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REVIEW ARTICLE

LIPOSOMES USED AS NOVEL TARGETED DRUG DELIVERY SYSTEM FOR CANCER TREATMENT

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ABSTRACT

Purpose of Review: In this review paper, we highlight the recent concepts and discuss some of the current advances and future prospects used in cancer therapy. We hereby use the nanoparticle based such as liposome preparation for targeting the cancer. ***Methods used for Review:*** We performed a non-systematic search of journals, authoritative guidelines such as WHO, NCBI, etc. and selected the most comprehensive and relevant research articles, clinical studies, translational articles and review articles on nanoparticle such as liposome-based cancer therapy. The selection of paper for the reviewing purposes are purely based on the originality of the paper as well as by observing the clinical uses. ***Recent Findings in Review:*** Cancer is a major public health problem worldwide. Systemic delivery of free drug is considered a major clinical failure of chemotherapy in cancer treatment, as limited concentration of the drug reaches at the tumor site which is site of action for the drug. Most active pharmaceutical ingredients (APIs) used in chemotherapy are highly cytotoxic to both type of cells i.e., cancerous cells and normal cells. According to this, targeting tumor vasculature is essential for tumor therapy. In this context (reference), the encapsulation of anticancer drugs in a nanoparticle i.e., liposomal system offers safe platforms for the targeted delivery of anticancer drugs for cancer therapy. This may also be helpful and useful for reducing the cytotoxic side effects of anticancer drugs on normal cells. This short review focuses on the use of liposomes in anticancer drug delivery, different liposomal formulations for cancer, and the mechanism of action of liposomal drug delivery for cancer therapy and some of the recent finding bioactive compound used in liposomal form for the cancer treatment.

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INTRODUCTION

Cancer is a medical term that is used to describe a heterogeneous group of diseases with an increasing incidence representing a global health problem (1). Cancer is the second leading cause of death worldwide after cardiovascular disease, and it is estimated that the incidence will increase by about 60% in the next few decades. According to the International Agency for Research on Cancer (IARC) GLOBOCAN 2020, 28.4 million new cases are expected in 2040, a 47% increase from 2020. In 2020, IARC estimates that 19.3 million new cases and 10 million deaths due to cancer throughout the world. Now Breast cancer is the most frequently diagnosed type of cancer in women (2.3 million new cases, 11.7% of all cases), followed by lung cancer (11.4%) and prostate cancer (7.3%). In 2020, new cases occurred in Asia (58.3% of all cases worldwide), followed by in Europe (22.8%) and the United States (20.9%). (2). Liposomes are the most commonly investigated nanostructures used in advanced drug delivery, first discovered by Alee Bangham in 1963 (3). Thus, pharmaceutical formulations based on nano-structures (nanoparticle) (e.g., liposomes (4), polymeric nanoparticles (5), electrosprayed particles (6), and Nano suspensions (7)) have shown better API Moreover, due to the complexity of solid tumors, a major challenge in cancer therapy is the effective penetration of anticancer agents encapsulated in nanocarriers (8). Liposomes are small artificial spherical-shaped vesicles that is formulated from cholesterol and natural non-toxic phospholipids. Due to their size, hydrophobic and hydrophilic character (in addition to biocompatibility), liposomes are best promising drug delivery systems. Liposomes can actively target cancerous cells and tumor tissues using an antibody-based approach. This can be formulated by adding certain antibodies on the liposomal surface it is called as immunoliposomes (ILP) which are very specific to the cancer cells or to the endothelial cells of the tumour vasculature (9).

Cancer: Cancer is a very lethal i.e., life-threatening diseases that leads to irregular and uncontrolled growth of malignant cells. These uncontrollable cells can invade in normal tissues and organs, causing undesirable growth and reactions that end up with leading to destroying the normal cells and tissues (10). Cancer is responsible for ~3.4 million deaths worldwide (11). Some of the well-known causes for cancer illness are smoking (which causing different type of cancer like lung (12), breast (13), and ovarian cancer (14)), being overweight

breast cancer, kidney, womb and bowel cancers), intake of processed meat (15), radiation (causes skin cancer) (16), family history, stress, environmental factors, and chance (17). Cancerous cells have the potency to spread in the human body through blood vessels and lymphatic streams, causing metastasis (spread) by forming a secondary tumour (18). Anticancer agents are typically administered to the patients to kill cancerous cells.

