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RECENT ADVANCEMENTS OF NEXT-GENERATION LIPOSOMAL CANCER DRUGS: A DETAILED REVIEW

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ABSTRACT

Liposomes are gaining traction as a new cancer therapeutic option. A liposome is the first nano-drug delivery system used in clinical trials for next-generation treatments, and it contains the phospholipid bilayer of three vesicles. Its technology is used to reduce drug toxicity, ADR and increase pharmacokinetic action, absorption ratio, drug distribution level. Coordinated theranostic manifestations in cancer treatment using multipronged liposomal drug delivery system has played a key aspect in the growth of cancer drugs such as Doxil, Daunoxome, and Depocyt. For the diagnosis and treatment of many cancers, nanomaterial drug carriers, such as liposomes, are being developed. The varieties of liposomes, composition, preparation, technology and use of cancer medications will be discussed in the upcoming review.

Keywords: Liposomes, Drug delivery, vesicles, Nanodrug, Cancer drugs, Technologies

1. INTRODUCTION:

Cancer is the most significant cause of mortality worldwide and its become century's most serious health issue. Every year, it claims the lives of millions of people worldwide, and its toll is growing at an alarming rate **[1]**. The most frequent

cause of death and disease in cancer patients is Surrounding tumor tissues, and distant organs are invaded by cancer cells. for several years, scientists have been studying the molecular process by which normal cells become cancer cells **[2]**. Because most genes have a modest mutation rate, the multiple harmful mutations identified in cancer cells are unlikely to arise sporadically during an average human lifespan **[3]**. Several Drug distribution methods have been developed to solve some of the issues associated with traditional cytoprotective medicines' lack of tumor selectivity and stability. Liposomal drug carrier systems are an advanced, mature, and adaptable technology, with numerous liposomal anti-cancer drug formulations licensed for cancer chemotherapy or in advanced phases of clinical research **[4]**. Many liposomal medicines are currently available for cancer treatment.

2.EFFECTIVE DRUG DELIVERY SYSTEM BASED ON LIPOSOMES:

Phospholipids in an aqueous media create closed bilayer structures for the first time and then it is used for the formation of Liposome. But one or even more lipid bilayers surround an aqueous region in a liposome and it is a first employed to investigate the physical behavior of biological membranes, such as lipid bilayer orientation, lipid physiochemical characterization, and ion transport across bio membranes **[5]**. Liposomes were initially injected as an intravenous route because of the high degree of its biocompatibility; The formulator might use different ways to make liposomes for other purposes, such as enhancing the performance of a drug's therapeutic index by increasing the percentage of drug molecules that target selective tissue or lowering the rate of drug molecules that reach hazardous areas **[6]**. In the liposome drug delivery system, more study was done for hydrophilic and hydrophobic surfaces in that Hydrophilic medications can be imprisoned in the aqueous interior of liposomes. In contrast, lipid-soluble Drugs can be incorporated into the phospholipid bilayer's hydrophobic core due to the unique structural features of liposomes **[7]**. The hydrophobic portion comprises two fatty acid chains with 10-24 carbon atoms each and 0-6 double bonds each **[8]**. Liposomes change from gel to liquid crystalline form at a transition temperature (TC). At the crystalline phase, the encapsulated medicines are released **[9]**. Only when the temperature is greater than the transition temperature can liposomes be produced but the transition temperature of a pure lipid liposome is 41.4°C. Lecithin, for example, has a wide transition temperature. The lecithin Kraft point, 58°C, is the highest temperature limit for liposome

synthesis. As a result, for liposome formation, such as thermosensitive liposomes, an average temperature of 41.4°C to 58°C is ideal. While the size of liposome vesicles is determined by phospholipid content **[8]**. Proteins, lipids (such as liposomes), carbohydrates, and synthetic polymers are carried by vesicles, which are microparticles or colloidal carriers. Vesicles offer some of the same advantages as drug-macromolecular conjugates (e.g., altered pharmacokinetics and biodistribution), but with the added benefit of a potentially higher drug dose. The cystalline that has received the most attention, Liposomes can indeed be made with various lipid compositions and forms, and they're nontoxic, degradable, and immune-inhibiting. During storage and use, however, many liposomes become unstable. Liposome stability can be improved by increasing or producing liposomal cholesterol **[10]**. During the assessment period, A particle size analyzer was used to determine the size of the particles of liposome vesicles and analyzer like Malvern Instrument, Malvern UK) and kept at 4 degrees Celsius in the fridge. Separately, for the cellular uptake investigation by a blank liposome formulation was made by adding rhodamine (10 g/10 mg lipid) to the lipid mixture to form a lipid film, then hydrating and extruding it. The surplus rhodamine in the extruded liposome formulation was removed using a PD-10 column **[11]**.

