Minireview Article

An overview of FDA approved liposome formulations for cancer therapy

Abstract:

One of the early achievements of researchers to develop Nano drug delivery systems were successfully manifested in the form of liposomes. Since the time of its invention in 1965, many technological advancements have been witnessed in Liposomal drug delivery systems ~~are~~ are a field of study. The capacity to change a drug's biodistribution profile, liposomes have been reported to enhance and improve the therapeutic index of different drugs. Drugs of various categories like antineoplastic, antifungal agents, and Anti-inflammatory agents properties and therapy genes have been extensively studied for efficient delivery using liposomes. US-FDA-approved products like Doxil®, Ambisome®, DepoDur™, etc have been seen to play an important part in the treating of a large number of patients across the world. This review aims to provide updated information about various approved and marketed liposome formulations and their role in the modern-day health care systems.

Keyword:

Liposomes, therapeutic applications, drug carriers, liposome technology, nanomaterials, clinical studies, and commercial products

1. Introduction:

Generally, liposomes are tiny spheroidal-shaped particles comprised of lipid bilayers having an internal hydrophilic cavity. Liposomes are prepared using phospholipids or synthesized amphiphiles are combined with sterols like cholesterol, the membrane permeability changes dramatically. Among the various techniques for the preparation of liposomes, one of the most commonly studied approaches is thin-film hydration. Lipids are soaked in such a solvent system, then the solution is removed using rotary evaporation, and the film is rehydrated in an aqueous solvent. Researchers are also researching reverse-phase evaporation, ethanol infusion, freeze-drying, ultrasound-assisted, membrane extrusion, homogenized, and recrystallization (1). Liposomes may be manufactured in a variety of sizes, compositions, charges, and lamellarity.

Owing to lipid bilayer-based medication for human utilization, formulations ~~are~~ are developed, and numerous compounds were undergoing various human studies as a result of significant improvements in liposome technology. Many medications' therapeutic indices improved when they were encapsulated in liposomes, owing to changes in their pharmacokinetic properties. APIs of various solubilities can be contained in liposomes; hydrophobic pharmaceuticals bind to the lipid bilayers, whereas medicines that are hydrophilic are confined inside the aquatic cavity.

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The debut of Doxil® to the US commerce in 1995 for such treatments for extra-ovarian primary peritoneal carcinoma patients and Kaposi's Sarcoma (AIDS-correlate Kaposi's Sarcoma) cancer following the inability of previous standard chemotherapy either resistance to that treatment was the first beneficial breakthrough in liposome-based pharmaceuticals (2). The Food and Drug Administration gave its approval to the first Nano-composites lipid-based ~~-~~product. Nexstar Pharmaceuticals USA followed suit, developing DaunoXome®, a liposomal solution for the administration of daunorubicin (DNR) for the treatment of Kaposi's tumor with advanced HIV infection. Later on, other products for the treatment of various malignancies were available. SkyPharma Inc.'s Depocyt®, Elan Pharmaceuticals' Myocet®, Takeda Pharmaceuticals' Mepact®, and Talon Therapeutics' Marqibo® are among these drugs. The leucovorin and fluorouracil combining treatment

medicines for metastatic pancreatic cancer were recently authorized. Merrimack Pharmaceuticals, Inc. markets this novel medicine as OnivydeTM. Even though the fact that cancer was the most intensively researched field of clinically approved liposomal medicines, liposomal products were also created for other disorders. The FDA authorized Amphotec® and Ambisome® for fungal infections in 1996 and 1997, respectively. Since the development of such liposomes of Amphotericin B, the treatments for fungal diseases has been successful (AmB). Vesicles have also become important carrier systems in the creation of vaccines. Since the invention of Epaxal® and Inflexal® V, liposomal medicines have received a lot of interest. Crucell, Berna Biotech produced both medicines for hepatic and influenza immunization.

