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# Advances in liposomes in targeted drug therapy

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**ABSTRACT**
Liposomes are formed through the self-assembly of phospholipids, resulting in a bilayer structure that exhibits both hydrophilic and hydrophobic properties. This unique structure allows liposomes to carry both hydrophilic and lipophilic drugs, enhancing drug solubility and stability while minimizing side effects. As a nanoscale drug delivery system, liposomes have shown significant advantages in targeted drug therapy, particularly in cancer treatment. To boost how well liposomal drugs work, these tiny drug delivery vehicles can be guided to tumors using a couple of main strategies. One way is passive targeting, which takes advantage of how long liposomes stick around in the bloodstream and how they tend to build up in sick spots with leaky blood vessels. The other is active targeting, where specific molecules are stuck onto the liposome's surface, allowing them to latch onto particular markers on the cells they're meant to hit. This article reviews the research advancements concerning liposomes in targeted drug therapy, with a focus on their structural characteristics, passive and active targeting mechanisms, and applications in the treatment of various diseases.

**KEYWORDS**
active targeting; passive targeting; targeted therapy; liposomes; liposome application; phospholipids

## 1 Introduction

Targeted therapy represents a precision medicine approach grounded in molecular biology and genomics, facilitating the selective eradication of tumors by specifically targeting key molecular determinants of cancer cell growth, proliferation, or survival. In contrast to conventional chemotherapy, which indiscriminately affects all rapidly dividing cells, targeted therapies are designed to focus on molecular characteristics unique to cancer cells, such as gene mutations, protein overexpression, or abnormalities in signaling pathways. [1] This specificity minimizes damage to normal cells. Liposomes are used as delivery vehicles for medications or vaccines, and they can carry these substances in a few different ways: attached to their outer surfaces using electrical attraction, tucked inside their lipid layers if the drug is fat-soluble, or dissolved within their watery centers if the drug is water-soluble. Compared to standard drug solutions, liposomal formulations offer a bunch of benefits. They can make poorly soluble drugs dissolve better, shield drugs from breaking down chemically or biologically while they're being stored and used, and cut down on unwanted side effects and toxicity. All this leads to the drug working better and being safer overall. Furthermore, liposomes can be chemically modified with specific surface ligands for targeted delivery and are compatible with biodegradable and non-toxic materials. Their unique capacity to encapsulate both lipophilic and hydrophilic compounds allows for the delivery of drugs with a diverse range of physiochemical properties.[2]

## 2 Structural properties of liposomes

Liposomes, typically nanoparticles (NPs) with diameters ranging from 100 to 500 nm, are formed through the self-assembly of phospholipids, which consist of a polar phosphate head group and a hydrophobic lipid tail. These phospholipids self-assemble to create lipid bilayer spheres that enclose an aqueous core. In aqueous solutions, phospholipids exhibit amphiphilicity, driven by the hydrophobic interaction of the acyl chains with the surrounding water. This chemical formation is further stabilized by hydrogen bonding, van der Waals forces, and various electrostatic forces. Due to the presence of both an aqueous core and a lipid bilayer, liposomes can encapsulate a range of hydrophilic and lipophilic molecules.[2]

## 3 Liposomes in targeted drug therapy

### 3.1 Passive targeting

Passive targeting methods are primarily employed in oncology due to the pathophysiological characteristics of cancer and its microenvironment. The passive targeting of tissues or cells by liposomes occurs through molecularly driven translocation, allowing these carriers to penetrate the tumor mesenchyme via the leaky tumor vasculature. Untargeted liposomes, ranging in size from 10 to 500 nm, can preferentially accumulate in tumors and inflamed tissues through the

enhanced permeability and retention (EPR) effect, which is attributed to the presence of abnormally leaky blood vessels and the absence of functional lymphatic vessels. To nail passive targeting, you've got to cook up a liposome formulation that can dodge the body's defenses like a pro—we're talking minimizing how quickly those scavenger cells of the mononuclear phagocyte system (MPS) gobble them up or clear them out. Stealth liposomes exemplify a successful passive targeting approach, as surface modification with polyethylene glycol (PEG) extends their circulation time. This strategy, which also leverages the inherent properties of liposomes, such as their electrical charge, can facilitate specific targeting of cancer cells. Cationic liposomes are another case in point; they've been shown to glom onto the negatively charged phospholipid headgroups on tumor endothelial cells, mainly through electrostatic attraction. Still, banking solely on the enhanced permeability and retention (EPR) effect isn't enough to completely sidestep the nasty side effects of cytotoxic agents. The EPR effect can vary wildly between tumors, and it's not always reliable in solid tumors, which can mess with how well drugs delivered through passive targeting actually work. Consequently, there has been an exploration of alternative targeting pathways with enhanced functionality.[3]

