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Liposome as Drug Delivey Systems

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ABSTRACT

Liposome Drug Delivery is spherical carriers that contain a lipid bilayer which is similar to the human cell membrane's phospholipids configuration. Drug delivery methods based on liposome are a promising development in pharmaceutical research that could greatly enhance therapeutic results, especially in the treatment of cancer. To get over current obstacles and maximize its application in clinical practice, more study and advancement are necessary. The goal of this article is to give a general overview of the liposomal drug delivery system, Methods of liposome drug delivery preparation, liposome formation process, liposome drug delivery in cancer treatment, and applications of the liposomal drug delivery systems were the main topics of the paper, In this context, the liposomal system encapsulates anti-cancer pharmaceuticals, providing secure platforms for targeted administration of anti-cancer drugs for cancer treatment. This can therefore lessen the cytotoxic effects that anticancer drugs have on healthy cells.

I. INTRODUCTION

Liposome discovery has led to a considerable advancement in drug delivery systems. Alec D. Bangham and his team at the Babraham Institute in Cambridge, England, found in 1961 that phospholipids in water-based solutions spontaneously formed enclosed bilayer structures.[1] Liposome Drug Delivery are spherical carriers that contain a lipid bilayer which is similar to the human cell membrane's phospholipid configuration. Drug delivery methods based on liposome are a promising development in pharmaceutical research that could greatly enhance therapeutic results, especially in the treatments of cancer [2] The technology of liposome advanced quickly in the 1970s and 1980s. Researchers created a number of liposome preparation techniques, including as reverse-phase evaporation, extrusion, and sonication. Liposomes come from the Greek words "lipos" meaning fat and "soma" meaning body are encapsulated phospholipid bilayer structures that were first known as bangosomes and then renamed.[3] The most significant application of liposomes is anticipated in the fields of biotechnology, medicine, and pharmacology, where they function as carriers for controlling the delivery of entrapped medications, including vaccinations, enzymes, genetic material, immunomodulators, cancer chemotherapeutics, diagnostics, antibiotics, antifungals, opthalmics, and aniashamatics [4] The Source of lipids and stability of phospholipids, which are regarded to be crucial excipients, greatly influence the performance of the product.[5] Liposome have evolved from a biomembrane model to a therapeutic medication carrier throughout time. There are several medicinal applications for liposomes, such as cancer treatment, fungal infections, vaccines, and, most recently, gene therapy [6]. Antibody-targeted liposomes exhibit low toxicity because they exclusively distribute to the target spot and are quickly eliminated from the body. According to a different study, not all substances that enter the target site can raise the drug's concentration there [7].These have been extensively researched as the preferable carrier for therapeutic agent administration over the past few decades due to their ability to capture a class of drugs that can be both hydrophilic and lipophilic. [8]

Structure of Liposome

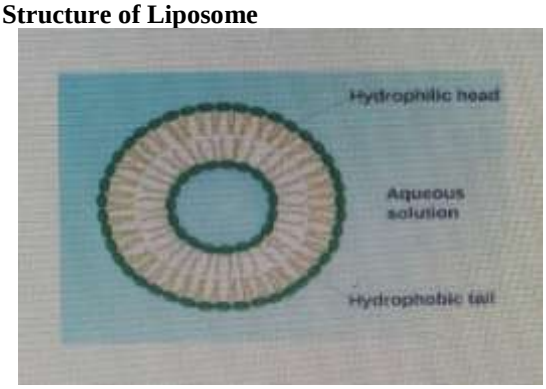

Figure 1: Structure of liposome

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Types of liposomes

1 .Multilamellar vesicles (MLVs): Multilamellar vesicles are known as MLVs. They can create compartments out of the aqueous volume in countless ways. They differ in the way they are prepared. Concentric spherical bilayers of LUV/MLV stacked like an onion can encapsulate a number of SUVs, etc. [9]

2. Small unilamellar vesicles (SUVs) : Depending on the lipids and production technique, liposomes might differ in size and charge. The size range of small unilamellar vesicles (SUVs) is 0.02 to 0.05. [10]

Advantages and Disadvantages of liposomes

Advantages of liposomes	Disadvantages of liposomes
Liposomes help reduce the amount of dangerous drugs that are exposed to sensitive tissues.	High production costs
Liposomes enhanced the therapeutic index and effectiveness of the medication (actinomycin- D)	Less solubility
Liposomes can be administered systemically or non-systemically and are completely biodegradable, biocompatible, non- immunogeni, flexible, and non-toxic.	Phospholipids can occasionally experience oxidation and reactions resembling hydrolysis
The stability of liposomes made via encapsulation was enhanced.	Short half-life
Effect of site avoidance	less stables
Liposomes reduce the toxicity of the encapsulating drug (taxol, amphotericin B	Leakage and fusion of encapsulated drug and molecules
Provides protection to unstable drugs from degradation	Can be unstable and have a short shelf life (10)