These drugs work by two mechanisms:

1.Killing the cancer cells through direct exposure to the chemical agent 2.And Inducing apoptosis (suicide of cancerous cells) (19).

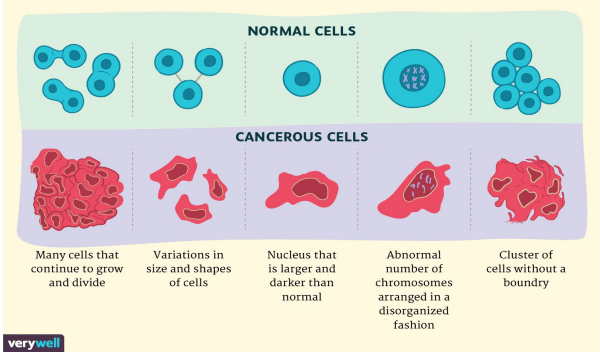

Image taken by verywell health (https://www.verywellhealth.com/): This image describe the difference between normal cells and cancerous cells.

Liposomes: Liposomes are basically small artificial vesicles of spherical shape that can be made from cholesterol and natural non-toxic phospholipids. Due to their size and hydrophobic and hydrophilic character (besides biocompatibility), liposomes are very promising systems for drug delivery. Liposome properties can differ considerably with lipid composition, surface charge, size, and the method of preparation. Furthermore, the choice of bilayer components determines the 'rigidity' and 'fluidity' and the charge of the bilayer. For example, unsaturated phosphatidylcholine species from natural sources (egg or soybean phosphatidylcholine) give much more permeable and less stable bilayers, whereas the saturated phospholipids with long acyl chains form a rigid, rather impermeable bilayer structure.

Liposomal vesicles are vary in sizes between 0.025 µm to 2.5 µm. They can be categorised according to the number of layers present (also referred as lamellae):

- Unilamellar - consisting of single phospholipid bilayer and
- Multilamellar - consisting of more than one unilamellar separated by layers of water (20) (>500 nm)).

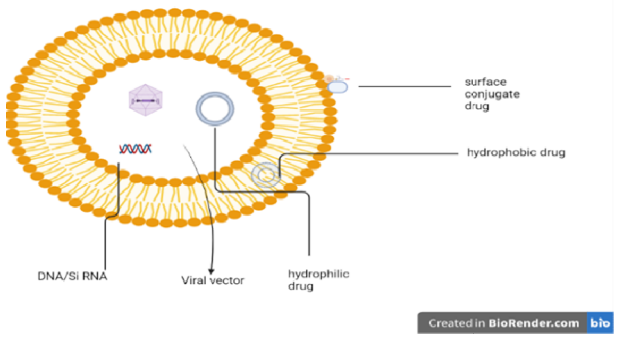

Image of liposomes created by author using biorender.com

Unilamellar vesicles are further classified in two categories which are as, small unilamellar vesicles (size range 20–100 nm) and

Large unilamellar vesicles (size >100 nm): Both the size and the number of lamellae in the liposomal structure are considered to be the most crucial factors which affecting the vesicles half-life and the quantity of Active pharmaceutical ingredient that is to be encapsulated (11). This flexible and unique variety of the liposomal structure differentiates liposomes as the preferred carriers for a broad spectrum of therapeutic drug.

Administration Route of Liposomal Drugs: Like many different drugs, Nano particle-based liposomal formulated medicines can be administered from a very wide variety of routes. Like, oral consumption (21) distinct injection methods such as intravenous (I.V.) administration and various local injections are among the common administration routes for liposomal drugs (22). Intravenous injection is used as the primary route of administration for many liposomal drugs which was approved by the FDA or the authorities which are responsible for approval of drug formulation. On the other hand, intradermal (I.D.), intraperitoneal (I.P.), subcutaneous (S.C.), and intramuscular (I.M.), are classified under the class of the local injection, are also utilized for administration route of liposomal drugs (22, 23, 24). Liposomes are very much suitable carrier for the delivery of proto-apoptotic membrane proteins into cancer cells to promote or induce cell death (27).

