency ablation for treating primary or metastatic liver tumors (ClinicalTrials.gov Identifier: NCT00093444).

4.4. Ultrasound-sensitive liposomes

Ultrasound is recognized for its ability to augment tissue and vascular permeability, accelerate drug release from carriers, and offer numerous advantages such as widespread accessibility, affordability, absence of ionizing radiation, and real-time dynamic imaging capabilities [70]. Beyond its diagnostic role, ultrasound, when combined with contrast agents or ultrasound-responsive liposomal Drug Delivery Systems (DDSs), is emerging as a novel tool for directly visualizing tumors and improving the targeted transportation of therapeutic drugs through both thermal and mechanical effects[71]. Mechanical effects from low-intensity ultrasound stem from acoustic cavitation, while high-intensity ultrasound induces thermal effects by elevating the medium's temperature through energy absorption. Ultrasound-responsive liposomes, which leverage different ultrasound intensities, play a pivotal role in enhancing drug delivery. Typically, these liposomes are prepared through lyophilization with mannitol or freezing under high-pressure gas, housing an air core within the liposome structure. Recent studies have highlighted that coupling with cRGD enhances liposomes' sensitivity to ultrasound, resulting in escalated drug release with increasing power density. Furthermore, cRGD coupling amplifies cellular uptake of calcein by human colorectal cancer (HCT116) cells, with further enhancement observed post-ultrasound treatment. Significantly,

sonication elevates their permeability, facilitating the controlled release of encapsulated calcein xanthophylls[72]. In summary, ultrasound-sensitive liposomes exhibit promising prospects in targeted drug delivery, offering controlled and localized drug release upon ultrasound stimulation in vitro.

4.5. Enzyme-responsive liposomes

Enzyme-responsive liposomal drugs represent a category of liposomal DDSs that undergo changes in their physicochemical properties in response to endogenous enzyme activity, thereby facilitating targeted drug delivery and controlled release of lipophilic drugs, proteins, and genes. This approach enhances drug water solubility, mitigates toxic side effects, and extends circulation time [73]. The coupling of enzyme substrate fragments to the liposomal material via covalent bonds, hydrophobic interactions, or electrostatic interactions imparts enzyme-sensitive characteristics to the liposomal carrier. In pathological conditions, various enzymes, such as cathepsin B, metalloproteinase, β-glucolaldehyde carboxylase, phospholipase, and glycosidase, are elevated in cancerous tissues. This biochemical aberration triggers structural changes in enzyme-responsive liposomes upon reaching the tumor site, leading to the release of encapsulated drugs and thereby enhancing therapeutic efficacy. For instance, studies have demonstrated elevated levels of secreted phospholipase A2 (sPLA2) in prostate cancer, breast cancer, and pancreatic cancers, making sPLA2-responsive liposomes a viable option for targeted drug delivery to tumor tissues, particularly in prostate cancer treatment[74]. Additionally, enzyme-responsive liposomes find applications in chemotherapy, gene therapy, photothermal therapy (PTT), and photodynamic therapy (PDT) for tumor treatment [75].

4.6. Ligand-targeted liposomes

Utilizing the heightened expression of specific receptors on tumor cells, drug carriers can be engineered to feature corresponding ligands on their surfaces, facilitating precise binding to tumor cells. This targeted approach elevates drug concentrations within tumor cells, amplifies efficacy, and diminishes toxic side effects. Consequently, ligand-targeted liposomes (LTLs), amalgamating the advantages of liposomal DDSs and biological therapies like monoclonal antibodies, have rapidly advanced in cancer therapy in recent years [76]. For instance, MBP-426 (ClinicalTrials.gov Identifier: NCT00964080), a liposome carrying oxaliplatin encapsulated in transferrin-conjugated N-glutaryl phosphatidylethanolamine, is currently undergoing phase Ib/II trials for second-line treatment of gastric, gastroesophageal, or esophageal adenocarcinoma in combination with leucovorin and 5-FU. Similarly, SGT-53, a liposomal drug adorned with an anti-transferrin receptor single-chain antibody fragment, is undergoing a phase I trial involving 11 patients with advanced solid tumors, reportedly free from dose-limiting toxicity. Furthermore, MM-302, by affixing single-chain antibody fragments targeting HER2 onto the surface of PEG-coated liposomes, achieves high therapeutic efficacy in cancer therapy through specific binding to HER2 receptors on tumor cells[77-78]. These clinical endeavors signify that modifying liposome surfaces with targeting ligands enhances their selective targeting of cancer cells and augments intracellular uptake upon reaching the Tumor Microenvironment (TME) [79].