Method Preparation of liposomes and drug Loading

The following method of preparing is used for the preparation of liposome:

1. Passive loading technique

Passive loading strategies are used to encapsulate drugs during the liposome manufacturing process. Lipids are dissolved in an organic solvent, dried to a thin layer, and then hydrated with an aqueous drug solution in this simple procedure. Despite its simplicity, this method usually results in poor encapsulation efficiency for hydrophilic medicines [8] The method of reverse-phase evaporation provides hydrophilic medications with increased encapsulation efficiency. The organic solvent is eliminated after lipids and the aqueous drug solution form a water-in-oil emulsion using this technique using a vacuum [11]. the freeze-thaw technique enhances macromolecule encapsulation by quickly freezing and thawing MLVs holding the medication. This strategy is frequently used in conjunction with other approaches to increase overall effectiveness [12] Sonication uses sound waves to split MLVs into SUVs, producing tiny, homogeneous liposomes. However, there is a risk of medicine deterioration due to the heat generated by this method [13] The process of extrusion involves pushing liposomes through a polycarbonate membrane to produce liposomes of consistent size while maintaining the integrity of delicate ingredients [14]

2. Active loading technique

A gradient is produced to encourage drug encapsulation after liposome production using active loading procedures. Because the pH gradient approach creates a pH difference between the liposome's outside and interior, it is effective with weak bases or acids. This technique can produce high encapsulation efficiency; for certain medications, it frequently surpasses 90%[15] An ammonium sulphate gradient method loads amphipathic weak bases using an ammonium sulphate gradient For medications like doxorubicin, it works incredibly well and offers ongoing drug retention. [16] the Ion gradients, such as calcium acetate, are used in the ion gradient technique to load. Because it offers better loading efficiency and greater stability, this method is especially helpful

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for medications that form insoluble calcium complexes.[17]

Passive Loading techniques are divided into three categories method

1. The method of mechanical dispersion
2. Method of solvent dispersion
3. Detergent removal (materials that have been enclosed)

Mechanical dispersion method

1. Sonication
2. Thawed and frozen liposomes
3. Membrane extrusion
4. The French press

1. **Sonication method:** This approach, which combines the rotary evaporator and handshaking procedures, is the most popular way to prepare SUV from MLV. Probably the most popular method for getting SUVs ready is sonication. In a passive atmosphere, MLVs are sonicated using a probe sonicator or a bath [18]. This method's primary drawbacks are a comparatively poor internal volume/encapsulation efficiency, the likelihood of phospholipid and chemical degradation, the removal of large molecules, metal contamination [19]

The sonication method is divided into two categories

1. **Probe Sonication** The process of inserting a sonicator tip straight into a liposome dispersion is known as probe sonication. A significant amount of energy is needed to disseminate the lipids using this method. The vessel needs to be submerged in a water/ice bath because the energy coupling at the tip produces local heat. After sonicating for up to an hour, more than 5% of the lipids can be de-esterified [20] Additionally, titanium may slough off due to the probe sonicator, contaminating the fluid. The primary drawback of this process is that the titanium fragment contaminates a solution by turning into sludge [21]
2. **Bath sonication**: A cylinder containing liposome dispersion is put into a bath sonicator, this method allows for greater control over the temperature of the lipid dispersion than sonication via dispersal, which uses the tip directly, The substance that is being sonicated can be kept in an inert atmosphere or in a sterile vessel apart from the probe units. For the production of SUVs, this method is more practical than probe sonication since temperature can be readily controlled. It is possible to obtain the sterile liposome, and titanium contamination is absent. [22]

2. Freeze thawed liposomes: SUVs are frozen quickly and thawed gradually. Aggregated materials are dispersed to low UV light by sonication. SUV fusion during the freezing and thawing stages leads to the creation of unilamellar vesicles. By increasing the phospholipid concentration and the ionic strength of the medium, this kind of synthesis is significantly impeded. 20% to 30% encapsulation efficacies were achieved [23]

Method of solvent dispersion:

Injection of ether (vaporisation of solvent)

An aqueous solution of the material to be encapsulated is gradually injected with lipids dissolved in diethyl ether or an ether-methanol mixture at 55°C to 65°C or with lowered pressure. As ether is subsequently removed under vacuum, liposomes are created. [24].The method's principal drawbacks are varying population sizes (70-200 nm) and exposing chemicals to high-temperature organic solvents[25].

Injection of ethanol: MLVs are created when a lipid-ethanol solution is introduced into a buffer. The creation of a varied population of liposomes (30-110 nm) is the drawback. Since ethanol is so difficult to extract from a solution, it is more likely to inactivate physiologically active macromolecules.