2. Clinically Available Liposome-Based Products:

2.1. Treatment Of cancer using Liposomes

2.1.1. Doxil

Doxil, a DOX hydrochloride-contents composition, has been the initial Food and Drug Administration-permitted PEGylated liposome nanotechnology is used to create a nano-drug delivery system. Doxil® was initially created in 1998 by Sequins Pharma in the United States for an intravenous infusion for such treatment of metastatic extra-ovarian primary peritoneal carcinoma, myelodysplastic syndrome, and Kaposi's tumor with advanced HIV infection. In a molar ratio of 56:38:5 (3), Doxil® liposomes are made utilizing wide bandwidth (Tm) lecithin N-(carbonyl-methoxy polyethylene glycol 2000)-1,2-stearoyl-sn-glycerol-3-phosphoethanolamine sodium salt (MPEG-DSPE), cholesterol, hydrogenated soy phosphatidylcholine (HSPC). A pilot clinical research investigation on 15-20 cancer patients was conducted to investigate the pharmacokinetics of DOX. Doxil has been comparable unbound Drugs at dosages of 50 mg/m^2 and 25 mg/m^2 in this research. Doxil® had a substantially lesser volume of administration (4 L) than the unbound drug, according to this investigation (254 L). In addition, Doxil elimination (0.1 L/h) was much less than the standard drugs (45 Litre/h). Doxil® had a two-phase elimination period with a quarter of 2 along with 45 hours, indicating that substantially all circulating DOX was bound to the lipid bilayer. Doxil showed between 4 and 16 times increased DOX amounts inside the tumors of individuals who used it (4). When encapsulated DOX is not accessible to cardiomyocytes and the myocardium, Doxil® has been demonstrated to minimize cytotoxic effects, a side effect of unbound DOX therapy (5).

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Comment [MK3]: PEG?

2.1.2 DaunoXome®

DaunoXome® is a germ-, pyrogen-, and chemical DNR citrate liposomal solution in only one vial for i.v. infusions. DaunoXome® was produced by Nexstar Pharma in the USA in 1996 for the treatment of Kaposi's tumor with advanced HIV infection (6). ~~thus~~thus, only one vial provides DNR (50 mg) source inside the liposomes containing 704 milligrams di-stearoyl phosphatidylcholine (DSPC) and 168 milligrams triglycerides. The safety, bioavailability, and possible effectiveness of liposomal DNR on increasing dosage in adults with Aids Associated Kaposi sarcoma were investigated (7). DaunoXome® was reported to be effective when administered at doses of approximately 50 to 60 mg/m2. These findings yield an AUC of 114.91 to 120.1 µg h^{-1} mL^{-1} (7,8). In comparison to normal DNR, the studies show an 11–12-fold increase., and they mimic the liposomal carrier's constant nature, as seen in mouse models experimental models (7,9). Similarly, when comparing DaunoXome®-treated patients to traditional DNR-treated people, excretion is much lower (10.5 vs. 233 milliliters, respectively) (8,9). In comparison to unbound DNR = 0.77 h, these two features enhanced DaunoXome half-life from 4-5.6 hr (7,8). In contrast, to unbound DNR, the research showed that DaunoXome® had a better pharmacokinetic profile.

Comment [MK4]: Is this unit correct? Check, please.

Comment [MK5]: What is AUC?

Comment [MK6]: What is DNR?

2.1.3 Depocyt®

SkyePharm Inc. created Depocyt, which is a kind of liposome. medication containing aracytidine (Enzon Technologies, Piscataway, New Jersey, USA) (Before- DepoTech Pharm, La Jolla, California, United States of America). Depocyt is a contaminant parenteral solution for free of something like the antimetabolite Ara-C/aracytidine that was created to treat neoplasia meningitis (NM) by regulated aracytidine release. Depocyt is a delayed-release composition that encapsulates the water-based solution containing solution in multivesicular pores with the DepoFoamTM structure granular. DepoFoamTM technology is made up of small spherical particles (3–30 m) that are ideal for the encapsulation of hydrophilic chemicals like Ara-C. 96 percent watery foam and 4% biocompatible lipid make up these lipid foam-based particles (10). Multivesicular DepoFoamTM particles have a high medication loading capacity due to their design. In general, they are larger than unilamellar or multicellular liposomes. phospholipids foaming residues were biocompatible and can be processed through the same metabolic routes as triglyceride, lipid bilayers, and triglycerides. Each container contains 50 mg aracytidine, which is contained in 10 mg/mL DepoFoamTM liposomes. In 0.9 percent preservative-free solution, each 5-mL vial consists of 50 milligrams aracytidine, 22 milligrams sterol, 6 milligrams Glyceryl trioleate, 28.5 milligrams di-oleoyl phosphatidylcholine (DOPC), and 5 mg dipalmitoyl phosphatidylglycerol (DPPG). The pH of either the Depocyt® mixture is kept between 5.5 and 8.5. Because DepoFoamTM particles have larger densities than the suspended media, they tend to settle to the bottom throughout time, necessitating modest agitating to s new the particle for infusion (10). Ara-C is recommended for adults to take 50 milligrams (5 mL Depocyt®) once every two weeks.