3.TYPES OF LIPOSOMES:

Liposomes are categorized according to their structural qualities, composition methods. The manufacturing process heavily influences liposome features such as size, number, and position of lamellae, lipid types employed, and liposome preparation conditions. This parameter affects the in-vitro and in-vivo properties of liposomes **[12]**.

3.1. according to structural parameters.

Liposomes are categorized structurally into three types of vesicles

Multilamellar large vesicles (MLV)

Small unilamellar vesicles (SUV)

Large unilamellar vesicles (LUV)

3.1.1. multilamellar large vesicles:

These liposomes have several lamellae and can range in size from 100 to 1000nm. An aqueous phase separates the concentric phospholipid bilayer membranes that makeup mlv.

3.1.2. small unilamellar vesicles:

There is only one lamella in these liposomes and is less than 0.1m in diameter. The smallest size that can be achieved is affected by the composition of the membrane and the aqueous medium. When the liposomes approach the minimal length, the size variation of the SUV population is limited.

3.1.3. large unilamellar vesicles:

These liposomes range in size from 0.1m to 1000nm, which is comparable to the size of living cells. These liposomes have a single lamella made up of a single lipid bilayer surrounding an aqueous compartment **[13]**.

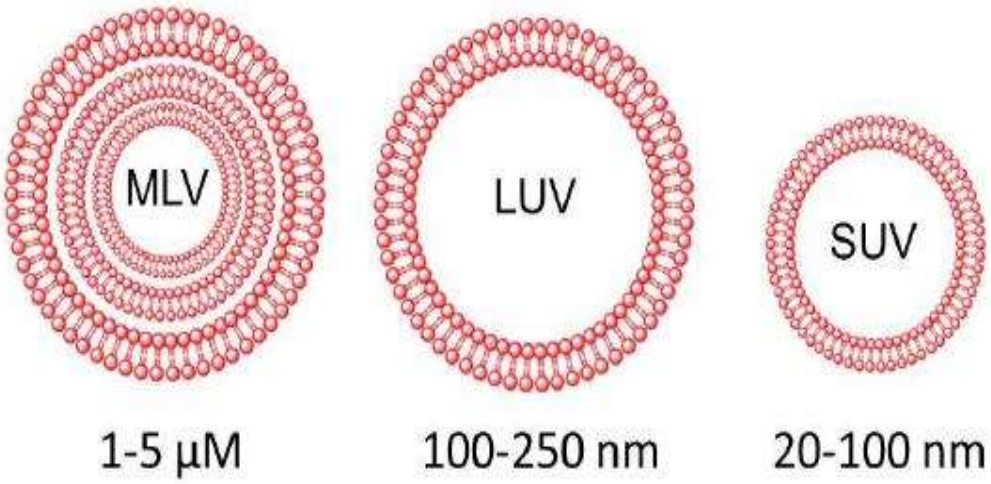

Figure 1: Structure of Vesicles

3.2. Composition of liposomes:

The primary composition of liposomes is based on two lipids, phospholipid, and cholesterol.

3.2.1. phospholipids:

Phospholipids are multifunctional compounds of the naturally occurring and are the primary components of biological membranes. Phospholipids play an active role in the growth and functionality of biological membranes when assembled as a lipid bilayer. They have a lipophilic/hydrophobic headgroup and a hydrophilic tail, making them amphiphilic. The sn-1 and sn-2 positions in phospholipids, the glycerol power base is esterified using fatty acids of various lengths and saturation. The last sn-3 position is esterified with phosphoric acid and then with alcohol. Depending on its structure, various forms of phospholipids are present in this alcohol. for example phosphatidylethanolamine(PE), phosphatidylcholine(PC), phosphatidylinositol(PI),phosphatidylglycerol(PG) **[14]**. The most used phospholipid in liposomes is known as Phosphatidylcholine(pc) and water does not dissolve them. In aquatic environments, they organize themselves in planar bilayer sheets to minimize the amount of water they absorb—the larger amounts of aqueous phase exhibit a negative interaction with the long hydrocarbon fatty chain **[15]**.