Method of reverse phase evaporation:

This process represented a turning point in liposome technology because it made it possible to create liposomes with a high aqueous space-to-lipid ratio and to entrap a significant portion of the provided aqueous material. Reversed micelles are produced during reverse-phase evaporation. Water-soluble substances are encapsulated into liposomes via sonication, which produces inverted micelles by mixing an organic phase with a buffered aqueous phase. As a result of the organic solvent's delayed removal, these inverted micelles become sticky and gel-like.[26] Liposomes are produced when the gel state collapses at a crucial point in the process, breaking up some of the inverted micelles. The extra phospholipids in the surrounding environment then form a complete bilayer around the surviving

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micelles. Reverse phase evaporation liposomes have four times the aqueous volume-to-lipid ratios of hand-shaken or multilamellar liposomes and can include a range of lipid formulations.[27] A two-phase system containing phospholipids is quickly sonicated in organic solvents such as isopropyl ether, diethyl ether, or a combination of isopropyl ether and chloroform with aqueous buffer to produce the water-in-oil emulsion. The organic solvents separate and solidify into a thick gel when the pressure is lowered. When leftover solvent separates during rotary evaporation at low pressure, liposomes are created. Up to 65% encapsulation efficiency is attained using this method in a medium with a low ionic strength, such 0.01 M NaCl. Small, large, and macromolecules have all been encapsulated using this method. [28] The main drawbacks of the method are the brief sonication times and the exposure of the encapsulated components to organic solvents. These conditions could lead to denaturation of proteins or breakage in DNA strands. An altered reverse phase evaporation method developed by Handa et al. yielded liposomes with a high encapsulation efficacy (about 80%) [29]

Detergent extraction (materials that have been entrapped)

Dialysis

Detergents at critical micelle concentrations (CMC) have been used to solubilise lipids. The micelles become increasingly phospholipid-rich and ultimately develop into LUVs as the detergent is eliminated. Dialysis was used to get rid of the detergents. A commercial product called LipoPrep (Diachema AG, Switzerland) employs a dialysis mechanism to get rid of detergents. In equilibrium dialysis, huge buffers devoid of detergent are poured into dialysis bags.

Removal of mixed micelles by detergent (cholate, alkyl glycoside, Triton X-100) (absorption)

This method involves combining a mix micelle with beaded organic polystyrene absorbers, including Bio-beads SM2 (Bio-Rad Laboratories, Inc., Hercules, USA) and XAD-2 beads (SERVA Electrophoresis GmbH, Heidelberg, Germany), to remove the detergent. Detergent adsorbers have the benefit of reducing low-CMC detergents without completely depleting them [30].

The chromatography of gel-permeation:

This method depletes the detergent using size-specific chromatography. Sephadex G-50, Sephadex G-l 00 (Sigma-Aldrich, MO, USA), Sephacryl S200-S1000 (General Electric Company, Tehran, Iran), and Sepharose 2B-6B can all be used for gel filtration. The liposomes cannot pass through the holes in the beads that are organised in a column. They penetrate the spaces between the beads. At modest flow rates, liposomes can be successfully isolated from detergent monomers. Pretreatment is essential because the larger polysaccharide beads absorb a lot of amphiphilic lipids. As part of the pre-treatment procedure, empty liposome solutions are employed to pre-saturate the gel filtration column with lipids [31].

Recent advancements in prepartionn methods

The goal of recent developments is to increase the scalability and efficiency of liposome preparation. Microfluidic techniques provide promise for large-scale manufacturing and continuous production due to their ability to precisely adjust liposome size and lamellarity. Using supercritical CO2 as a solvent, supercritical fluid techniques offer a solvent-free, ecologically friendly technology that works well with thermolabile materials.[32] Dual asymmetric centrifugation, which does well with semisolid formulations and can create Liposomes that are tiny and highly concentrated combine homogenisation and mixing in one step. The organic lipid phase is forced through a membrane and into an aqueous phase by the membrane contactor technology, which provides a scalable, continuous process with good control over size distribution. By altering the ethanol injection method, for as by using cross-flow injection techniques, the properties of liposomes may be better regulated and they can be created continuously and in huge quantities.[33]

Mechanism of Liposome Vesicle Formation

Mechanism of Liposome Vesicle Formation Although the composition of the lipid formulations (cation, anion, and neutral lipid species) can affect their properties, any lipid vesicles can be prepared using the same technique[34]The process's general elements include hydrating, sizing, and prepping the lipids for hydration while swirling to distribute the vesicles uniformly [35]. When researching liposome synthesis, the stiffness of the bilayer membrane is a crucial consideration. Both gel and liquid crystal (or "fluid") states are possible for the

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hydrated single-component phospholipid bilayer. Upon increasing the temperature, the gel bilayer membrane melts and becomes liquid. The transition temperature (Tc) is where this happens. The Tc of bilayers relies on.

