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Review Article

EXPLORING LIPID-BASED DRUG DELIVERY IN CANCER THERAPY VIA LIPOSOMAL FORMULATIONS

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ABSTRACT

In many countries across the world, cancer is a leading cause of death. Cancer is the biggest cause of death worldwide, with approximately 10 million fatalities expected in 2020, accounting for nearly one in every six deaths. Mutations in ~300 human genes can unleash cell division, potentially leading to cancer. The effectiveness of existing conventional therapies for a number of cancers is, however, inefficient in terms of safety and efficacy. Medication systems based on lipid can be configured to treat tumors passively with increasing safety by reducing toxicity and increasing efficacy by target drug delivery. Lipid-based drug dosage form is the new identified technological design to overcome problems such as water-soluble solubility and bioavailability. A wide range of product specifications determined by indication of disease, route of administration, price evaluation, safety, toxicity, and efficiency could be customized to lipid formulations. This analysis explores the current state of lipid drug delivery studies, including the production of cancer liposomes, different cancer-focused strategies, and liposomal formulation of numerous anti-cancer drugs.

Keywords: Lipid, Drug delivery systems, Liposome, Cancer, Treatment.

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INTRODUCTION TO CANCER

Nowadays, cancer is treated mostly with chemotherapy, surgery, and radiotherapy. Chemotherapy treatment was identified for cancer in the early 20th century [1]. German scientist Paul Ehrlich coined the term "chemotherapy" mainly interested in alkylating agents and described with the term to describe the chemical treatment of disease. Globally, cancer remains mostly cause of death [2]. There were approximately 7.6 million cancer deaths worldwide alongside 12.7 million new cases recorded worldwide annually by The International Agency for Research on Cancer [IARC] [3]. Chemotherapy has been most commonly used to treat cancer. Chemotherapy for cancer means preventing cancer cells from dividing, growing, and spreading. It acts by killing the dividing cells. A wide range of chemotherapeutic agents is used to achieve these goals [4]. In certain ways, the effectiveness relies on the treatment stage. The advantages of chemotherapy usually outweigh the risk of side effects [5].

The development of cells combined with malignant activity is predominantly extreme: Invasions and metastases (other characteristics) [6]. It is mainly associated with the relation between genetic vulnerability and environmental variables [7]. Through all these circumstances, oncogenes and cancer suppressors have accumulated genetic changes that offer cancer cell malignancy, such as uncontrolled proliferation [8].

Most chemotherapy drugs act by deteriorating the mitosis and targeting cells that are rapidly dividing. Since the cells are damaged, those drugs are called cytotoxic [9]. Chemotherapeutic drugs decrease mitosis through numerous mechanisms such as damaging DNA and cell division inhibition [10]. Chemotherapy kills cancer cells by inducing a predetermined sort of cell death termed apoptosis.

During cancer therapy, tumors with rapid expansion become more susceptible to chemotherapy, since most of the targeted cells undergo cell division at all times [11]. Tumors having modest growth like lymphoma indolent react more mildly to treatment. Based on the subclonal tumor populations, heterogeneous malignancies could also show variable responses to chemotherapy regimens [12].

The anti-cancer actions of chemotherapy are also influenced critically by various immune system cells [13] such as Oxaliplatin and cyclophosphamide intervene tumor cells and are recognizable by the immune system that mobilizes antitumor-like immune cells [14]. Chemotherapeutic agents causing the death of cancer cells may render non-responsive cancers receptive to immune control therapies [15].

Cancerous cells are likely to nurture rapidly, and chemotherapeutic drugs are acting by killing the fastest-growing cells. As these anti-cancer drugs are free, so it travels throughout the human body, acting, and killing the other normal fastest-growing cell too [16]. Damage to normal cells causes severe adverse effects. Here adverse effects are not always bad as it is an effect of the chemotherapeutic drug but to normal cells [17]. The normal living cells of the body which are fastest growing and likely to be damaged and affected by chemo drugs are:

1. Bone marrow [Blood-forming cells]
2. Hair on the body
3. Normal cells in the gastrointestinal tract, mouth, and system of reproductive (Fig. 1)

Some of the chemo drugs/molecules can harm the cells in the bladder, heart, lungs, kidneys, and nervous system. Along with this patient can take some of the medicines which can protect the adverse effect of chemo drugs to the normal cell [18].