A phases I/II experimental study for Depocyt pharmacological research has been started, inside Elevated CSF aracytidine levels were retained for further than fourteen days for both spinal and ventricle fluids, independent of the medication injection site (11). The ultimate ½ of inside the ventricular Depocyt® remained 141 hours, compared to 3.4 hours for conventional Ara-C. Depocyt® has been especially in comparison to methotrexate in a clinical trial in individuals with having neoplastic meningitis caused by a solid tumor, and the outcomes were revealed equal response times. Depocyt® also enhanced the phases of neurological development, and aracytidine efficiency is a consequence of either the level of concentration or time of exposure. When compared to normal Ara-C preparations, Depocyt® is more effective in killing tumor cells within meninges and CSF (12).

Comment [MK7]: What is CSF?

2.1.4 Myocet

Myocet would be a non-PEGylated sustained-release DOX ~~that~~ that has been authorized for use in metastatic breast cancer as a first-line medication in conjunction with cyclophosphamide. Most (Elan Pharma, Princeton, New Jersey, USA) was created to minimize DOX's while avoiding cardiotoxicity its anti-tumor effectiveness (13). Most liposomes were roughly 150 to 250 nm in size and have a 45:55 molar ratio of cholesterol to acidic egg phosphatidylcholine (EPC). The ratio of medication to lipid is roughly 0.27. The bone marrow has little trouble recognizing these liposomes due to their increased size. Because of their large size, vesicles have less interaction with normal tissues, which minimizes several acute and chronic toxicities. Myocet® liposomes were created for this purpose, active dosing of amphoteric weak bases was employed (12). Blank liposomes were prepared in such an acid sodium citrate buffer solution (pH 4.0, 300 mM citrate), then Disodium carbonate was added to keep the pH around the liposomes at roughly 7.3. Finally, these lipid bilayers are heated briefly while incubated with DOX. DOX enters the cell membrane and becomes protonated within the lipid nanoparticles' aqueous core as a consequence. Attracted to the negative membrane-connected lipids aid in the formation of "ion pairs" with DOX, facilitating DOX entry into the liposome (14). When DOX is protonated, it has a hard time traversing the lipid bilayer, resulting in an encapsulation efficiency of over 99 percent (15).

Myocet was analyzed to free Drug in experimental toxicity experiments on Beagle dogs, and it was shown that Myocet had a superior toxic potential than free DOX. Harasym and colleagues found that in a tumor cell model, the greatest tumors concentration was 2–3 times greater for Myocet than for unbound DOX, and in an ascitic model, the peak amount of tumors Medicament exposure has been Ten times greater for Myocet than for free DOX. These findings influenced the decision to use Myocet in human research. In the stage, I clinical trial, 38 patients with resistant tumor cells were given the same dosage of Myocet and unbound DOX via i.v. injection (12). When compared to free DOX, Myocet showed less myelosuppression and gastric side effects in the trial. Most showed comparable treatment outcomes and progression-free survival durations in a phase 3 investigation in

individuals with breast cancer treatment. Moreover, Myocet had considerably decreased cardiovascular problems and heart failure rates. Baptist and colleagues compared a combination of Myocet (60 mg/m^2) and cyclophosphamide (600 mg/m^2) with cyclophosphamide and unbound -DOX mixture at the same dosage in participants with breast cancer treatment in another multicentric study. Due to a mixture of Myocet and cyclo-phosphamide, the findings indicated equal effectiveness with low toxicity (12,15).

2.1.5 Mepact®

Takeda Pharma Limited, formerly IDM Pharma SAS, sells Mepact, a Mifamurtide (MFT) is a drug that contains the liposome. The impact was also the first acceptance treatment for the design of acute, relapsed, or refractory, non-metastatic bone metastases approved in 2004 by the European Medicines Agency (EMA) in association with perioperative in children, teenagers, and teens who have had a full macroscopic surgical removal, combined chemotherapy is used. Impact -comprises lipid membrane-enclosed muramyl tripeptide phosphatidylethanolamine (L-MTP-PE) in 100 nm multilamellar vesicles (16). MTP-PE is a compound of MTP and dipalmitoyl phosphatidylethanolamine (DPPE), which is a kind of manufactured lipotropic variant of muramyl dipeptide (MDP) (a component of bacterial membrane derived from natural sources). Monocytes, -cytokines, and macrophages such as tumors necrosis component alpha, interleukin-1b, il6, il-8, and il-12 are all activated by muramyl dipeptide. Artificial lipids are utilized to make Mepact -liposomes, such as 1-palmitoyl-2-oleoylphosphatidyl-choline and dioleoyl-phosphatidylserine (DOPS). Even while MFT demonstrated no toxicity against regular or cancer cells in vitro, its anti-osteosarcoma benefits in vivo are attributed to an immunological reaction to osteosarcoma lungs metastasis. After death from chemotherapy, cells of macrophages have a "flipped phosphatidylserine" to the exterior membrane; hence, contains phosphatidylserine lipid that sends Both inactive and active mifamurtide components to reach the immune reactions of the lungs (12).
Lipid-based MFT's pharmacologic properties were studied in healthy people as well as patients with greater, osteogenic sarcoma with metastatic spread and recurrence (17). The findings revealed that an individual 4 mg dosage of MFT may be safely administered to normal volunteers who are in good health that MFT had lower pharmacokinetic variance [the coefficient of determination (percent CV) both in AUC and peak concentrations (Plasma concentration) was less than 30%]. In adolescents with osteogenic sarcoma, a stage III clinical study of L-MTP-PE administered in inclusion to standard treatment revealed an improvement in 6 -year net lifespan from 70% to 78 percent (12,17).