4.7. Magnetic liposomes

Magnetic fields are known for their safety and the absence of limitations in tissue penetration depth, leading to their utilization in various biological applications including disease diagnosis and tumor treatment [80].However, the weak interaction between organisms and magnetic fields results in negligible biological effects at low magnetic field strengths. To overcome this limitation, magnetic-responsive nanomaterials serve as a medium to convert magnetic field energy into chemical, mechanical, and thermal energy, thereby exerting significant biological effects. The integration of magnetic-responsive nanomaterials into tumor therapy holds promise for enhancing therapeutic efficacy, thereby addressing major human diseases. In recent years, magnetic liposomes have emerged as a compelling area of research in cancer therapy. For instance, in a human clinical trial, LTLD was combined with magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) for breast cancer therapy[81]. This approach has the potential to improve local control in palliative chemotherapy for de novo stage IV breast cancer or neoadjuvant chemotherapy in stage II/III disease, potentially reducing the need for extensive surgical interventions or even obviating the necessity for surgery altogether. Overall, magnetic liposomes enable precise and localized medical interventions by navigating within the body under the influence of external magnetic fields.

5. Clinical application of liposome in cancer

In the realm of cancer treatment, the ultimate goal is to effectively eradicate all cancer cells without inducing any adverse effects. Conventional cancer therapeutic agents lack selectivity in their targets, often leading to the destruction of both cancerous and healthy cells during treatment, thereby causing significant side effects on the organism. Hence, researchers are actively seeking to enhance the specificity of cancer treatment drugs and augment their bioavailability. Increasing evidence suggests that liposomal Drug Delivery Systems (DDSs) heighten anticancer effects by inhibiting cancer cell proliferation, inducing tumor cell apoptosis, and enhancing drug cytotoxicity. Moreover, the combination of liposomal DDSs with other clinical therapies has demonstrated improvements in patient survival rates. For instance, liposomal drugs can be integrated into therapeutic regimens such as Photodynamic Therapy (PDT), Photothermal Therapy (PTT), radiotherapy, gas therapy, and immunotherapy for cancer treatment.

5.1. Reducing systemic toxicity and enhancing anti-tumor effect

Traditional chemical drugs commonly employed in cancer treatment, such as paclitaxel, adriamycin, cisplatin, and methotrexate, lack the ability to selectively target tumor cells, leading to collateral damage to normal cells [82]. Furthermore, their limited bioavailability in tumor tissues often necessitates increased dosages during treatment, elevating the risk of toxicity to normal cells and fostering organism resistance [83].

For instance, paclitaxel functions by inhibiting cell division and growth, but its poor water solubility mandates dissolution in dehydrated ethanol and polyethoxylated castor oil during clinical use, culminating in hypersensitivity reactions and severe side effects such as peripheral neuropathy, neutropenia, alopecia, mucositis, arthralgia, and myalgia[84-85]. These side effects constrain dose escalation, resulting in suboptimal therapeutic outcomes. In response, a liposomal formulation of paclitaxel was developed to enhance its safety profile

while maintaining or augmenting its anticancer efficacy, eliminating the toxicity associated with polyethoxylated castor oil present in the traditional formulation. This liposome-entrapped paclitaxel (LEP-ETU) demonstrated potential for shorter infusion times, elimination of routine pre-dosing, reduced side effects at similar doses, and potentially increased efficacy, especially with higher doses, in a phase I study [86].

Similarly, adriamycin, a widely used anthracycline anticancer drug, is hindered by cumulative dose-dependent cardiotoxicity, which poses a risk of life-threatening congestive heart failure [87]. Additionally, adriamycin's non-specific tumor targeting and adverse effects on multiple cell types in the body necessitate cautious dosing to mitigate side effects. Encapsulation of adriamycin in liposomes attenuates cardiac risk while preserving antitumor efficacy by enhancing stability in circulation and selective passage through tumor vasculature, thereby minimizing release in plasma and healthy tissue and reducing cardiotoxicity [88]. PEG liposomal adriamycin (PLD, Caelyx) exhibits prolonged circulating half-life, favorable pharmacokinetics, and specific tumor tissue accumulation owing to PEG-coating, demonstrating comparable efficacy to conventional adriamycin but with reduced toxicity, as evidenced in myeloma and cutaneous T-cell lymphoma treatments [89-90]. These clinical illustrations underscore the superior efficacy of lipid formulations in exerting anticancer effects while mitigating toxic effects on normal cells.

