Liposomes for Cancer Treatment: An update

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ABSTRACT

Liposomes' capacity to transport medications precisely to malignant cells while reducing harm to healthy tissues has made them a viable approach in the treatment of cancer. Both hydrophobic and hydrophilic medications can be encapsulated in these lipid-based vesicles, which are made of phospholipid bilayers, providing a range of therapeutic alternatives. Liposomes enhance the pharmacokinetics and biodistribution of chemotherapeutic drugs in cancer therapy, increasing their effectiveness and decreasing side effects. To further improve treatment results, targeting ligands can be added to the liposome surface to increase their selectivity for tumor cells. Drugs like doxorubicin (Doxil) already have approved liposomal versions and are being used in clinical settings. Optimizing liposome stability, drug loading capacity, and targeting efficiency is still difficult, though. This study examines the uses, difficulties, and prospects of liposomes in cancer treatment, emphasizing their potential in combination therapies and personalized medicine for better cancer care.

Selective drug delivery is made possible by the addition of targeting ligands to the liposome surface, which allow for precise binding to cancer cell receptors. This strategy has been especially helpful in raising the therapeutic index of cytotoxic medications like Paclitaxel and Doxorubicin, which are anticancer medicines. For example, ovarian and breast malignancies have been successfully treated with the liposomal version of doxorubicin (Doxil). Additionally, the creation of combination therapies—which may help overcome drug resistance and improve treatment outcomes—is made possible by the capacity to integrate different therapeutic molecules into a single liposomal carrier.

Keyword – Liposomes, Targeted drug delivery ,Cancer therapy, Phospholipid bilayers , Hydrophilic and hydrophobic drugs ,Chemotherapeutic agents , Paclitaxel ,,Combination therapy,Drug resistance,

INTRODUCTION

Liposomes, spherical vesicles composed of phospholipid bilayers, have been used since the 1960s to encapsulate both hydrophilic and lipophilic drugs, enhancing cancer treatment by improving drug delivery and stability. In vitro drug stability can be assessed by dialyzing liposomal samples and measuring drug concentration over time using spectrophotometry. Cancer remains a leading

cause of death globally, with breast and prostate cancers being the most common among women and men, respectively. Staging is crucial in cancer diagnosis, with the TNM system (tumor, node, metastasis) developed by the AJCC being widely used. Treatment decisions are influenced by factors like cancer stage, patient age, and overall health. Early-stage cancers may be treated surgically, while advanced cancers require multimodal therapies including chemotherapy, radiation, hormone therapy, and sometimes photodynamic therapy. Although effective, these treatments often lead to severe side effects.

A major challenge in cancer treatment is chemotherapy resistance, driven by mechanisms like survival pathway activation, epigenetic changes, and drug efflux by ABC transporters such as P-glycoprotein, MRP1, and ABCG2. Nanoparticles like liposomes are being explored to overcome multidrug resistance and improve therapeutic outcomes

How they operate

By delivering medications to precise locations, liposomes can decrease adverse effects and increase the stability and bioavailability of medications. They can also enhance the drug's tissue distribution and pharmacokinetics.

Examples of medications based on liposomes

Among the medications based on liposomes are:

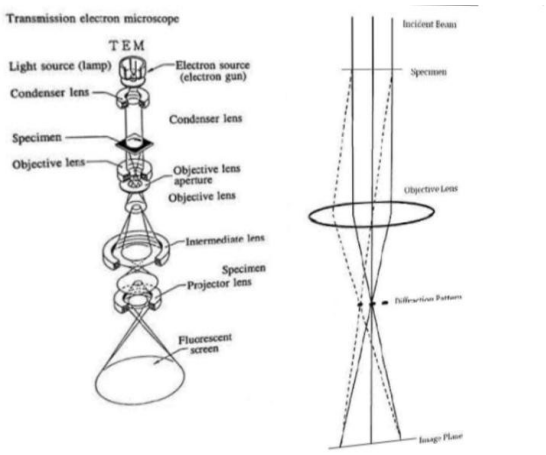
Doxil: A polyethylene glycol coated doxorubicin (DOX) liposome used to treat Kaposi's sarcoma

Depocyt: A liposome that contains the cell-cycle cytotoxic medication citarabine, which is used to treat cancerous tumors.

Mepact: An osteosarcoma treatment liposome formulation.

CHARACTERISTICS OF LIPOSOME

1. **Electron Microscopy Transmission (TEM)**: Transmission Electron Microscopy (TEM) provides accurate measurements of liposome size by visualizing their core structure. However, it cannot detect organic surface ligands due to low electron density. TEM also requires a high vacuum, which may cause liposome aggregation, and it has limited sampling, making results potentially unrepresentative of the entire formulation. Therefore, multiple techniques should be used to determine liposome size accurately.