1. Length of the acyl chain.
2. Saturation degree.
3. The Polar Head Group.

The basic materials used to create liposomes vary depending on their intended function, Liposomes can be generated using three main techniques: mechanical methods, solvent dispersion approaches, and techniques that rely on the fusion or size alteration of the generated vesicle [36]

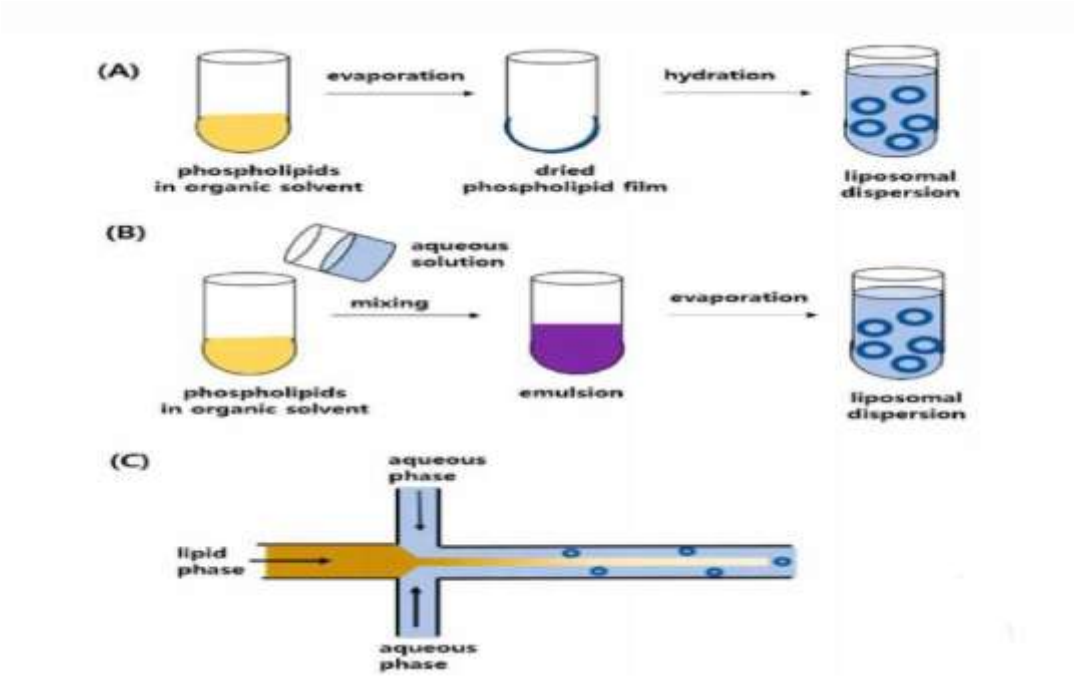

Figure 2.[A] The lipid bilayers' stacks swell when the solvent evaporates and a dry [thin] lipid layer formed. The lipid film is subsequently rehydrated in a saline buffer, which eventually contains hydrophilic dugs to be collected. [B] The formation of (polydispersed) multilamellar vesicles is encouraged by the solvent's successive mixing and churning [C].the last phases of preparation, which comprise purification and shrinking of the liposomes.

CHARACTERIZATION OF LIPOSOMES

1. **Size and polydispersity:** Dynamic light scattering evaluates the size distribution using light scattering from suspended particles, its best suited for analyzing smaller particles but can struggle with polydisperse samples or particles with irregular shapes. Laser diffraction measures particle sizes based on the pattern of light diffraction .It works well for a broad size range but can be less accurate for very small particles or those with irregular shapes.[37]
2. **Zeta potential:** A common analytical metric for characterising the surface of nanoparticles is zeta potential. Nanoparticle stability, circulation durations, protein interactions, particle cell permeability, and biocompatibility can all be gleaned from zeta potential. The most widely utilised lipids in the production of liposomes include DSPC, cholesterol, and lipid- PEG. Liposomes are one of the most widely used drug delivery vehicles in nanomedicine.By getting beyond surface charge-related toxicities that frequently restrict dosage, the zeta potential can enhance the biological performance of nanomedicines while lowering overall efficacy and therapeutic value.[38]
3. **Encapsulation Efficiency:** A good drug carrier, liposomes can dissolve lipid-soluble medications in the double layer of lipid bilayers and dynamically make insoluble

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medications more soluble. A crucial factor in regulating the liposome's quality is entrapment efficiency (EE). However, because liposomes are not encapsulated, particularly because they are hydrophobic and can self-aggregate in water, it is challenging to assess their quality. To assess drug EE, it is crucial to extract the drug that is not entrapped from the drug-loaded nanoparticles without damaging the liposome.[39]