2.1.6 Marqibo®

Vincristine (VCR) sulfate liposomal infusion marqibo, established in Talon Pharma, Inc. in the United States, has been approved to treat older patients with Philadelphia copy of the gene leukemia (ALL) who have relapsed twice or more or whose disease has progressed within a week of two or more anti-leukemia treatments. For a single dosage, each container contains 5 mg/31 mL (0.16 mg/mL) VCR sulphate. VCR is contained in options, which are sphingomyelin/cholesterol liposomes with an aqueous inner core (18). These options were created to increase VCR delivery and retention. Additionally, these options prolong the circulate period of the contained VCR and let the medicine gently enter the tumor vascular. Because of the large concentration of encapsulated medication in target tissues, these variables result in increased activity. The VSLI contains sphingomyelin (SM) and triglycerides in a molar ratio of around 60:40 (mol: mol), with a lipid membrane mean size of 100 nm. The SM/Cholesterol lipid ingredient and the VSLI liposome's tiny mean particles size lead to poor binding affinity, resulting in a longer liposome circulation period. The vesicles encapsulate more than 95 percent of the medication (19).
When compared to the untreated VCR, Marqibo -has a longer systemic circulation and actively directs VCR to cancers by discharge through fenestrations that characteristic tumor neovasculature (12). The effectiveness and safety of Marqibo -as a single agent were investigated in a phase 2 trial, which included a single-arm open investigation in refractory cancer patients with severe non-Hodgkin

lymphoma. Marqibo was administered at a dosage intensity that was almost double that of standard-free VCR. The tolerability profiles of the patients in this trial were equivalent to that of standard-free VCR (20).

2.1.7 Onivyde™

Merrimack Pharmaceuticals Inc. received FDA approval for Onivyde, and irinotecan (IRI) lipid nanoparticles infusion, in 2015. Onivyde, in combination with fluorouracil and leucovorin, is intended for the treatment of metastatic pancreatic adenocarcinoma who have progressed on gemcitabine-based treatment. OnivydeTM is a liquisolid formulation of a water-soluble semi-synthetic derivative A topoisomerase inhibitor, IRI HCL trihydrate. IRI is entrapped inconsistency or as a result of the precipitation sugar octasulphate salt by OnivydeTM vesicles, which seem to be unilamellar phospholipid bilayer spheres with a diameter of 110 nm, using an ion transfer process in watery space. Intra-liposomal drug stabilization technique, that wraps medication into long circulation lipid membrane nano-vesicles, was used to create Onivyde (21). Synthetic polymer or nonpolymeric charged anions, as well as intra-liposomal capturing compounds like poly-phosphate and sucrose octasulfate, were utilized in this method. In this technique, a high-pKa polyallylamine gradation was used. This allows IRI to be encapsulated in liposomes at a large drug: lipid ratios (and over 800 g IRI each mol of phospholipid). The drug's half-life in the bloodstream was also demonstrated to be raised to 56.8 hours. The vesicle is made up of 3:2:0.015 DSPC, triglycerides, and methoxy-terminated polyethylene glycol (MW-2000)-di-stearoyl phosphatidylethanolamine (MPEG-2000-DSPE), which encapsulates more than 90% of the medication (22).
Using humans intestinal (HT29) and mammary (BT474) cancer transgenic models, lipidomic IRI was compared to free IRI. Due to dramatically larger entrapment efficiency and prolonged drug persistence in vivo (21), liposomal IRI demonstrated a considerably increased cytotoxic effect. The effectiveness and safety of OnivydeTM were proven in a random, open-label NAPOLI-1 clinical study for patients with multiple myeloma Adenocarcinoma of the pancreas whose tumor had advanced after taking the chemotherapeutic drug gemcitabine (or a similar drug) is a drug that is used to the treatment. Patients in the trial who took leucovorin/fluorouracil with OnivydeTM patients lasted on average, it takes 6.1 months., comparable to 4.2 months for those on fluorouracil or leucovorin individually (23).

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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