2. **DLS, or dynamic light scattering**:Dynamic Light Scattering (DLS) is the most commonly used method to determine liposome size, particle size distribution, and zeta potential. It measures the hydrodynamic diameter based on Brownian motion and light scattering fluctuations. While DLS is quick and easy to use, it requires particles to be dispersed in a solvent and is limited by low sensitivity to particles smaller than 10 nm and interference from light-absorbing substances.
3. **Spectroscopy of Fluorescence Correlation (FCS):** Autocorrelation analysis can be used to quantify the size of FCS, which quantifies the duration of brief bursts of photons from individual nanoparticles traveling through a small focal volume of approximately 1 fL (10−15 L).

4. **Efficiency of Encapsulation (EE):**Encapsulation efficiency (EE) refers to the amount of drug successfully enclosed within liposomes compared to the total drug initially used in the formulation. After preparation, liposomes usually contain both encapsulated and free (unencapsulated) drug. Techniques like size-exclusion chromatography can separate these based on size—free drug stays in the gel, while drug-loaded liposomes pass through. Alternatively, dialysis with membranes of suitable pore size can achieve the same. Once separated, the liposomes are broken open to release the drug, and the amount is measured using methods like spectrophotometry or HPLC.

Content of Phospholipids: The Bartlett phosphate assay is a simple spectrophotometric technique used to measure how much phospholipid is present in liposomes. It works by converting the phospholipids into inorganic phosphate using acid, which is then detected with ammonium molybdate. While this method helps determine phospholipid content, other factors like the type of lipids used, how many layers the liposomes have, the stiffness of the bilayer, the lipid-to-drug ratio, how the drug is released, and how it interacts with the liposomes also

play important roles in how well the drug is encapsulated and how effective the liposomes are. These more complex features are explored in greater detail in other scientific reviews.

PREPARATION OF LIPOSOME

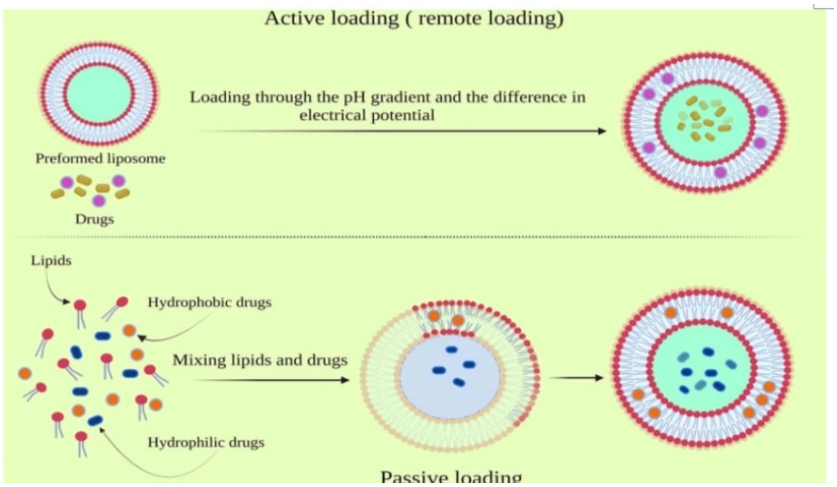
1. **Hydration of Thin Lipid Films:**Thin lipid film hydration is a simple and widely used method in research labs for making liposomes. It involves dissolving phospholipids in an organic solvent, evaporating the solvent to form a thin lipid layer, and then hydrating it to produce liposomes. Techniques like extrusion and sonication help reduce size variability. While this method is easy and reproducible, it has low encapsulation efficiency for hydrophilic drugs. Despite this, it has been successfully used to encapsulate drugs like doxorubicin.
2. **Evaporation in the Reverse Phase:** Reverse phase evaporation is a relatively simple method used to improve the encapsulation efficiency (EE) of drugs in liposomes. It involves mixing an aqueous drug solution with a lipid-containing organic phase to form an emulsion. After evaporating the organic solvent, liposomes form in an aqueous suspension. This method has been used to encapsulate drugs like carboplatin, doxorubicin, and tacrine hydrochloride.
3. **Rehydrating after dehydration:** Dehydration-rehydration is another method used to improve drug encapsulation efficiency in liposomes. It involves freeze-drying (lyophilizing) preformed small unilamellar vesicles and then rehydrating them in an aqueous solution. During rehydration, liposomes reorganize and can passively trap the target compound. To preserve the bilayer structure and prevent aggregation, lyoprotectants are added. This method has been successfully used to encapsulate DNA, RNA, and radiocontrast agents like diatrizoate and iotrolan.
4. **Methods of Microfluidics:** Microfluidic hydrodynamic focusing (MHF) allows precise control over liposome size and uniformity using solvent displacement. It works for both hydrophilic and hydrophobic drugs by adjusting flow rates in a microfluidic device. Other methods for measuring nanoparticle size include AFM, absorption spectroscopy, ultracentrifugation, and NTA.