Almost all the anti-cancer drugs/molecules used in chemotherapy are highly cytotoxic to both cancerous as well as normal cells [19]. Therefore, specific site targeting with tumor vasculatures is crucial for cancer decrement. Encapsulation of anti-neoplastic molecules inside liposome delivery gives protected podia for the site-specific delivery of antineoplastic drugs/molecules for the main usage of cancer (Fig. 2) [20].

Because encapsulation of anti-cancer drugs will help to minimize the cytotoxic adverse effect of the drug to a normal cell with target-specific delivery [21,22]. The drug inside liposome delivery offers the opportunity of growing effectiveness while decreasing the toxic adverse effects of antineoplastic agents [23-26]. Liposome with encapsulation of drug can impact the tissue distribution of drug with its

pharmacokinetic behaviors. They were one of the first to be formed into nanosized restorative items and are the original of nanoparticles based on lipids [27-30]. Alec D. Bangsham and his associates introduced an investigation of fluid lecithin gems in the long history of such particles in 1965 [24,31]. Univalent cations and anions have first been demonstrated to disperse liquid lecithin crystals from spontaneously forming in the same manner as the propagation of ions over a biological membrane [32-34]. Such systems became an effective model for cell membrane studies due to the capacity of these liquid lecithin crystals or spherulites to encapsulate and release solutes [31-33]. The successful size-dependent properties were demonstrated by the lipid-based drug delivery systems [LBDDS] [34,35]. LBBDS is being encouraged by the obvious benefits of increased biocompatibility and flexibility. These devices are economically and feasible for the formulation of topical, nasal, pulmonary, or parenteral pharmaceuticals. Due to the disease conditions, how the lipid formulations are manipulated and cost stability, toxicity and efficacy, they could be adjusted in different ways to satisfy a large number of product requirements [36,37].

INTRODUCTION TO LIPID-BASED DRUG DELIVERY SYSTEM

In the '90s, Paul Ehrlich [A German scientist], declared the word "magic bullet," which means different chemical vehicles/carriers which possess the ability to destroy damaged cells without any effects on live cells [10]. Many of the approaches which are depending on the number of chemical and physical properties were adopted to improve the specificity through drug delivery technology [38]. Lipid-based drug delivery is tiny spheroidal vesicles that are created from natural phospholipids and cholesterol. As liposomes are tiny, biocompatible, lipophilic as well as hydrophilic, they are good systems for drug delivery [39]. Liposome characteristics might vary according to lipid content, size distribution, zeta potential, and manufacturing technique. In addition, the main component of bilayer components such as phospholipids and cholesterol controls the "sturdiness" or "flexibility" and zeta of the liposome [40].

Unsaturated phospholipids species origin from supernatural sources such as soybean or egg phosphatidylcholine are far more penetrable and less stable bilayers, whereas the saturated phospholipids, such as dipalmitoylphosphatidylcholine form an intact, rather resistant bilayer structure [41-45].

After mixing the lipids in an aqueous medium, it constitutes a closed configuration with vesicles due to its intrinsic properties. Any of the hydrophilic or hydrophobic drugs can be encapsulated inside these liposomes. As phospholipid is amphipathic with an aqueous medium, the thermodynamic phase properties and self-inherent features of closing will impact the entropically focused impounding of their hydrophobic units into spherical bilayers. These films are called as lamellar (Fig. 3) [46-49].

Among all lipid-based drug delivery, liposomes are convinced as a sphere-shaped vesicle having a size between 30 nm to some micrometers. Liposomes contain one or more lipidic bilayers in which polar head parts are arranged in a way to the inner and exterior parts of the aqueous phase [50-53]. Along with this, self-accumulation of the polar head is not incomplete to conventional bilayer structures which may be governed by temperature, shape, and ecological and preoperational conditions but may self-closed into several types of colloidal small particles [54].