4. **Lamellarity Assays:** It provides new ways to measure the dielectric characteristics of individual liposomes adsorbed on a metal electrode utilising liquid scanning dielectric microscopy in force detection mode. Lamellarity describes how many lipid bilayers there are in a liposome which is important for understanding its structure and functionality. Separation between lamellae gives sight into the spacing between the lipid bilayers which can affect drug encapsulation and release of the drug.[40]
5. **Invitro Drug Release:** Drug release tests are required for quality control to ensure batch- to-batch consistency as well as the characterisation of liposome products. To prevent interference from liposome-bound active pharmaceutical ingredient (API), in vitro drug release testing of liposomal formulations frequently necessitates a separation step, such as dialysis or solid phase extraction, to separate and then quantify the released API. But these methods of separation take a long time, and when dialysis or liposome rupture occurs during the separation process, they might create an artificial gradient in drug concentration, which could lead to an incorrect measurement of the medication that is released [41]

APPLICATIONS OF LIPOSOME IN MEDICINE AND ROUTE OF ADMINSTRATION

The encapsulation in liposomes may change the temporal and spatial distribution of encapsulated drug molecules throughout the body, lowering harmful side effects and improving treatment effectiveness. Applications for liposomes in pharmacology and medicine include therapeutic and diagnostic uses of liposomes that contain drugs or other substances, as well as their use as a form, instrument, or reagent in basic research on cell interactions, recognition processes, and/or the mechanism or action of specific materials [42] The way liposomes interact with cells and what happens to them in vivo after injection greatly influences the advantages and disadvantages of liposomal drug carriers. Research on liposome interactions with cells, both in vitro and in vivo, has revealed that endocytosis or simple adsorption are the main interactions [43] Fusion with the cell membrane is very rare. The exchange of bilayer elements, such as lipids and cholesterol, which are membrane-bound compounds that interact with components of cell membranes, is the fourth potential contact [44] The way that liposomes behave in vivo is affected by these interactions. The body has an intricate defence mechanism in place to protect itself.[45]. The immune cells consume minute particles, germs, bacteria, and colloids, whereas larger things that enter the body encourage thrombus formation and eventually passivate their surface by coating with bio macromolecules [46] Although this immune system reaction has led to a lot of work to create biocompatible and unidentifiable surfaces, it has also restricted the potential applications of microparticle drug] carriers to the same immune system cells. Like all other natural substances, liposomes are made of natural ingredients. Macrophages swiftly remove them from the bloodstream; they are primarily present in the spleen, liver, and bone marrow [47]

Liposome mode of action

Liposomes' biodistribution and pharmacokinetics differed from those of free drug particles, as was shown in the preceding section. In certain instances, this can be utilised to boost the encapsulated drugs' therapeutic effectiveness. Drug-loaded liposomes have seven different types of benefits. They can be used as an aerosol, a (colloidal) solution, or in (semi)solid forms as gels and creams. In [48]

ROUTES OF ADMINISTRATION:

1. **Subcutenous route**: Liposomes are fascinating in their potential for targeted drug delivery The two most important considerations for employing them to transport agents to the lymphatic system by subcutaneous injection are the size of the liposome and the injection site's anatomy. lipid composition surface charge and PEG coating generally don’t have a big impact on how well the liposomes are absorbed by the lymphatic system and taken up by lymph nodes. The smaller liposomes and specific anatomical injection sites could improve the efficiency of

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getting the therapeutic or diagnostic agents to the lymphatic system. This method has a lot of promise in areas like cancer treatment and immune response monitoring.[49]

2. **Nasal Route:** Liposomes indeed contribute significantly to overcome the limits of drugs delivery via the nasal route. There advantages such as better absorption and retention in the nasal mucosa make them a powerful tool in delivering drugs like Nifedipine and vaccines systemically. The intranasal route is particularly promising for brain drug delivery , where liposomes can enhance CNS penetration and provide sustained drug release.[50]
3. **Intravitreal Administration** : Intravitreal administration of drugs indeed offers a significant advanatges for treating problems affecting the eye's posterior portion such as reaching elevated levels of the medication in the vitreous and avoiding systemic side effect. however the need for repeated administrations due to rapid drug clearance from the vitreous humor poses challenges including the risk of complications like endophthalmitis lens damage and retinal detachment this is why liposomes drug delivery has been used .Liposomes can mitigate such challenges by reducing local toxicity at effective dose, prolonging the amount of time that active molecules remain in the eye, preventing unstable medications like peptides and nucleic acids from breaking down in vivo. A viable way to improve the security and effectiveness of intravitreal medication administration is through liposomes transforming the treatment landscape for ocular disease[51]
4. **Topical Drug Delivery:** Liposomal formulations have indeed revolutionized drug delivery over the past decade. their superiority in comparison to traditional dose forms, particularly for topical and intravenous delivery from several key advantages like liposomes can significantly decrease more severe side effects and incompatibilities by minimizing undesirable systemic absorption, due to their high affinity with biological membranes liposomes can ensure a significant medication accumulation at the intended location, liposomes can readily incorporate drugs that are hydrophilic and hydrophobic making them highly versatile in drug formulation.[52]
5. **Oral drug delivery :** The most popular method of drug administration is oral delivery through the gastrointestinal system, and liposomal carriers have demonstrated significant promise in improving drug solubility and shielding therapeutic molecules from the harsh conditions of the GI tract. Their nanoscale size and lipid bilayer membrane can greatly enhance oral absorption. Convectional liposome availability and stability in the GI tract have been difficult to achieve, nevertheless. To address these issues The surface of liposomes has been modified for example, adding polyethylene glycol to the liposomes' surface can increase their stability and lengthen the time they spend in circulation within the body. using chitosan a natural polymer to coat liposomes can enhance their mucoadhesive properties allowing them to better adhere to intestinal mucosa and improve absorption[53]