ACTIVE VS PASSIVE LOADING OF DRUG IN LIPOSOME

The Deamer research group was the first to use remote (active) loading of drugs into liposomes by creating a pH gradient across the liposomal membrane. In this method, uncharged drug molecules diffuse into the liposome and become protonated inside, making them unable to exit. This technique works best for drugs with a pKa $\leq$ 11 and a logD between −2.5 and 2.0 at pH 7. An example is the FDA-approved liposomal formulation Doxil®, where doxorubicin is loaded using

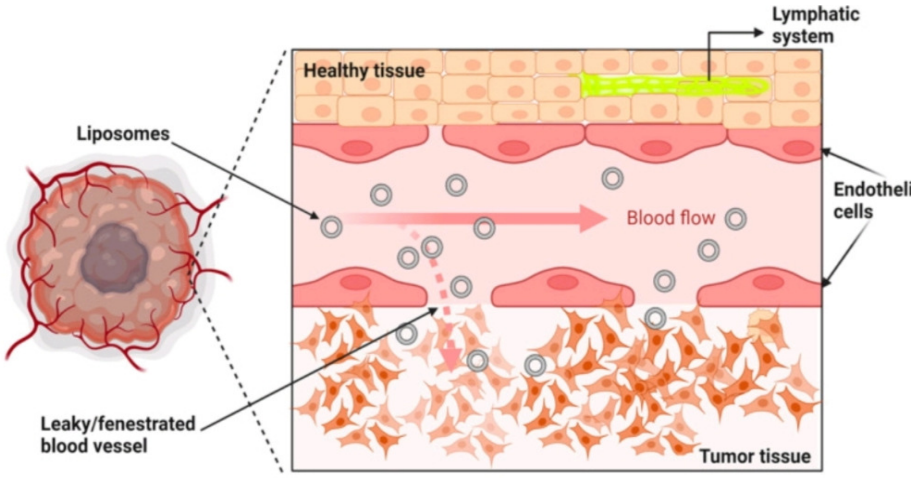
an ammonium sulfate gradient. Inside the liposome, doxorubicin forms a sulfate salt, leading to controlled release and a prolonged plasma half-life.

The main difference between active and passive loading lies in the loading process. Active loading involves loading preformed liposomes using gradients, resulting in high encapsulation efficiency and stability. It is more suitable for hydrophobic or weakly basic drugs. Passive loading, on the other hand, involves mixing drugs with lipids during liposome formation and is more effective for hydrophilic drugs, though it often leads to lower drug retention and efficiency.



METHOD FOR DIRECTING LIPOSOMES TOWARD CANCER

1.The EPR Effect of Liposomes (Passive Targeting): Long-circulating liposomes and nanoparticles take advantage of the leaky blood vessels in tumors. Unlike healthy tissues with tightly packed endothelial cells (5–10 nm gaps), tumor vessels have larger gaps (100–700 nm), allowing liposomes to pass through and accumulate in the tumor. Additionally, tumors lack efficient lymphatic drainage, preventing the removal of these particles. This phenomenon, known as the enhanced permeability and retention (EPR) effect, enables passive targeting of tumors by liposomes.



2. Active Liposome Targeting: Most nanomedicines rely on passive targeting, such as the EPR effect, to reach tumors, but few have received FDA approval due to limited effectiveness and off-target toxicity. Passive targeting lacks true specificity for tumor cells, reducing clinical success. To overcome this, researchers are focusing on active targeting, which uses molecular techniques to bind directly to tumor-specific markers, improving precision and efficacy.

3. Local Stimuli to Cause Liposome Drug Release: Drug release from liposomes at tumor sites can be enhanced by exploiting tumor-specific conditions such as higher temperature, acidic pH, and increased proteolytic enzymes. External stimuli can also trigger release. For example, pH-sensitive polymers like polyacrylic acid are added to liposomes stable at normal pH but hydrolyze in the acidic tumor environment ($pH \leq 6$), enabling targeted drug release.

CONCLUSION

Because of their physicochemical characteristics, which enable them to overcome a number of obstacles and restrictions with medication administration, liposomes make an appealing delivery mechanism. Numerous biomedical fields have been significantly impacted by the use of liposomes to enhance medication delivery. It has been demonstrated that liposomes enhance the stability and biodistribution of therapeutic drugs, resolve issues with tissue and cellular uptake in target regions in vivo, and lessen systemic toxicity linked to medicines that are not encapsulated. But despite the extensive preclinical research on liposomes, only modest progress has been made in bringing them to the clinic. Such translational limitations will need to be addressed in future studies. Experts in pre-clinical, clinical, and toxicological applications as well as other phases of pharmaceutical development will need to collaborate and communicate constantly in order to achieve this.

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