In cosmetic and pharmaceutical industries liposomes are widely utilized as carriers for many drugs and materials. The use of liposomes in food and farming productions for encapsulating to produce drug delivery systems that can capture unsteady compounds [e.g., antimicrobials, anti-cancer, flavors, antioxidants, and bio-active elements] and protect their functionality is broadly studied. Both hydrophobic and hydrophilic compounds can entrap in Liposomes, to avoid degradation of the entrapped drug/molecules and release of the encapsulated at designated targets [55,56]. Because of liposome's non-toxicity, biocompatibility, biodegradability, and skill to entrap both hydrophilic and lipophilic drugs [57] and abridge targeted drug delivery to cancerous tissues, it is superior as an investigational system and commercially as a drug-delivery system. Many studies have been conducted and continue on liposomes to decrease drug toxicity and/or site-specific delivery [58].

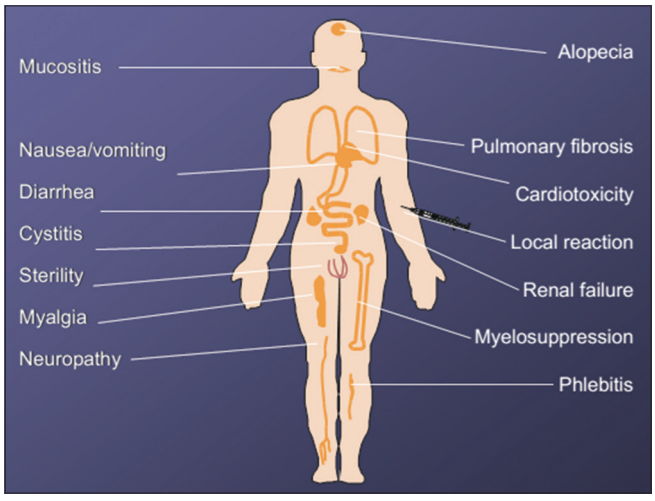

Fig. 1: Side effects of chemotherapy

CLASSIFICATION OF LIPOSOMES

The breadth of liposomes varies from 0.025 μm to 2.5 μm. Furthermore, they are made of one or more bilayer vesicles. In determining, the circulation half-life of liposomes size of the vesicle is a critical parameter and the amount of drug encapsulation inside the liposomes is affected by both size and number of bilayers [59].

Considering the number of vesicles and particle size of vesicles in the liposome, it can also be classified as categories: Multi-lamellar vesicles/bilayer [MLV] and uni-lamellar vesicle/Bilayer. Uni-lamellar vesicles/bilayer also classified into two subcategories: Large uni-lamellar vesicles/bilayer [LUV] and small uni-lamellar vesicles/bilayer [SUV]. The vesicles with one phospholipid bilayer sphere enfolding the aqueous solution are uni-lamellar vesicles [60]. The vesicles which have an onion-type structure are multi-lamellar liposomes. Typically, several uni-lamellar vesicles/bilayers will be customized on the inside of the other vesicles with smaller size and making a multi-lamellar structure of concentric phosphor lipid spheres divided by bilayer of water (Fig. 4) [61].