5.2. Combination therapy for enhancing anti-tumor effect

5.2.1. Combination with PDT

Photodynamic therapy (PDT) involves the accumulation of a photosensitizing chemical, known as a photosensitizer (PS), either actively or passively within the tumor site. Upon exposure to a specific wavelength of light, the PS is activated to eradicate malignant cells [91]. Despite PDT's evident advantages, such as its non-invasive nature, low drug resistance, and minimal toxicity, its application is hampered by various factors. These include the lipophilic properties of most PSs, their short plasma half-life, limited tissue permeability, and the low specificity of PSs for tumors. Additionally, tumor hypoxia poses a challenge to oxygen-dependent PDT efficacy [92].Tissue penetration presents another significant obstacle in PDT, particularly concerning PS delivery and light irradiation. To surmount these challenges and augment PDT efficacy, liposomes serve as versatile nanocarriers for PS delivery, facilitating their accumulation in tumors and optimizing therapeutic outcomes in cancer treatment [93].

In particular, liposomal doxorubicin (DOX) has been co-encapsulated with various PSs for combination therapy. For instance, bifunctional liposomes encapsulating DOX and Ce6 have shown enhanced efficacy in tumor therapy[94]. DOX/ZnPc co-loaded MSNs@CaP@PEGylated liposomes enable the combination of PDT and chemotherapy for tumor treatment (Ma et al., 2018). Furthermore, Foslip®, a commercially available liposomal PS formulation, has received approval for treating advanced head and neck squamous cell carcinoma due to its ability to prolong PS circulation time in the bloodstream**.** Additionally, Ciaftalan zinc (CGP55847®), a liposomal PS, has been employed in patients with upper gastrointestinal tract squamous cell carcinoma**.**

In conclusion, the integration of liposomes with PDT represents a promising approach in cancer therapy, improving drug delivery, enhancing specificity, and minimizing side effects.

5.2.2. Combination with PTT

In Photothermal Therapy (PTT), photothermal agents are employed to elevate the temperature of local cells and tissues. When temperatures reach 42–46 ◦C, cellular necrosis occurs[95]. Temperatures ranging from 46–52 ◦C lead to rapid cell death due to microvascular thrombosis and ischemia. When temperatures surpass 60 ◦C, as typically achieved by PTT, disruption of the plasma membrane results in instant cell death (Li et al., 2020). Generally, PTT agents exhibit limited selectivity for tumor tissue, necessitating high doses to ensure therapeutic efficacy. Consequently, accumulation of photosensitizers (PSs) in non-tumor tissues and stray light beyond the treated tumor volume may induce severe side effects [96]. To address these challenges, liposomes have been combined with PTT for cancer treatment.[97] engineered a liposomal Drug Delivery System (DDS) allowing precise spatiotemporal control of drug release. The drug is encapsulated within temperature-sensitive liposomes containing glycoproteins, with rapid release triggered by external laser irradiation inducing a photothermal effect on nanoshells coupled to it. This induces a phase transition in the liposomes, causing disintegration and drug release. Approximately 60–70% of the drug is released rapidly at normal physiological temperatures within minutes of laser irradiation. This liposomal DDS facilitates direct delivery of anticancer drugs to tumor tissues for cancer therapy. Additionally, You et al. developed near-infrared light-sensitive liposomes encapsulated with hollow gold nanospheres (HAuNS) and doxorubicin (DOX). Their results demonstrated rapid and continuous release of DOX from the liposome complex (DOX &HAuNS-TSL) under near-infrared light irradiation, corroborated by in vivo antitumor studies [98].

Despite these successful examples, the penetration depth of PTT is limited, restricting its therapeutic effect on deep tumors. Therefore, a comprehensive consideration of the advantages and disadvantages of PTT is essential for different tumor types and treatment needs. Combining PTT with other treatment methods may enhance efficacy.