LIPOSOME AS TARGETED DRUG DELIVERY SYSTEM IN CANCER TREATMENT

The use of liposomes in the treatment of cancer has proven successful. Although there has been a lot of study on the use of liposomes in cancer therapy and it deserves greater attention, this is outside the purview of this review [54] The most effective liposome applications in cancer therapy are covered in this article. Compared to free drug, liposomal versions of anti-cancer medications have been shown to administer treatment to solid tumours with less toxicity (Allen and Cullis 2013; Sutradhar and Lutful 2014). The market and clinical research are examining a number of products for use as anti-cancer drug delivery vehicles (Allen and Cullis 2013).[55] Developments in liposomal vesicle formation have made disease-specific targeting and controlled drug release possible. Given that chemotherapy, radiation therapy, and surgical resection are the main cancer treatments, this trait is advantageous. Chemotherapy injections into the body are required for certain cancers [56] Most APIs used in chemotherapy have a high toxicity level to both healthy and malignant cells. Since the free medication enters the bloodstream directly, there are a number of potential drawbacks and restrictions. The chemotherapeutic drug can be absorbed by both healthy and cancerous tissues, resulting in significant toxicity in the liver, kidneys, and heart, among other organs. Patients may be given the highest dose of chemotherapy to increase the amount of medication absorbed by cancer cells

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[57] The ability of cancer treatments to shrink and eliminate tumours without harming healthy tissues is crucial for extending survival times and enhancing patient quality of life [58]. Using an antibody-based technique, liposomes can actively target cancer tissues. To accomplish this, particular antibodies that are exclusive to cancer cells or the endothelial cells of the tumour vasculature can be attached to the liposomal surface of immunoliposomes (ILP) [59] The first-line treatment for cancer is chemotherapy; however, its efficacy is limited by severe toxicity, poor tissue selectivity, a limited therapeutic index, and a high chance of drug resistance. These ailments may result in disastrous outcomes when treating cancer. Drug delivery to cancer cells is targeted via nanoscale liposomal formulations. Certain liposomal compositions are utilised in the treatment of cancer. Breast cancer and lymphomas are among the solid and haematologic neoplasms that can be treated with DOX, an anthracycline antibiotic made from Streptomycin peucetiusvar. caesius.[60]

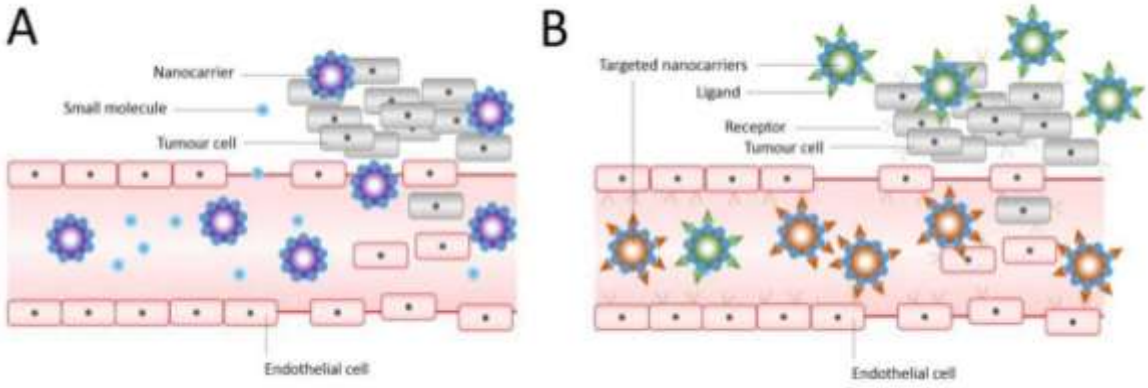

Figure 3. Active targeting of nanocarriers through passive A and B, Through the leaky vasculature, nanocarriers selectively infiltrate tumours; in other cases, their size affects how long they remain in the cancerous tissue. Due of their small size, drugs without nanocarriers can freely enter and exit tumour blood arteries, causing their effective concentrations to rapidly decrease. In [61] The EPR effect occurs when drug-loaded nanocarriers that are too big to diffuse back into the bloodstream, which causes an accumulation to increase. In active targeting, ligands grafted onto nanocarriers attach to receptors that angiogenic endothelial cells or cancer cells (over)express. Reproduced and altered with consent In a number of ways, local hyperthermia may enhance the liposomal formulation's ability to transport drugs Through inducing drug release at a temperature comparable to the liposomes' lipid phase transition, increasing blood flow to the site of action by promoting liposome accumulation there by improving endothelial permeability to liposomes and target cell permeability to API released by liposomes, fortifying the target cells' fusion or endocytosis effect to the drug that is straight from liposomes, and improving medication release from liposomes by lowering the target site of action's local pH [62] According to another research, the reticuloendothelial system's pharmacokinetics of liposome clearance are influenced by vesicle size, lipid composition, surface coating, and charge, including the interaction between liposomes and plasma proteins In [63]