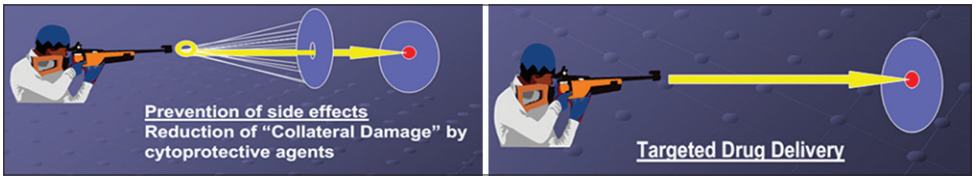

Fig. 2: Targeted drug delivery of chemotherapy

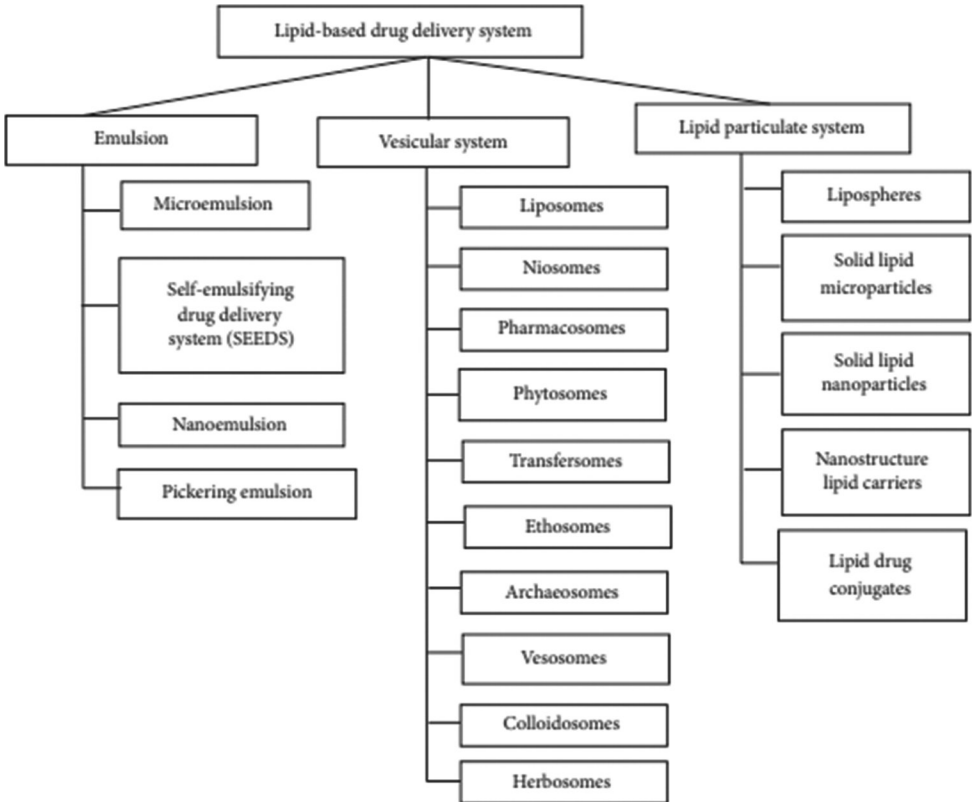

Fig. 3: Different types of Lipid-Based drug delivery system

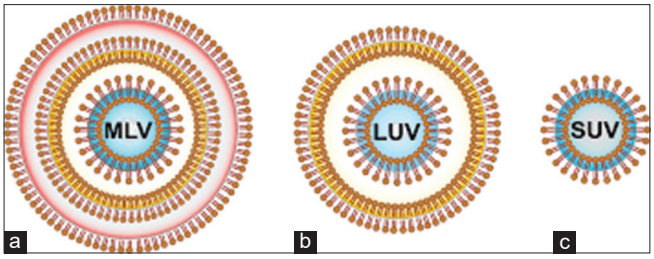

Fig. 4: (a) Multi-lamellar vesicles, (b) large uni-lamellar vesicle, (c) small uni-lamellar vesicles

DIFFERENT METHODS OF LIPOSOME PREPARATION

Liposomes are prepared by many different approaches, which contain the usage of power-driven liposome preparation, solvent evaporation, detergent removal from phosphor lipid/detergent vesicle mixtures [62]. For the preparation of liposome, quantities, and classes of phosphor lipid, time of hydration of vesicles, and ionic and zeta potential properties of the aqueous medium, are key features that regulate the final liposome structure [63].

Multi-lamellar vesicles preparation

Multi-lamellar vesicles have the easiest method of preparation in all liposome manufacturing methods. For this type of method, liposome generation can be done using solvent for the dissolving of phospholipid and drying/evaporation of the resulted mixture. The amalgamation of phospholipids such as cholesterol, egg lecithin, and phosphatidylcholine/phosphatidylglycerol in a molar ratio of 0.99:0.89:0.1 is used, respectively. In a typical ratio of 2:1 and 1:1 chloroform or a mixture of chloroform and methanol/ethanol are used, respectively. Primarily, every lipid constituent needs to be solubilized in the solvent mixture individually, after mixing them in a suitable amount with the other solubilized lipid compound to check the even mixing of the lipids in the mixture. Subsequently, nitrogen gas is to be used to make/generate a thin film from the mixture. Likewise, in above to eradicate any residue of the solvent mixture, the thin film of the lipidic compound is adequate to dry entirely in a closed chamber till complete evaporation [64,65].

Uni-lamellar vesicles preparation

In liposomes uni-lamellar vesicle/bilayers are the one widely used and most popular type. Uni-lamellar liposome permits a uniform distribution of encapsulated molecules within a particular internal aqueous medium. The uni-lamellar liposome can be prepared by many methods such as extrusion through membrane filters, ethanol injection, ultra-sonication, freeze-thaw, and detergent methods. Many scientists have used a combination of diverse small uni-lamellar vesicles/bilayer [SUVs] populations to achieve ternary giant uni-lamellar vesicle/bilayer with even property [66-68].