### 3.2 Active targeting

Back in 1906, the insightful Paul Ehrlich really kicked things off when he came up with the "magic bullet" idea—the notion of being able to guide drugs straight to their target within the body. Ever since then, researchers globally have been on the hunt for these "magic bullets," striving to pinpoint specific cells for better diagnoses and treatments. What's usually involved in active targeting is sticking a targeting ligand onto the outer layer of a liposome, aiming to boost how well the liposomal system delivers its payload. Various targeting ligands have been employed for active targeting, including antibodies, nucleic acids (aptamers), peptides, whole proteins (e.g., transferrin), and small molecules such as vitamins (e.g., folic acid). Several factors are considered in the selection of target ligands, including the relative degree of overexpression or selective expression of objectives, the ligand-directed agent absorption by target cells, and the extent of coverage of the target molecule. Additionally, ligands must be hand-picked to make sure they latch onto the cells you're aiming for while steering clear of healthy ones. When it comes to tweaking liposomes to do specific jobs, there are basically three main routes you can take. The first one is all about attaching the targeting ligand you want to the lipid right at the start, before you even mix it in with the other lipid ingredients to whip up your liposomes. The second method entails functionalizing the liposome with the desired targeting ligand immediately after its preparation. This method utilizes lipids with end-group modifications that include a PEG spacer group functionalized at the terminus with an amine, carboxylic acid, thiol, or maleimide group.The third is that you can add functionalized lipids to already-made liposomes. This method hinges on the natural tendency of these lipids to insert themselves from a micellar solution into existing liposomes, even those carrying drugs. The targeting molecule is modified in a separate process. This prevents the activated lipids from messing with other liposome ingredients, particularly those found in the buffer solution.[3]

## 4 Advances in Liposome Research in Disease Treatment

### 4.1 Liposomes for respiratory drug delivery systems

Liposomes are extensively utilized for various respiratory diseases. Liposomal aerosols offer several advantages over conventional aerosols, including: 1. gradual delivery; 2. mitigated local inflammation; 3. reduced toxicity; and 4. enhanced stability in large aqueous nuclei. [4]

A significant reduction in Calu-3 cell viability was observed when treated with free 3C and free HIPS-1635, either alone or in combination. This finding indicates the high toxicity associated with the free drug and underscores the significance of encapsulating it in a carrier to mitigate its toxic effects. Nanoparticles carrying 3C really packed a punch when it came to killing off cells, likely because they got more 3C inside the Calu-3 cells, boosting its effectiveness. On the flip side, the 3C-loaded nanoparticles with that lipid coating (3C NP-Lip) were much gentler on the cells, causing less cell death compared to just plain 3C nanoparticles or even when those nanoparticles were teamed up with HIPS-1635. This backs up the idea that the lipid coating makes the nanoparticles safer. It looks like the bigger size of the NP-Lip keeps them from getting inside cells as easily, which in turn keeps the toxicity down. [5] [HIPS-1635 is a Quorum Sensing Inhibitor (QSI), which is primarily used to interfere with the bacterial quorum sensing system, thereby inhibiting bacterial resistance and virulence expression] [3C is a 5-cyano 3C is a 5-cyano thiazolylurea derivative, a newly developed antibiotic used as a Mur A/Mur B inhibitor to inhibit the cell wall of bacterial cells and has been shown to be effective against a wide range of Gram-negative bacterial strains].

Once delivered directly into the lungs, an encapsulated drug tends to stick around longer and spread throughout the lung tissue more effectively than its unencapsulated counterpart. Free drugs, you see, are quick to diffuse across the lung lining and get whisked away into the bloodstream. Now, these encapsulated drugs? They ' ve got a few exit strategies from the lungs: (1) the drug can seep out either by directly diffusing across the liposome membrane or as the liposomes

break down, releasing the drug, which then diffuses across the lung mucosa; (2) immune cells can gobble up the intact liposomes; and (3) the liposomes can be cleared out by the mucociliary escalator, that little cleaning system in your lungs [6].

### 4.2 Liposomes in nucleic acid therapy

Liposomal recombinant DNA technology in nucleic acid therapy, along with studies of gene function and gene therapy, relies on the effective delivery of nucleic acids to cells both in vitro and in vivo. Non-viral vectors will be developed for the selective delivery of genes to malignant cells. By attaching nutrient ligands to the vector (liposomes), the delivery system will exploit the increased demand for nutrients in rapidly proliferating cells. Additionally, the vector will incorporate passively charged lipids to enhance nucleic acid binding along with a novel pH-sensitive surfactant. This surfactant is designed to increase the quantity of nucleic acid escaping the endosome, thereby improving transfection efficiency.[7]

In their work, Bi et al. cooked up some positively charged liposomes, TAT-PEG-SN 38, jazzed up with TAT, a cell-penetrating peptide (CPP), and PEG, acting as a shield. They then put these liposomes to work, investigating how well they could deliver survivin siRNA. DLS showed these tiny liposome particles were in the ballpark of 105 to 148 nm, with a zeta potential swinging between +3.74 and +13.83 mV. Slapping transferrin (Tf) onto TAT-PEG-SN 38 seriously boosted the liposomes' punch, making them better at taking out tumor cells. Western blot results made it clear that Tf-L-SN 38/P/siRNA did a much better job of silencing the survivin gene compared to the plain-Jane TAT-PEG-SN 38/siRNA. On top of that, Tf-L-SN 38/P/siRNA really brought the heat when it came to fighting tumors, slamming the brakes on tumor growth by a whopping 76.8% compared to the control group. Digging into the how-it-works side of things, they found that Tf-L-SN 38/P/siRNA mainly waltzes into cells via Tf-mediated endocytosis and then gets pulled inside through a lattice protein-mediated pathway. Turns out, Tf only plays a supporting role in getting Tf-L-SN 38/P/siRNA into the cells.[8]