5.2.3. Combination with radiotherapy

Radiotherapy (RT) remains a cornerstone in cancer treatment, yet enhancing its efficacy while minimizing side effects remains a significant challenge. Nanomedicine innovations have introduced effective strategies for radiation sensitization, particularly through metal nanoparticles such as platinum-based or hafnium-based ones, which have emerged as promising radiosensitizers. Liposomes, acting as carriers for antitumor drugs, not only enable targeted tumor treatment but also reduce toxic side effects. Leveraging liposomes facilitates the delivery of radiosensitizing drugs to the tumor site, thus enhancing the antitumor response[99-100]. Currently, the combination of liposomes with RT is being employed in the clinical treatment of various cancers, including breast and cervical cancers (ClinicalTrials.gov Identifier: NCT02850419; NCT00054444; NCT04580771).

Presently, simultaneous RT with paclitaxel and cisplatin has become a common clinical regimen for treating cervical cancer. Compared to the traditional approach of combining cisplatin with RT, the strategic utilization of paclitaxel liposomes has led to more rational enhancements and optimizations in treatment efficacy, post-treatment survival rates, and complication rates among cancer patients [101]. Concurrent chemoradiotherapy is currently the standard treatment for advanced cervical cancer, with paclitaxel combined with platinum

being one of the most effective chemotherapy regimens. However, due to paclitaxel's water insolubility, paclitaxel liposomes are commonly selected as anticancer drugs in ongoing clinical trials. In one such trial, the combination of paclitaxel liposomes and platinum with RT showed effectiveness in treating advanced cervical cancer [102]. Additionally, liposomal cisplatin formulations have demonstrated advantages over free drugs when combined with RT, owing to their tumor selectivity, prolonged drug half-life, and enhanced radiosensitization. Moreover, an ongoing phase IIA trial is investigating the liposomal HPV-16 E6/E7 multipeptide vaccine (PDS0101) alongside chemotherapy and RT in patients with stage IB3-IVA cervical cancer. PDS0101 aims to boost the immune system's response to cervical tumor cells infected with human papillomavirus (HPV16) (Clinical Trials.gov Identifier: NCT04580771), with outcomes currently under evaluation.

In conclusion, combining liposomes with RT holds significant promise, but addressing technical and clinical challenges is imperative to ensure its effectiveness and practical feasibility.

5.2.4. Combination with gas therapy

Recent discoveries have highlighted the extensive involvement of the Tumor Microenvironment (TME) in cancer development and progression. The TME is often characterized by hypoxia, weak acidity, and elevated levels of hydrogen peroxide and glutathione, crucial for sustaining tumor proliferation, energy metabolism, drug tolerance, and invasion[103]. Consequently, modulating the TME holds promise for effectively targeting cancer cells. Gas molecules such as NO, H2, CO, O2, H2S, and SO2 have been identified as regulators of cancer evolution. Adjusting their concentrations in the TME can influence the Warburg effect in cancer cells [104-106], thus inhibiting proliferation and promoting apoptosis without impacting the activity of normal tissue cells or their physiological functions. Additionally, gas therapy presents as a safe and effective "green" treatment for cancer, with no residual risks in the body.

Presently, gas therapy is primarily administered through inhalation, which can result in systemic toxicity and pose challenges in achieving targeted on-demand gas delivery. Liposomes, with their inherent echogenicity, serve as promising carriers for therapeutic gases [107]. Lee et al.'s group investigated the use of echogenic liposomes for intravenous delivery of NO, demonstrating its ability to induce breast cancer cell death [108]. Despite its promise, the preparation and optimization of liposomes in combination with gas therapy present technical challenges. Moreover, achieving precise drug release at anticipated timing and location remains a significant hurdle in gas therapy.

5.2.5. Combination with immunotherapy

In recent decades, considerable attention has been directed towards understanding how remodeling the Tumor Microenvironment (TME) affects the anti-tumor capacity of immune cells. Despite the growing popularity of immunotherapy in cancer treatment, its effectiveness is hampered by the short half-life and retention time of therapeutic agents within the TME [109]. Achieving successful immunotherapy relies on accurately delivering drugs to antigen-presenting cells, a feat achievable through Drug Delivery Systems (DDSs)[110]. Various types of nanocarriers have been studied in clinical settings for different cancer types, with liposome-based DDSs showing promise in targeting specific components of the TME [111].