Giant Uni-lamellar vesicles manufacturing

Giant liposomes can be prepared by several methods using, non-electrolyte, distilled water, and/or zwitterions. The attendance of ions imparting a surface charge causes attraction between members and prevents the separation of the membrane vesicles during the re-hydration and swelling process. There is much literature for the manufacturing of giant liposomes, using physiological strength buffers/media (Table 1). GUV can be prepared and manufactured using many techniques such as electro formation, giant uni-lamellar liposomes prepared in quick manufacturing, by physiological buffer/media for preparation of giant uni-lamellar liposomes/vesicles, and osmotic shock method. Furthermore, many scientists have used microfluidic as size reduction and reparation of GUV and mechanical characterization [41,69,70].

LIPID-BASED DRUG DELIVERY - FORMULATIONS DESIGN

In spite of the fact that lipid-based formulations are as yet a powerful apparatus for formulating meds that are poorly dissolvable, the plan of these formulations might be challenging. In their amazing examination, Porter *et al.* have as of late plotted six proposals for the creation of lipid formulations, as summed up underneath [71].

It is essential for the formulations, the dispersion to maintain drug solubility.

- Colloidal species properties developed after GI processing are probably more critical than formulation properties themselves, which are more likely to enhance absorption.
- Higher lipid [>60%] and lower surfactant [<30%] and cosolvent [<10%] levels normally results in more robust pharmacological solubilization after dilution.
- The medium-chain of triglycerides can increase drug solubility and formulation stability, but the long chain of triglycerides enables the colloidal bile salt lipid species to become more efficient, thus providing higher biodisponibility.
- SMEDDS formulations of Type IIIB offer a smaller droplet size after scattering. Although, it is also dependent on the surfactant structures employed, and nondigestible surfactants typically offer higher bioavailability.
- If two surfactants are utilized as opposed to a solitary, one the scattering of type IV formulations [surfactant/cosolvent] is probably going to be more successful.

PATENTS AND EXCIPIENTS USED FOR LIPID-BASED DRUG DELIVERY

Table 2 shows a rundown of the primary sorts of lipid particles that are the subject of patent applications. Licenses concerning polymer lipid mixture nanoparticles [PLN] have additionally been remembered as the option for the previously mentioned kinds of nanoparticles [72]. PLN comprises a blended lattice of lipids and polymers wherein the polymer is either acquainted with improving the qualities of nanoparticles or encouraging the incorporation of drugs [73]. Likewise, licenses are additionally referenced for functionalized and variable-shape nanoparticulate frameworks.

There is a wide scope of lipid excipients accessible from suppliers of excipients. Since these lipids impact the absorption cycle, the qualities of different excipients should be known [87]. For lipid-based formulations, miscibility; dissolvable limit; self-dispersibility and capacity to advance self-scattering of the formulation; edibility and destiny of processed items; regulatory issues; bothering, harmfulness, virtue, synthetic solidness; similarity with cases; softening point, and cost are the factors that decide the decision of excipients [88].

Table 1: Merits and Demerits of Unilamellar Liposome Preparation Methods

Liposomes manufacturing method	Demerits	Merits
"Electro formation [74]	To spread over in little ionic strength buffers/media	Preparation of im-mobilized giant liposomes/vesicles
Rapid preparation of giant liposome [75]	Buffer/media with ionic little strength [a maximum of 50 mM]	Easy, firm single-step manufacturing procedure
Giant uni-lamellar manufactured in biological buffer [41]	Time unbearable and tedious procedure	By many physiological salt solutions, such as 100 mM KCl plus 1 mM CaCl2

Table 2: Patents for types of lipid nano and microparticles

Lipid particle type	Patient no.	Reference
Functionalized LNC	WO2010113111	[76]
SLN	EP0605497	[77]
Anisometrical SLN	WO9420072	[78]
LDC	US6770299	[79]
LNC	WO0164328 WO2009037310	[80,81]
SLN	US20070053988	[82]
PLN	US20080102127 WO2011116963	[83,84]
NLC	EP00/04111 WO00/67800	[85,86]

Dietary oils comprising medium and long-chain fatty oils, alongside different solvents and surfactants, are much of the time chosen for the planning of lipid-based formulations. Numerous lipids have a lipophilic portion [unsaturated fat] and a hydrophilic portion and are amphiphilic. As the length of the unsaturated fat, chain builds, the dissolving point increments, yet it diminishes with the expansion in unsaturated fat unsaturation and improves the defenselessness to oxidation [89]. Table 3 alludes to a rundown of solubilizing excipients utilized in lipid-based formulations [90].