Liposomal Drug Delivery: Active and trigger based targeting

Active targeting : Active Targeting of liposomes indeed holds great potential for improving drug delivery by increasing accumulation at the target site or achieving intracellular delivery to target cells. This approach involves modifying the surface of liposomes Target cell receptors can be bound by certain ligands the liposomal contents are released intracellularly through receptor-mediated endocytosis. By decreasing the drug's diffusion away from the tumour, this technique can increase the drug's overall effectiveness while preserving a larger concentration of the medicinal component at the site of action [14]

Trigger based targeting: Trigger release liposomes are indeed a fascinating area of research offering improved medication release management and more accurate targeting. These liposomes fall into two general categories:

1. **Environment responsive liposomes:** These use the local environment of the target site,

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including pH variations or the presence of particular enzymes, to initiate the release of the medication

2. **Externally triggered liposomes:** These are triggered by physical stimuli from the outside, such light, heat, or ultrasound.

Both types provide more control over the release of the medication's timing and location, improving its ability to target damaged tissue. Incorporating target specific components like antibodies further improves the precision of drug delivery**.[64]**

Physiological dependent release: The development of bio responsive nanomaterials and vesicles has opened up new possibilities to distribute drugs in a targeted and controlled approach. Drugs release may be precisely controlled thanks to these materials' ability to react to several physiological stimuli, such as changes in pH, redox environments, and the presence of particular enzymes.

Additionally integrating these responsive functionalities with vesicles that are responsive to physical stimuli, such ultrasound or light offers even greater control over therapeutic delivery [65]

External stimuli dependent Release: Using external stimuli to control drug release is a fascinating and highly effective concept when designing a medication distribution system the accuracy and control of a drug's release timing and location can be significantly improved by these stimuli-responsive devices. Here are a few key external; stimuli used in these systems

1. **Temperature:** Thermo-responsive polymers play a crucial role here, they can undergo phase changes or aalter their physical properties bin response to temperature variations allowing for controlled drug release.
2. **Magnetic field:** Magnetic field nanoparticles can be incorporated into drug carriers enabling drug release in response to a magnetic field outside the body.
3. **Light:** Light sensitive materials which can be used to trigger drug release upon exposure to specific wavelengths of light.
4. **External Field:** Electrically responsive polymers can change their properties when an electric field is applied facilitating drug release
5. **Ultrasound:** ultrasound waves can induce mechanical vibrations leading to the release of drugs from carriers[66]

RECENT ADVANCEMENT IN LIPOSOME DRUG DELIVERY

There have been several exciting advancement in liposomal drug delivery recently

1. Targeted and stimuli responsive Liposomes that can respond to certain stimuli, such pH, temperature, or enzymes [67] These stimuli responsive liposomes improves therapeutic efficacy and minimises negative effects by precisely releasing their medicinal payload at the target place.[68]
2. Enhanced drug solubility and stability: Liposomes are being engineered to enhance stability and solubility of poorly soluble medications. This is particularly useful for drugs that are difficult to formulate in traditional delivery systems.[69]
3. Applications in cancer therapy: Liposomes formulations are increasingly being used in cancer treatment. They can minimise harm to healthy organs and lessen systemic side effects by delivering chemotherapeutic drugs straight to tumour cells, recent studies have also explored combining liposome drug delivery with other therapies such as immunotheraphy for more effective cancer treatment.[70]
4. Nucleic acid delivery: Liposomes are being used to deliver nucleic acids such as siRNA, mRNA, for gene therapy applications. This approach has shown promise in treating genentic disorders and certain types of cancer .[71]
5. Vaccine delivery: Liposomes are being explored as carriers for vaccines including Mrna vaccines. Their ability to protect and deliver the vaccine components effectively makes them a valuable tool in vaccine development.[72]

Liposomal Delivery: Hybrid Liposomes

Assessing the impact of amphiphilic polymers on the properties of liposomes, hybrid liposomes made of phospholipid and amphiphilic chitosan have been developed the successful produce of the hybrid liposomes was confirmed by physicochemical properties as zeta potential, particle size, and shape [73] A combination of micellar and vesicular molecules in a solution of buffer can be ultrasonically sonicated to create hybrid liposomes.[74] Hybrid liposomes are lipid-based vesicles designed to encapsulate and deliver both hydrophilic and hydrophobic medications, which makes them extremely adaptable for medical use. These liposomes typically consist of