### 4.3 Brain-targeted liposomes

Liposomes for the brain targeting the biocompatible and biodegradable properties of liposomes have recently prompted their investigation as drug delivery systems for the brain. Liposomes of varying diameters, including both small (100 nm) and large variants, can freely diffuse across the blood-brain barrier (BBB). Notably, small unilamellar vesicles (SUVs) that are coupled with brain drug transporter carriers may traverse the BBB through receptor-mediated or absorption-mediated transcytosis.

Wang et al. reported that mannose-coated liposomes can effectively reach brain tissue and that mannose coating enhances the transit of drugs across the blood-brain barrier (BBB). Typically, when administered systemically, enkephalin, leupeptin, and mefenfluramine kyoforphin do not cross the BBB. However, due to the versatility of the method, anti-amitriptyline is able to cross the BBB. Nanoparticles (NPs) were prepared using various stabilizing agents. It was found that amitriptyline levels in the brain were significantly increased when the drug was adsorbed onto the NPs, particularly when the particles were encapsulated or stabilized with polysorbate 85.[9]

Rodrigues and colleagues engineered liposomes decked out with both RVG and transferrin. This yielded spherical nanoparticles, little bubbles really, loaded with DNA. These souped-up liposomes can actually slip past the blood-brain barrier, ferrying plasmid DNA into primary neuronal cells safe and sound, without it being chopped up by nucleases. When it came to getting neuronal cells to take up the DNA, these RVG and transferrin-enhanced liposomes blew the individual protein or plain-Jane liposomes out of the water, showing way better results. Digging into the how, the researchers found that cells gulp down these DNA-filled liposomes through a process that doesn't rely on energy. Furthermore, liposomes modified with RVG can generate nanoparticles ranging from 20 to 50 nm, which are substantially smaller than their unmodified counterparts and thus more readily internalized by cells. These liposomes can effectively deliver oligonucleotide miRNA inhibitors into U87 cells, leading to the inhibition of miRNA-92b expression and subsequently suppressing the growth of malignant glioma. Additionally, liposomes that are dual-modified with the cell penetration RVG peptide and penetratin can actually bust through the blood-brain barrier to ferry plasmid DNA (pApoE2), which codes for ApoE2, right into brain tissue. This shows real promise as a therapeutic strategy for tackling Alzheimer's disease.[10]

## 5 Challenges faced

The porosity and pore size of tumor vasculature vary depending on the type and state of the tumor. As a result, passive targeting might not pan out for every type of tumor. Some drugs just don't permeate the entire tumor mass effectively, which throws a wrench in the works when it comes to hitting all the tumor cells evenly. Plus, in most solid tumors, that

high pressure from the interstitial fluid can really put the brakes on nanocarriers spreading uniformly throughout the tumor tissue, potentially paving the way for multi-drug resistance down the line.

Moreover, simply slapping antibodies onto liposomes doesn't automatically translate to better drug delivery. There are a few potential sticking points: the body might clear out these targeted liposomes faster, the cells might not actually pull them inside efficiently, the drug might leak out too soon, the liposomes themselves might fall apart in the bloodstream, or the antibodies might create a roadblock, preventing the drug from really getting deep into the tumor because of binding site issues or the cancer cells dialing down their receptors.[11]

Despite strong encapsulation and cell entry, cationic peptides' transfection is limited by endosomal entrapment and lysosomal breakdown. Therefore, improving endosomal escape and preventing lysosomal degradation of peptide liposome nanoparticles is a critical issue that needs to be addressed in future research on peptide liposome nanoparticles.[10]

## 6 Summary and outlook

The current liposome technology has been progressively optimized and validated clinically, providing an ideal foundation for a promising new approach.

Now that we have a much better handle on how liposome properties affect their behavior in the body, we can actually start to intelligently design liposome-based delivery systems for a range of cancer-fighting drugs. Think about it: just like pegylated liposomal doxorubicin (PLD) uses polyethylene glycolated liposomes to passively target tumors, we could do something similar with camptothecin analogs, antiangiogenic agents, and even antisense oligonucleotides. And for truly targeted delivery, we can attach monoclonal antibody (MAb) shards or other ligands to the liposomes, making sure they go exactly where we want them to.

This review highlights that the progress and enhancement of liposomes presents an elaborate challenge, necessitating the simultaneous optimization of multiple bunches to ensure the safety and efficacy of the final liposome formulation. Even though liposomes have already gotten the green light for use in a bunch of different areas of healthcare, there's still plenty of room for improvement. We've still got to tackle the limitations we've talked about. In conclusion, liposomes have the potential to enhance therapeutic applications by providing key properties that may lead to improved clinical outcomes, reduced toxicity, and fewer side effects.

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