3.2.2. cholesterol:

The molecule of the amphiphilic organic sterol is known as cholesterol. The molecule in which the “hydroxyl group” can establish phospholipids contains

hydrogen bonds and a steroid ring with bulky Formation connected to the flexible carbohydrate. The 27-carbon molecule used to form cholesterol was found as the membrane of eukaryotic cells, where it accounts for 30–50 mol percent of the total lipid molecules. Cholesterol has been linked to various essential functions, membrane permeability modulation, elasticity with stiffness, membrane strength. The most commonly utilized sterol is cholesterol in liposome formulation because it can minimize liposome aggregation and increase the integrity of the liposomal membrane. Liposomes have higher natural fluidity and cell membrane movement than lipid monolayers because of their spherical three-dimensional form. To control membrane fluidity, promote bilayer stability, limit permeability of encapsulated active compounds, sterols such as ergosterol, stigmasterol, lanosterol, -sitosterol, and cholesterol have been added to liposomes. Sterol molecule is found within the bilayer of phospholipids. At C17, the sterol carbohydrate tail binds to the chains of hydrophobic fatty acyl, whereas the sterol hydroxyl group binds to the hydrophilic head group of phospholipids **[16]**. Cholesterol is essential in the formation of liposomes and it becomes a few of the plasma membrane's most significant structural components in mammalian cells. Through hydrogen bonding of fatty acids, cholesterol has been shown to significantly impact artificial vesicles of fluidity and permeability, increasing mechanical strength and cohesiveness. Cholesterol regulates the dynamics of lipid bilayers and is necessary for proper cell activity. Cholesterol interaction with membrane phospholipids reduces passive permeability to tiny molecules, improving membrane cohesion **[17]**.

4. PREPARATION OF LIPOSOMES:

Liposomes can be prepared by two method

4.1. Passive loading mechanisms.

4.2. Active loading mechanism.

4.1. passive loading mechanisms:

There are three types of passive loading mechanisms:

4.1.1. Mechanical dispersion method.

4.1.2. Solvent dispersion method.

4.1.3. Detergent removal method (removal of non-encapsulated material)

4.1.1. mechanical dispersion method

The following are types of mechanical dispersion methods:

(a)Sonication.

(b)French pressure cell.

(c)Freeze-thawed liposomes.

(d)Lipid film hydration by handshaking, non-hand. shaking or freeze drying **[18]**.

(a). Sonication:

Sonication is the most widely utilized process for preparing SUVs. In a passive

atmosphere, MLVs are sonicated using either a bath or a probe sonicator. The inner volume/encapsulation effectiveness of this approach is one of its key drawbacks, the likelihood of phospholipid and chemical degradation, elimination of large molecules, metal contamination from either the probe tip, and the chance of phospholipid and chemical degradation, and the presence of MLV in addition to SUV.

The Sonication can be further divided into two types;

1. Probe Sonication
2. Bath sonication

1. probe sonication:

A Probe sonicator tip is directly immersed in the liposome dispersion—approach of very high into the lipid dispersion primarily because of the energy input. Because localized heat is caused by energy coupling at the tip, the vessel must permanently be submerged in a water/ice bath. During Sonication for 0.5 to 1 hour, it is possible to de-esterify more than 5% of the total lipids. While utilizing Titanium could rip off from the probe sonicator, contaminating the solution.

2. bath sonication:

A bath sonicator is used to disperse the liposome dispersion in a cylinder. In comparison to Sonication via dispersal using the tip directly, the lipid dispersion can usually be easier under the control temperature. The sterile tank can be used for safe material to be sonicated, removed from the probe components, or in a completely inert environment **[19]**.

(b) french pressure cell:

From dilute or concentrated aqueous solutions of egg phosphatidylcholine, 1-40 mL of homogenous unilamellar liposomes can be made as a simple, quick, and almost quantitative procedure. At room temperature, Aqueous lipid suspensions are placed in a French pressure cell chamber and quickly extruded at 20,000 psi through a tiny opening. In a single pass, well over 70% of the squeeze-out lipid is converted into a homogenous population of single-wall bilayer vesicles; Reprocessing the lipid through all the French pressure cells results in a transformation of over 90%. Ninety-five percent of these liposomes had a 150-300 A (mean 200 A). At reduced pressure, In pressure cells, multilayered liposomes of tiny size (980 mean diameter; > 95 percent between 500 and 1,500 A) are created (3,000 psi). The French pressure cell was found to be successful in releasing nascent plasma lipoproteins from intact Golgi apparatus membrane compartments isolated from rat liver. This discovery showed that the French pressure cell might disperse multilayered suspensions of hydrated phospholipids into smaller liposomes **[20]**.