DRUG LOADING INSIDE THE LIPOSOMES

There are two techniques for drug loading, which are attained either actively [i.e., after liposome formation] or passively [the drug/molecules get entrapped during liposome/vesicle formation]. Hydrophobic and water-insoluble drugs/molecules such as amphotericin B or annamycin could be straight entrapped into liposomes/vesicles during lamellar creation, and the quantity of uptake/encapsulation and preservation is directed by drug to lipid ratio. About 100% encapsulation of drug inside the liposome is not attainable, but mostly reliant on the solubility of the drug in the liposome membrane [91-94]. Passive drug loading of water-soluble/hydrophobic drugs/molecules can be governed by the capability of liposomes/vesicles to encapsulate aqueous buffer/media comprising a dissolved drug/molecule during lamellar/vesicle formation. Encapsulation efficiency [<30%] is inadequate with entrapped volume enclosed in the liposomes/vesicles and drug/molecule solubility. pH gradient is the technique in active loading, where 100% entrapment can achieve through water-soluble/hydrophilic drugs which have protonizable amine functions (Table 4) [95-97].

Table 3: Utilization of solubilizing excipients in lipid-based and industrially accessible formulations

Water-insoluble excipients	Triglycerides	Surfactants
Beeswax,	Long-chain triglycerides	Polysorbate 20 [tween 20],
Oleic acid,	Hydrogenated soyabean oil,	Polysorbate 80 [tween 80],
Soy fatty acids,	Hydrogenated vegetable oil,	Sorbitan monolaurate [Span20],
D-α-Tocopherol [vitamin E],	Corn oil, Olive oil,	D-α -Tocopheryl PEG 1000 succinate [TPGS],
Corn oil mono-di-triglycerides,	Soyabean oil, Peanut oil,	Glyceryl monooleate,
Medium chain [C8/C10] mono and diglycerides,	Sesame oil.	Polyoxyl 35 castor oil [cremophor EL],
Propylene glycol esters of fatty acids.	Medium-chain triglycerides	Polyoxyl 40 hydrogenated castor oil [cremophor RH40],
	Caprylic/capric triglycerides derived from coconut oil or palm seed oil	Polyoxyl 60 hydrogenated castor oil [cremophor RH60], PEG 300 oleic glycerides [Labrafils M-1944CS], Labrafils M-2125CS, Labrasols, Gelucires 44/14

Table 4: Aids of drug loading in liposome

Aids of drug loading in liposome	Cases
Solubility improvement in lipophilic and amphiphilic drugs	Minoxidil, Peptides, Anthracyclines, Amphotericin B
Passive loading and specific targeting to the immune system's mononuclear phagocytic cell	Amphotericin B, Antimonials, vaccine, immune-modulators, porphyrins
Extended-release delivery of locally and systemically administered liposomes	Cytosine, Doxorubicin, cortisones
Site-avoidance and targeting mechanism	Amphotericin B and Doxorubicin
Targeted Site-specific	Anti-cancer, Anti-inflammatory molecules, anti-infectious agents
Better transfer of water-soluble and surface charge molecules	Chelators, Genes, and plasmids
Enhanced penetration into cells and tissues	Anesthetics, Corticosteroids, insulin