Liposomal drugs play a crucial role in inducing immunogenic cell death (ICD). Liposomal formulations loaded with DOX, such as Caelyx/Doxil®, are increasingly utilized in combination with immunotherapy. Doxil demonstrates superior efficacy in immunocompetent mice compared to immunodeficient mice by promoting dendritic cell (DC) and CD8 T cell proliferation through ICD, thus enhancing the effectiveness of immunotherapy. Importantly, Doxil induces a stronger immune response compared to an equivalent dose of free DOX [112]. In clinical settings, Doxil is often combined with other immunotherapies such as anti-PD-1 antibodies and tumor necrosis factor receptor alpha agonists[113]. Additionally, the combination of bevacizumab, which obstructs blood flow to the tumor, and liposomal doxorubicin hydrochloride, which induces cell death or inhibits division, is administered for breast cancer treatment (ClinicalTrials.gov Identifier: NCT00445406).

Moreover, a phase I/II trial investigated the efficacy of PDS0101 alone or combined with pembrolizumab in reducing tumor size in patients with locally advanced human tumor virus-related oropharyngeal cancer that had spread to nearby tissues or lymph nodes. PDS0101, a vaccine composed of a specific peptide, stimulates the body's immune response to kill tumor cells, while pembrolizumab, an immunotherapy with monoclonal antibodies, enhances the immune system's attack on cancer cells and interferes with their growth and spread (ClinicalTrials.gov Identifier: NCT05232851).

Overall, combining liposomes with immunotherapy enhances its efficacy, reduces adverse effects, and improves drug delivery and absorption. This combined approach has garnered significant attention in current medical research and is expected to play an increasingly important role in immunotherapy. However, the specific regimen and drug selection for combination therapy should be individualized based on the type of disease and patient condition, with close monitoring and efficacy evaluation being essential.

5.3. Challenge of clinical transformation

While liposomes hold immense promise for clinical translation and have garnered significant attention for their potential in drug delivery, they encounter various challenges and obstacles in transitioning from laboratory studies to reliable and effective clinical applications. For instance, liposomes carrying antitumor drugs may face instability due to their phospholipid bilayer structures, leading to hydrolysis and leakage that can impact drug bioavailability. Moreover, their industrial-scale production and clinical utilization remain restricted. Additionally, liposomes may induce hepatotoxicity, necessitating further investigation before their clinical application. Understanding the mechanisms of drug release and therapeutic principles of liposomes in vivo at the molecular biology level will aid in designing liposome Drug Delivery Systems (DDSs)[114]. In clinical practice, it is crucial to consider the biosafety, potential allergic reactions, drug interactions, and mechanisms of lipid nanomaterials.

5.3.1. Industrial production of liposome

Determining the optimal physicochemical parameters for liposome preparation is crucial for their clinical utility. Manufacturing liposomal drug products for commercialization poses technical challenges, primarily centered around adhering to good manufacturing practices and ensuring chemistry, manufacturing, and control. Typically, small quantities of liposomal

materials are employed in preclinical and early clinical investigations. The transition from laboratory-scale to clinical-scale production involves optimizing formulation parameters and potentially altering formulation methods. Moreover, large-scale production is susceptible to batch-to-batch variations in physical and chemical properties, necessitating stringent control over these properties for industrial-scale manufacture of liposomal drugs for cancer therapy.

A notable example highlighting the challenges in manufacturing liposomal drug therapeutics is Doxil®. Manufacturing and sterility issues led to the suspension of Doxil® production in 2011, resulting in treatment delays for patients[115]. Additionally, the high cost of raw materials and the complex multi-step manufacturing process contribute to the expense of liposomal drug production. Regrettably, commercially producing nanosized drugs, such as liposomes, incurs higher costs compared to producing free drugs[116]. This cost discrepancy may deter pharmaceutical companies from mass-producing liposomes for cancer therapy. Therefore, the clinical benefits of liposomal drugs must sufficiently outweigh development and manufacturing expenses to improve their cost-effectiveness for cancer therapy.

5.3.2. Biological evaluation and screening

Conducting in vitro evaluations is crucial to identify biocompatible liposomal candidates before progressing to animal testing. However, conventional in vitro models lack the complexity of biological tissues and control over fluid dynamics, limiting their ability to fully capture the intricate interactions between liposomes and cells. To address these limitations, biomimetic "organ/tumor microarray" tools have emerged as promising alternatives [117]. These tools incorporate tumor-like spheres into microfluidic channels, offering a more comprehensive understanding of liposome-cell interactions and the impact of liposome particle size on accumulation and diffusion.

In addition to in vitro studies, the assessment of liposome performance in vivo requires the use of animal models. However, the lack of tumor models that faithfully represent human cancers poses a significant challenge[118]. This discrepancy between preclinical study outcomes and clinical trial results presents a major obstacle in interpreting in vivo data. Despite the establishment of various animal models, such as cell line-based subcutaneous and in situ xenografts, patient-derived xenografts, and genetically engineered mouse models[119-120], no single model fully recapitulates all aspects of human malignancy.