(c). Freeze-thawed liposomes:

MLVs are extruded through polycarbonate filters with identical pore sizes, resulting in a nanosized population with a higher internal volume than LUVs liposomes is known as freeze-thawed. Chromatographic purification was used to purify EggPC (Lipoid, Italy). MLVs were prepared by weighing appropriate amounts of egg PC (up to 300 mg) into a flask of a rounded bottom with or without cholesterol (99 percent Plus purity, Sigma, UK) and dissolving the phospholipid with chloroform (HiPerSolv, BDH, UK). Freeze-thawing effects on the size and lamellarity of PEG-lipid liposomes During the freeze-thawing process, MLVs containing PEG-lipid shrank in size and lamellarity, similar to MLVs without PEG-lipid. However, the addition of PEG-lipids increased these increases, even more, demonstrating that PEG-lipids had an effect on the EggPC bilayer during the freeze-thawing method. PEG-lipids facilitate the Formation of unilamellar structures during the freeze-thawing of vesicles **[21]**. Under vacuum, the Rotational evaporation in a water bath at 55°C for 15 minutes eliminated the chloroform. To remove any excess solvent, the flask was purged with nitrogen for 1–2 minutes; before the flask was flooded with nitrogen, spun gently in the water bath for 30 minutes, and shaken to form MLVs, glass beads were added to aid dispersion. The suspension had to be annealed in the water bath for another 2 hours before being stored under nitrogen in a refrigerator at 4°C **[22]**.

(d). Lipid film hydration by handshaking, non-hand shaking, or freeze-drying:

This procedure entails, A "Flash rotatory evaporator" or "handshaking" is used to cast the lipids from their organic solution as film stacks; the Formation of a film occurs. The film is then dried in a nitrogen-deficient environment. Following the aqueous phase dispersion of the film stacks, Only when liquid is hydrated, it swells and rips away from the flask's wall, vesiculating and forming multilamellar vesicles (MLV). Under the nitrogen canopy, liposomes are preserved. Large unicellular cystalline (LUVv) with larger trapping volumes can be generated, Rather than rotating movements, a stream of nitrogen provides agitation in this method, which differs from the handshake method. A lipid solution in a mixture of chloroform: methanol is spread throughout the conical flask with a flat bottom. At room temperature, nitrogen is passed through the flask to evaporate the solution without disturbing it. The flask is flooded with saturated nitrogen following the drying process until the dried layer's opacity vanishes within 15-20 mins. After Hydration, in the next stage, the bulk fluid added in lipid was swollen **[23]**.

4.1.2. Solvent dispersion method:

a) Ether injection:

At 55°C to 65°C, or under lower pressure, a lipid-mixed diethyl ether solution or an ether-methanol combination is progressively introduced into the encapsulating drug's aqueous solution. The liposome formation process results in the elimination of ether under a vacuum. The technique's principal drawbacks are the heterogeneous population (70 to 200 nm) and the exposition of organic solvents to encapsulated molecules at extreme temps **[24]**.

(b). Ethanol injection:

Rapid injection of an ethanol lipid mix into a significant amount of buffer, and The MLVs form instantly. The method's drawbacks include a diverse population (30 to 110 nm) and highly dilute liposomes. Because ethanol creates an azeotrope with water removing all of it is complex, and even tiny levels of ethanol, the probability of specific physiologically active macromolecules inactivating are considerable **[25]**.

(c). Reverse phase evaporation method:

This approach benefits advanced liposome technology by creating aqueous space-to-lipid ratio liposomes and entangling the considerable aqueous substance as a proportion offered for the first time. Inverted micelles are used in reverse-phase evaporation. A type of micelles is generated in an inverted position by sonicating an organic phase containing those amphiphilic molecules and a buffered aqueous phase that will contain water-soluble compounds that will be enclosed within the liposomes. The delayed removal of the organic solvent causes these inverted micelles to become sticky and gel-like. At a critical point in this process, the gel state collapses, disrupting part of the inverted micelles. Evaporation in the reverse phase A variety of lipid formulations can be used to create liposomes and a four-fold higher aqueous volume-to-lipid ratio than hand-shaken or multilamellar liposomes. Liposomes form when the leftover solvent is separated during rotating evaporation under decreasing pressure. High encapsulation effectiveness of up to 65 percent can be attained with this approach in an ionic-weak medium, such as NaCl concentration: 0.01 M. Small, significant, and macromolecules have all been encapsulated using this technology. The main disadvantage is materials come into interaction with organic solvents and are enclosed with subjected to brief durations of Sonication. These circumstances may cause DNA strands to break or some proteins to become denaturated **[26]**.

4.1.3. Detergent removal method (removal of non-encapsulated material:

(a). Dialysis:

Detergents with high critical micelle concentrations (CMC) dissolve lipids. So

when detergent is removed, those micelles become more phospholipid-rich and finally clump together to develop LUVs. Dialysis was used to eliminate the detergents with Commercial equipment named LipoPrep (Diachema AG, Swiss), as dialysis system format, is available to remove detergents. Dialysis with dialysis bags immersed in large detergent-free buffers is also possible (equilibrium dialysis) **[27]**.