Table 5: Liposome characterization and methodology

S. No.	Evaluation parameter	Methodology
1	Liposome composition	Lipid Content by HPLC Free and encapsulated drug by SPE cartridge
2	State of encapsulated drug	Fluorescence studies X-ray diffraction [small angle] Cryo-TEM
3	Internal environment	Internal Volume Internal pH
4	Liposome morphology and number of lamellae	Atomic force microscopy [AFM] Cryo-TEM
5	Lipid bilayer phase transition	Differential scanning calorimetery [DSC] Thermal Gravimetric Analysis [TGA] Differential Thermal Analysis [DTA]
6	Liposome size distribution	Dynamic light scattering [DLS] Size-exclusion chromatography [SEC-MALS] Static light scattering and field flow fractionation [FFF]
7	Grafted PEG at the liposome surface	NMR spectroscopy Cryo-TEM Fixed aqueous layer thickness [FALT]
8	Electrical surface potential or charge	Zeta potential Electrophoretic mobility distribution
9	*In vitro* leakage under multiple conditions	*In Vitro* drug leakage using bottle rotating apparatus

LBDDS SYSTEMS [LIPOSOME] CHARACTERIZATION

As per USFDA draft guidance for liposome injection, various physicochemical properties of liposomal injection are required to be determined and compared with the reference product [98].

As per the guidance, *in vitro* liposome characterization should be conducted on at least one batch of the ANDA and the RLD or reference standard products. Attributes that should be included in the characterization of ANDA's claiming equivalence to the RLD or reference standard are (Table 5):

Table 6: Available LBDDS in market

Branded Product	Drug Name	Therapeutic Category
Abelcet/AmBisome	Amphotericin B	Fungal infections
DaunoXome	Daunorubicin	Hematological malignancy
DepoCyt	Cytarabine	Lymphomatous meningitis
DepoDur	Morphine sulfate	Pain relief
Doxil	Doxorubicin	Kaposi's sarcoma and solid tumors
Epaxal	Inactivated hepatitis A virus	Hepatitis A
Evacet	Doxorubicin	Ovarian cancer
Inflexal V	Inactivated hemagglutinin of influenza virus strains A and B	Influenza
LipoDox	Doxorubicin	Kaposi's sarcoma and solid tumors
Marqibo	Vincristine sulfate	Acute lymphoblastic leukemia
Visudyne	Verteporfin	Photodynamic therapy

LIPOSOMES FOR ANTI-CANCER THERAPY

Liposome formulation of the anticancer drug is less toxic than the available free drug of an anti-cancer molecule, anthracyclines drugs working with the principle of stopping the growth of separating cells by interposing into the DNA and because of that kill mainly rapidly separating cells. Hair, gastrointestinal mucosa, and blood cells are also having these cells. Hence, the class of drug/molecule is highly toxic [98-101].

The maximum applicable, utilized, and examined is Adriamycin [Doxorubicin hydrochloride; Ben Venue Labs., Bedford, Ohio]. The dosage of the drug is also restricted by its increasing cardiotoxicity along with the above-mentioned acute toxicities with various formulations that were tried and studied. In every case, the high toxicity and adverse effect were decreased up to only 50%. However, liposomes can decrease the acute and chronic toxicities due to encapsulation of anti-cancer drugs inside the liposome [102]. For a similar aim, the entrapment efficacy was in various cases negotiated due to the reduced bioavailability of the drug/molecule, especially if the tumor/cancer is not phagocytic or located in the organs of the mono-nuclear phagocytic system [103]. In most cases like systemic lymphoma, the result of liposome entrapment efficiency displayed better efficacy due to the continuous release effect, that is, extensive attendance of therapeutic concentration in the bloodstream, whereas in many other cases, the confiscation of the drug/molecule into tissues of the mono-nuclear phagocytic system decreased its efficiency [104].

RECENT LIPID-BASED DRUG DELIVERY ADVANCES IN CANCER TREATMENT

Nano drugs can likewise be utilized to improve the reaction of patients in the mix with other restorative systems. A few antitumor specialists have been concentrated in nano-formulations as stated below (Table 6).

CONCLUSION

Lipid-based drug delivery systems can be designed to target tumors effectively. Nevertheless, if the aim is to achieve an optimum anticancer activity, the biological fate of nanomedicine needs to be monitored. LBDDS is one of the latest technologies that have been developed to resolve challenges such as water solution solubility and bioavailability. Effective drug deposition in tumor tissues, careful regulation of the drug release, and drug retention over minimal lethal concentration are also necessary. In the production of such colloids, the incorporation

of passive/active drug targeted techniques is predicted to contribute greatly to cancer control.

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AUTHORS' CONTRIBUTIONS

All the authors contributed equally to writing the manuscript, analyzing the data, read, and approved the manuscript.

CONFLICT OF INTEREST

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