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phospholipid bilayers and may be modified with additional components such as polymers, surfactants, or other nanoparticles to enhance their properties.[75] There are some prominent uses of hybrid liposomes and these are:

1. **Drug Delivery:** Hybrid liposomes are more useful for targeted drugs delivery the involvement of polymers or nanoparticles in the liposomal structure improves drug encapsulation stability and effectiveness, which aids in regulated medication release, this is used for Cancer Therapy, antiviral , and antimicrobial drug delivery.
2. **Controlled Release of drug**; Hybrid liposome can provide a mixing lipids and polymers to produce a controlled release of medicinal medicines.Through improved patient compliance and a decrease in dose frequency, these systems can provide medications over a long amount of time [76]
3. **Gene Therapy**: Hybrid Liposomes have been explored for gene delivery applications. They offer protection for nucleic acids like RNA and DNA and they can facilitate cellular uptake. Cationic liposomes mixed with polymers or peptides enhance the delivery system.[77]
4. **Antimicrobial therapy:** Hybrid liposomes are used in antimicrobial therapy to enhance the delivery and activity of antimicrobial agents such as antibiotics or antifungals. The hybrid liposomal formulations can help to protect drugs from enzymatic degradation and enhance their action against resistant pathogens.[78]

REGULATORY AFFAIRS IN LIPOSOMAL DRUG DELIVERY

Nanoparticles and liposomal products have made important improvements to the treatment of many ailments and conditions. The creation of various forms of therapy regimens is aided by drug delivery systems.[79] Liposomal drug delivery is a field that has grown significantly over the years with a focus on enhancing the pharmacokinetics bioavailbility and therapeutic outcomes of various drugs. Liposomes as delivery systems are vesicular structures composed of phospholipid bilayers that encapsulate drugs[80].Regulatory affairs in liposomal drug delivery regulatory affairs surrounding liposomal drug delivery are complex and involve a comprehensive set of guidelines,due to the unique nature of these systems.[81].Both the formulation and manufacturing processes must meet specific criteria to guarantee quality, safety, and efficacy. Authorities such as the European Medicines Agency, the US Food and Drug Administration, and other global agencies have created frameworks for the approval and commercialization of liposomal formulations.[82].The frameworks include requirements on preclinical testing clinical trials, good manufacturing practices and post marketing survellince.[83]. The FDA and EMA require liposomal formulations adhere to strict GMP standards,ensuring consistent and high quality production. This includes defining specifications for Particle size, stability, encapsulation effectiveness, and zeta potential.[84] Liposomal drug products must undergo extensive characterization to demonstrate that the drug delivery system is reproducible and scalable. Stability studies including accelerated stability testing are necessary to ensure that liposomal formulations maintain their intergrity under various environmental conditions.[85].Liposomal formulation must undergo preclinical toxicity studies and animal pharmacokinetic studies. Preclincal results are crucial in determining whether the liposomal carrier improves the therapeutic efficacv and reduces toxicity compared to conventional drug formulations as well as potential immune response to liposome components.[86].Toxicological studies for liposomal drugs must be conducted in accordance with ICH guidelines especially concerning the assessment of the immunogenicity of liposomal formulations and the impact of residual solvents used in manufacturing[87].New drug applications or biologics licence applications are submitted to regulatory agencies for approval of liposomal formulations. Orphan drug designation may also apply to liposomal formulations for rare diseases offering incentives such as market exclusivity and faster approval timelines.[88, 89]

Future Perspectives

The future of liposome drug delivery is bright with ongoing innovations in materials, technologies and therapeutic areas. By improving their targeting stability and ability to co- deliver and genetic materials, Liposomes have the potential to completely change how many diseases, including cancer, are treated neurological disorders and genetic conditions[90]. Continued research into nanotechnology ,gene theraphy, and personalized medicine will further enhamce the capabilities of liposome based drug delivery system. Liposomes offer an opportunity to co-deliver multiple drugs or therapeutic agents that can act synergistically.[91]

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This could improve treatment outcomes in complex diseases such as cancer, where combination therapies targeting different pathways or mechanisms are often more effective.[92]Advances in biomarker profiling and individual patient characteristics will likely enable the developments of personalized liposomal drug delivery system. These formulation could be tailored to the patients disease profile genetic makeup and response to treatment optimizing therapeutic outcomes.[93]

II. CONCLUSION

Liposomes can improve hydrophobic medications' solubility and bioavailability this allows for the effective distribution of weakly water soluble chemicals that would otherwise be inaccessible. It is possible to create liposomes to deliver medications to particular tissues and cells. reducing off targets effects and minimizing toxicity. By encapsulating the drugs within a liposome it can reduce exposure to sensitive tissues decreasing adverse effects often seen with convectional drug administration methods. This is especially useful for medications that have a restricted therapeutic window.

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