(b). Detergent (cholate, alkyl glycoside, triton x-100) removal of mixed micelles (absorption):

Shaking a Micelle solution containing beaded organic polystyrene adsorbers, such as XAD-2 beads (SERVA Electrophoresis GmbH, Heidelberg, Germany) and Bio-beads SM2 (Bio-Rad Laboratories, Inc., Hercules, USA) achieves detergent absorption. The primary advantage of employing detergent adsorbers is that they could still remove detergent with a lower CMC, which isn't completely depleted **[26]**.

5. LIPOSOMES TECHNOLOGY:

This section focuses on liposome technologies that have been developed expressly to create therapeutically applicable liposome-based products. Each technique has its characteristics to optimize drug delivery by preserving the therapeutic agent's specific capabilities, thereby reducing its downsides.

5.1. Stealth liposome technology:

The use of stealth technology in developing a drug delivery device that resists identification by mononuclear phagocytes has been studied. The polymer(s) strands are connected to the method in this system or drug molecules, which can help to increase the effectiveness and safety of medicinal agents. PEGylation refers to converting polyethylene glycol (PEG) into another substance and incubating a reactive PEG derivative with the target molecule is a standard method of PEGylation. Because the active moiety of a liposome is covalently linked to a PEG, it is protected from the receiver's immune system; immunogenicity and antigenicity are both reduced as a result of this. It alters the physicochemical properties of active moiety as well. Such as alterations in overall hydrodynamic size, As a result, renal clearance is reduced, and the time it spends in circulation is extended. It also gives hydrophobic medicines hydrophilicity and reduces dosage frequency **[28]**.

5.2. Non-pegylated liposome technology:

Non-PEGylated liposome (NPL) is a novel drug delivery technology that combines the benefits of PEGylated liposomes with none of the PEG has specific adverse side effects, including hand-foot syndrome (HFS). In comparison to standard DOX and Doxil®, Injection of NPL Doxorubicin (NPLD) has a higher Profiles of safety. Not

only does NPLD lower the toxicity level of DOX in cardiac, However, it also reduces Doxildose-limiting ®'s effects, such as HFS. A mixture of techniques is used to achieve the NPLD liposome's specialized composition and a one-of-a-kind manufacturing technique, providing the appropriate physicochemical features. Compared to traditional DOX, NPLDs have a longer circulation time and less cardiotoxicity. NPLD doesn't exist PEG coating because They don't induce the agonizing HFS that PEG-DOX has as a dose-limiting side effect **[29]**.

5.3. DEPOFOAM™ liposome technology:

Pacira Pharmaceuticals is a pharmaceutical company based in Parsippany, New Jersey, United States of America, introduced DepoFoamTM, a unique extended-release medication delivery technology. DepoFoamTM is the underlying technology of a number of commercially accessible technologies, including Depocyt®, DepoDurTM, and Exparel®. DepoFoamTM technology encapsulates pharmaceuticals without changing their molecular structure in a multivesicular liposomal platform. The multivesicular liposomes release the drug(s) for1–30 days. DepoFoamTM comprises microscopic granular spheroids (3–30 m), and lipid particles with only one layer made up of a bound medication are held in a honeycomb of "non-concentric inner aqueous chambers." A single bilayer lipid membrane separates several non-concentric aqueous chambers in each particle. Synthetic analogs of naturally occurring lipids are used to create bilayer lipid membranes that separate each partition from the adjacent sections (DOPC, DPPG, cholesterol, triolein, etc.) **[30]**.

6. ADVANTAGES OF LIPOSOMES:

a. Therapeutic index of drug and efficacy will increase.

b. Liposomes are a simple fabrication process and cost-effective.

c. It may reduce size polydispersity, and products are unilamellar and of controlled size with high encapsulation efficiencies.

d. It also increases both the pharmacokinetics and therapeutic index.

e. Liposomes are used as the drug delivery carriers for sustained and controlled.

7. DISADVANTAGES OF LIPOSOMES:

a. Phospholipid is subjected to oxidation and hydrolysis.

b. Encapsulated medicines leaking and fusing, which is a disruption in the stomach

8. LIPOSOMES AS A CANCER TREATMENT TARGETED DRUG DELIVERY SYSTEM:

Liposomal vesicle advancements have resulted in being Controlled medicine release, and targeted drug delivery is used in this study (disease-specific localization).