5.3.3. Questionable safety

In clinical trials, the use of liposomal drugs often faces termination due to safety concerns. For instance, PEG liposomal DOX hydrochloride underwent termination (ClinicalTrials.gov Identifier: NCT00524459) due to questionable safety issues. Monitoring adverse events revealed one serious adverse event and several other adverse events, although no patient deaths occurred in the dosing group. The serious adverse events included hypersensitivity reactions, while other adverse events occurred across varying degrees of severity, encompassing conditions such as anemia and other blood and lymphatic system disorders, gastrointestinal disorders like indigestion, neurological disorders such as headaches, and skin and subcutaneous tissue disorders like hair loss. These safety concerns likely contributed to the termination of the clinical trial.

Similarly, during phase II clinical development of Manganese Superoxide Dismutase Plasmid Liposome, adverse events were monitored for up to 2 years, with all-cause mortality

monitored for up to 5 years. A single death occurred in the MnSOD PL (0.3 mg) + paclitaxel + carboplatin group, classified as a grade 5 event according to CTCAE v3.0 (ClinicalTrials.gov Identifier: NCT00618917). Additionally, patients across all dose groups experienced serious adverse events such as anorexia, dehydration, pneumonia, and thrombosis, along with other adverse events including edema, constipation, nausea, and fatigue. Consequently, the trial was later terminated due to these safety concerns.

In summary, while liposomal DDSs show promise in cancer therapy, they encounter safety challenges in clinical settings. Despite many clinical trials being terminated due to liposomal safety issues, it's essential to recognize that safety concerns are part of the development process for any drug.

6. Conclusion and future perspectives

In recent years, the rapid advancement of liposomes has facilitated the combination of a diverse array of drugs through physical adsorption or chemical bonding, laying the groundwork for enhanced efficacy and synergistic therapy. These technological strides have led to the widespread adoption of liposomes, owing to their versatile sizes, hydrophilic properties, and charged characteristics, rendering them suitable as drug delivery systems (DDSs). Compared to other nano DDSs, liposomes boast several advantages, including meeting clinical production standards, minimal batch-to-batch variability, ease of synthesis, scalability, and biocompatibility. With an expanding comprehension of tumor molecular mechanisms and the evolution of lipid nanomedicine, liposomal drugs present novel opportunities for anti-tumor therapy.

Nevertheless, further research is imperative to elucidate nuanced aspects of liposomal DDSs to enhance their targeting, stability, drug loading capacity, and production efficiency, all aimed at optimizing therapeutic efficacy. Targeted delivery optimization is a primary focus, which entails two key directions. Firstly, the development of novel ligands capable of recognizing and binding specific markers is essential to enhance liposomal specificity. Secondly, the design of smart liposomes responsive to environmental stimuli like low pH and high enzyme activity for precise drug release is pivotal for future investigations.

Enhancing stability and prolonging circulation half-life is another critical aspect. Apart from current surface modifications such as PEGylation, refinement of liposome structure and exploration of new lipid compositions and bilayer structures can bolster their physical and chemical stability. Moreover, improving drug loading capacity is crucial, necessitating the development of efficient novel drug encapsulation technologies to augment loading efficiency. The adoption of a co-delivery strategy to encapsulate multiple drugs simultaneously holds promise for achieving synergistic efficacy or overcoming multidrug resistance.

Additionally, advancements in production and scale-up are imperative, including the development of automated and standardized liposome production technologies to reduce costs and ensure consistent product quality. Safety and toxicity assessment remain paramount, mandating comprehensive evaluation of biocompatibility, toxicology, long-term stability, and metabolic degradation pathways of novel liposomes in vivo.

Furthermore, integration with personalized medicine to tailor personalized liposomal DDSs based on patients' genomic information and disease characteristics is warranted. Lastly, the convergence of cutting-edge technologies such as gene editing and nanorobotics with liposomal DDSs promises revolutionary treatment options for specific diseases. In conclusion, despite the challenges, liposomes are poised to evolve into more efficient, safe, and intelligent DDSs in the future, offering new avenues for treating a wide spectrum of diseases.

Declaration of Competing Interest

The authors affirm that they do not have any conflicts of interest to declare in this study.

Data availability

The research described in the article did not utilize any data.

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