First-line therapies for cancer are surgical resection, radiation therapy, and chemotherapy; this characteristic is highly beneficial. Some cancers necessitate systemic chemotherapy treatment. Until now, APIs used the majority of chemotherapy be exceedingly hazardous to both cancerous and non-cancerous cells. As a result of the free medicine being administered straight into the bloodstream that circulates the body, individuals suffer from many adverse effects and limits. Cancerous and non-cancerous tissues both absorb the chemotherapy agent, causing a lot of damage to several hearts, kidneys, liver and other internal organs. As a result, to maximize the quantity of medicine taken up by cancer cells, patients are sometimes given the highest possible dose of chemotherapy **[31]**. Encapsulating chemotherapeutic drugs into liposomal structures can reduce the medication's natural tissue absorption and boost its therapeutic index. Liposomes can be passively targeted to concentrate on the tumor (typically for 24–48 hours), to enhance the EPR effect, in which leaky tumor arteries connect with absent lymph outflow **[32]**. Liposomes could actively target cancer tissues via an antibody-based technique. By binding antibodies specific towards the liposomal surface, this can be accomplished known as immunoliposomes (ILP) which are cancer-specific or endothelial cells of tumor vasculature **[33]**. By activating medication releases at a temperature near to the lipid phase transition temperature of liposomes; The efficacy of a liposomal formulation for medication delivery could be improved by local hyperthermia. by increasing blood flow to the active region, by increasing endothelial permeability to liposomes, enhancing liposome amassing at the point of action, and by increasing target cell permeability to API produced from liposomes **[34]**. the pore size of endothelial tissues of the renal glomerulus is 40–60 nm. however, the Sinusoidal endothelium of a liver and spleen, on the other hand, has a pore size of about 150 nm; these liposomes are easily removed from circulation by macrophages within spleen and liver **[35]**. DOX-loaded magnetic liposomes (citric acid-coated magnetic nanoparticles) have also been used in the combination of chemotherapy and thermotherapy. By rotary evaporation and ultrasonication, Magnetic liposomes with a size of 130 nm have been developed using hydrogenated soy phosphatidylcholine /cholesterol and DOX.

In vitro cytotoxicity and hyperthermia experiments on cancer that affects the colorectal revealed the magnetic liposomes were toxicity killing Approximately 56% of tumor cells **[36]**. Vaccination-based cancer immunotherapy isn't a standard cancer

treatment option right now. Many scientists are looking for novel techniques & formulations which is helpful for the application of immunotherapy for cancer treatment **[37]**. Liposomes are a type of targeted medication that can diagnose cancer. Some extracellular enzymes, such as secreted phospholipase A2 (sPLA2) (elevated in the prostate, breast, and pancreatic cancers), matrix metalloproteinases (MMPs) (specifically, MMP-2 and MMP-9 promote in breast, colorectal, pancreatic, and lung cancers), urokinase plasminogen activator (uPA) (elevated in several human cancers, including breast, bladder, colon) **[38]**.

9. APPLICATION OF LIPOSOMAL DRUGS IN CANCER TREATMENT:

Chemotherapeutics are the initial treatment for cancer, other treatment for cancer have limitations because of poor tissue selectivity, unrecognized toxicity, and a small therapeutic index with a high risk of developing drug resistance. Most of the circumstances can cause cancer treatment to fail spectacularly. The use of nanoscale liposomal preparations has been shown to help with drug delivery onto tumor cells **[39]**. The first approved drug in liposomal by the FDA is Doxil, and it is unrelated by three principles: (a).PEGylated nanoliposomes are used to avoid RES and prolonged drug circulation (b).transmembrane ammonium sulfate gradient by doxorubicin for high stability, which allows drug release for drug release cancer. (c). the high -t(m)pc &cholesterol composed by Liquid order in lipid bilayer **[40]**. **Table 1**, Represent the liposomal drugs for cancer includes the route of administration, drug delivery system technology, indication.

9.1. Doxil:

Doxil®, a nano-drug delivery based on Stealth liposome technology also the first nano-drug delivery device to be authorized by the FDA, and it contains Doxorubicin hydrochloride. Doxil® was created by Sequins Pharmaceuticals in the United States in 1995 to treat metastatic ovarian cancer, breast cancer, and HIV-related Kaposi's sarcoma as an intravenous injection. To reduce the risk of infusion responses, Vials with only one dosage containing 20 mg/10 mL and 50 mg/25 mL are available then administered by intravenous infusion 1 mg/min as a starting point **[41]**. When taken alone or in combination with other anti-cancer medications, doxorubicin is used by anthracycline type for significant anti-cancer activity, which could be effectively treated at various tumor tissues. Breast cancer patients receiving neoadjuvant chemotherapy, anthracyclines are used in conjunction with doxorubicin. Although their efficacy has been established, some issues that arise during treatment, such as

cardiac toxicity, have yet to be resolved. Clinical trials have also confirmed the effectiveness of a PLD/NPLD combined regimen in breast cancer neoadjuvant chemotherapy, particularly in patients who have an HER-2 receptor that is positive. In parallel clinical investigations, PLD contains doxorubicin encapsulated in small unilamellar vesicles with a diameter of about 100nm, and NPLD consists of a doxorubicin citrate complex in unilamellar vesicles of 150nm[4]. PLD and NPLD were evaluated, and Both exhibited good efficacy in most physiological phases of breast cancer and each pathological stage of breast cancer. PLD/NPLD should be used instead of standard doxorubicin for treating tumors like breast cancer, ovarian cancer, according to a meeting of oncologists, pharmacologists, and cardiologists convened in Florence **[42]**.

9.2. Daunoxome:

DaunoXome® is a single-dose vial of DNR citrate liposomal formulation of the intravenous route. It is germ and pyrogen-free and used to develop the treatment of AIDS- RELATED Kaposi's sarcoma **[43]**. It also belongs to the anthracyclines family; 50 mg of DNR base is contained in liposomes comprising 168 mg cholesterol and 704 mg di-stearoyl phosphatidylcholine (DSPC) in each dose of a single vial. 2125 mg sucrose, 94 mg glycine, and 7 mg calcium chloride dihydrate are present in the aqueous dispersion in these liposomes (25 mL/vial). Liposomes have a neutral charge, and a bilayer made up of “DSPC and cholesterol” in a 2:1 molar ratio, with an average particle size of 45 nanometers. The weight ratio of lipids to drugs is 18.7:1. (total lipid: DNR base) corresponds to a DSPC: Cholesterol: DNR molar ratio of 10:5:1 **[44]**. DNR's particular lipidic formulation had to be proven to create strength of good physical with liposome, Increasing the stability of DNR contained in the formulation and reducing protein binding **[45]**. The DaunoXome® particles reduce the reticuloendothelial system (RES) absorption are small and relatively neutral, resulting in longer drug circulation **[46]**. Myelosuppression, esophagitis, stomatitis, alopecia, cardiotoxicity, nausea, vomiting, mucositis, and diarrhea are all common side effects of daunorubicin treatment. If extravasation occurs, it can cause serious harm to soft tissue **[47]**. Liposomal DNR was investigated for safety, pharmacokinetics, and probable usefulness for treating a patient with HIV-associated Kaposi's sarcoma. They discovered that DaunoXome® was most effective at dosages ranging from 40 to 60 mg/m2. From this data, both mean plasma and area under the curve (AUC) varied 114.91 to 120.1 g h1 mL **[48, 49]**. Daunorubicin is a NON-PEGylated liposomal technology used for treating

AIDS RELATED &kills the Tumor cells in the specific site of an organ through a liposomal drug delivery system.

9.3. Depocyt:

The antimetabolite cytarabine encapsulates multivesicular lipid-based particles in DepoCyt® (cytarabine liposome injection). Cytarabine is also known as cytosine arabinoside and comprises 4amino-1—D-arabinofuranosyl-2(1H)-pyrimidinone (C9H13N3O5, molecular weight 243.22). The method used for the preparation of Depocyt was Depofoam technology. DepoFoamTM technology is made up of small spherical particles (3–30 m) that can encapsulate hydrophilic chemicals like Ara-C. The aqueous foam, which has 96%, and biodegradable lipids with 4% make up all such lipid foam-based particles Cytarabine encapsulated in multivesicular liposomes for injection as a treatment for NM may provide a therapeutic advantage. DTC 101 (DepoCyt, cytarabine liposome injection) is a sterile, injectable suspension of cytarabine, an antimetabolite, encapsulated in multivesicular, lipid-based particles (DepoFoam technology). DepoFoam is a proprietary drug-delivery method that allows medicinal ingredients to be released over time. Compared to normal cytarabine or methotrexate, DepoCyt 50 and 75 mg intrathecal infusions for two weeks sustain cytotoxic cytarabine concentrations in the CSF, which may be beneficial in the treatment of NM. The deposit can be given every two weeks due to its better pharmacokinetic profile; This prolongs when therapeutic cytotoxic doses of cytarabine (>0.1 g/mL) are present **[30]**. the ADR effect 50% for cytarabine Fever, 38% for headache, 38% for back and neck discomfort, and 38% for nausea or vomiting were among the symptoms of grade 1–2 magnitude 25 %.

In about 15% of individuals, 3–4 degree nausea or vomit occurred **[50]**. deposit is administered intrathecal, unlike unencapsulated cytarabine, provides a significant pharmacokinetic benefit, maximizing the S-phase–specific cytotoxic medicines that have therapeutic promise in the cell cycle. Furthermore, the novel formulation's longer CSF t1/2 of cytarabine may enable less frequent dose given, which is particularly advantageous for intrathecal delivery. Compared to intrathecal cytarabine or methotrexate, The use of DepoCyt appears to improve the total response rate and the duration to progression, length of response, and patient survival having NM related to Neoplastic meningitis, according to findings from a controlled trial **[30]**.

Table 1: Cancer Drugs

CLINICAL NAME	ACTIVE AGENT	DRUG DELIVERY TECHNOLOGY	INDICATION	ROUTE
DOXIL (1995)	doxorubicin	STEALTH-liposome technology	Ovarian cancer, breast cancer, kaposis sarcoma.	Intravenous Route.
DAUNOXOME (1996)	daunorubicin	NON-PEGylated liposome technology	Aids-related kaposis sarcoma	Intravenous Route.
DEPOCYT (1999)	cytarabine	Depofoam technology	Neoplastic meningitis	Intratechal Route.
MARQIBO	vincristine	conventional technology	Acute lymphoblastic leukaemia	Intravenous Route.
LIPUSU	paclitaxel	Albumin bounded drug conjugates	Solid tumor, Breast cancer	Intravenous Route.

9.4. Marqibo:

Marqibo it is action mechanism is well-defined, documented anti-cancer effectiveness vincristine (VCR), a staple of treatment for acute lymphoblastic leukemia, hematologic malignancies, and solid tumors. Vincristine is a liposomal injection made by conventional technology. VCR is an anti-cancer medication that works in the M-phase of the cell cycle and is dose and exposure time-dependent. An elimination pattern of exponential characterizes standard VCR's pharmacokinetic profile; given an initial distribution that isn't too long, A lower half-life for elimination is followed by a prolonged half-life for elimination. VCR does have a large distribution volume, indicating that it is extensively spread and binds to tissue. In addition to clinical value as a standalone treatment, maybe as part of a multi-agent regimen, these qualities would reduce medication exposure and administration to target tissues. Marqibo® is a sphingomyelin and vincristine sulphate nanoparticle formulation based on cholesterol that has been developed to circumvent dosage and pharmacokinetic constraints of traditional VCR **[51]**. VSLI (Vincristine sulfate liposome injection), Marqibo®, is a proprietary VCR nanoparticle formulation based on sphingomyelin and cholesterol developed to address the dosage and pharmacokinetics constraints of regular regularity VCR. As previously stated, Longer exposure levels result in a higher percentage of cells progressing to mitosis, when VCR exerts its cytotoxic effects, resulting in increased in vitro cytotoxicity **[52]**. VSLI is a unique VCR nanoparticle formulation based on sphingomyelin and cholesterol that was created to be distinct from regular VCR and overcome its dosage and pharmacokinetic constraints. It showed that VSLI is safe, tolerable, and has potential activity in individuals with advanced relapsed/refractory leukemia and lymphoblastic. The FDA recently granted VSLI expedited approval **[51]**.

9.5. Lipusu:

In 2006, lipusu became the first paclitaxel injectable liposome approved in China. It is involved in the technology of albumin bounded drug conjugates. It kept the free drug's growth-inhibitory efficacy while lowering the toxicity **[53]**. Paclitaxel is an alkaloid that suppresses endothelial cell proliferation, motility, and tube formation by stabilizing microtubules **[54]**. Liposomes are small artificial vesicles made up of one or more layers of lipid that are used in the body to deliver drugs, vaccines, and enzymes to specific cells. Liposomal drug delivery technologies have recently progressed from doxorubicin encapsulation to paclitaxel encapsulation to reduce systemic toxicity **[55]**. Chemotherapeutic treatment may cause the patients with extreme to life-threatening adverse effects. Dose-limiting toxicity and aqueous insolubility in the therapeutic administration of paclitaxel are its drawbacks. In recent years, many researchers have looked into the best paclitaxel premedication **[56]**. A traditional premedication treatment for paclitaxel-associated hypersensitivity involves 12 and 6 hours before paclitaxel, 20 milligrams dexamethasone was administered orally, as well as H1 and H2 antagonists given before paclitaxel. Although this approach effectively prevents life-threatening hypersensitivity events, mild reactions (such as flushing and rash) Around 40% among all sufferers still have this problem. Approximately 3% of sufferers get potentially deadly response **[57]**.

10. CONCLUSION:

The liposome drug delivery system is an excellent cancer therapy option, and the technology utilized in medications is highly recommended. In the liposomal delivery increase the bioavailability and accumulation of a drug at a site, Doxil drug is used as effective liposomal formulation of stealth technology for treating each cancer stage to and also drugs like Daunoxome,Depocyt,Marqibo,Lipusu has the different techniques to effectively next-generation medication for tumor cells, In Market, Some medication delivery techniques based on liposomes are already available, while many others are now undergoing research and clinical studies. The success of liposomal formulations in anti-cancer therapy is evidence that liposomes have made a name for themselves in the world of medicine for nano carrier-based drug delivery systems.

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