Liposomes used as Targeted Drug Delivery System for Cancer treatment

Targeting Mechanism of Action of liposome in cancer therapy: Liposomes are able to target tumor cells by using passively or actively. When the liposome reaches the cancerous cells and the tumor environment through the targeting mechanism, it releases its therapeutic API content here and exert its effects by different type of mechanisms. Consequently, the surface charge of the membrane, lipid composition,type of target cells, type of cancer, as well as the presence of specific ligands on the membrane of liposome, which can influence the cell-liposome interaction (25). After liposome injected into the body, the drug-containing liposomes travel to different tissues through blood vessels and eventually it reaches to their target cells based on their surface ligands. These liposomes bind to the cellular receptors by using these ligands, the process is called specific absorption (26).

Treatment: Treatment include advancements in liposomal vesicle development have achieved and shows both controlled drug release and targeted drug delivery mechanism. A number of different types of liposomal formulations of anti-cancer agents have been shown to deliver the drug at the site of solid tumors also called site of action with very less toxicity with if compared to free drug. Currently, there are many products available in the market and in clinical development for use as anti-cancer drug delivery vehicle.

Some of them are here briefly discussed using various data

Doxil (US), or Caelyx (outside-US): It is a PEGylated liposomal formulation which encapsulating anticancer drug doxorubicin commercialized by Johnson & Johnson company. In 2011, an imbalance between the demand and supply of Doxil was observed as the manufacturing unit was shut down for some time due to some quality control issues in the unit. To address the Doxil shortage in USA, FDA allowed temporary importation of LipoDox a liposomal formulation.

Lipo Dox: Is the same liposomal formulation as Doxil formulated basically in USA and made in India by Sun Pharma pharmaceutical unit and FDA approved the first generic version of Doxil in 2013, formulated by Sun Pharmacompany (Berger *et al*. 2014; Chou *et al*. 2015). In a recent study, it was found that Doxil was also active against refractory ovarian cancer, and later approved by the FDA for

Barenholz 2012). Recently, it has been approved for the treatment of breast cancer also (Barenholz 2012) in USA and for the treatment of multiple myeloma in combination with velcade in countries like Europe and Canada (Blade *et al*. 2011; Barenholz 2012).

Dauno Xome: It is the registered trademark of Galen, which is the liposomal formulation of daunorubicin as an API approved by FDA basically for the therapy of AIDS related to Kaposi's sarcoma (Cooley *et al*. 2007; Petre and Dittmer 2007).

Myocet: It is the registered trade mark for Cephalon, which is a non-PEGylated liposomal formulation of doxorubicin as an API. Myocetformulated with combination of cyclophosphamide which was approved for the treatment of metastatic breast cancer in Europe but was not yet approved by the FDA for use in the United States (Batist *et al*. 2001). Myocet in combination with Herceptin (trastuzumab) and Taxol (paclitaxel) for the treatment of highly dangerous and aggressive HER2 contained positive metastatic breast cancer the Sopherion Therapeutics in the United States and Canada is conducting a pivotal phase III global registrational trial for this (Baselga *et al*. 2014). Vincristine is the liposomal formulation ,formulated by talon which were registered with the trade name marqibo.

Marqibo: Itwasbasically approved by the FDA for the treatment of acute lymphoblastic leukaemiain 2012 (Sarris *et al*. 2000; Rodriguez *et al*. 2009). Celator Pharmaceuticals Inc. developed CPX-351, which is a liposomal formulation of daunorubicin and cytarabine as API. The CPX-351 showed promising results in phase III clinical trial on the patients with secondary acute myeloid leukemia (AML) by improving the induction response about over 40% (Riviere *et al*. 2011; Cortes *et al*. 2015). Previously in phase II trial, CPX-351 had already showed some survival benefits and the data on over survival could be expected approx. in the first 4th month of 2016 (Lancet *et al*. 2014). Another liposomal formulation of Celator contains irinotecan Hcl and floxuridine and registered as CPX-1. The CPX-1 completed phase II clinical trial on the patients with advanced colorectal cancer (Batist *et al*. 2009). MM-398 is also an liposomal spherical encapsulating irinotecan developed by Merrimack pharmaceuticals.

MM-398: is being evaluated in the clinical trials for its ability to treat various cancers, which are resistant to chemotherapy such as pancreatic, colorectal, lung and glioma (Ko *et al*. 2013; Roy *et al*. 2013; Saif 2014). Another liposomal formulation developed by Merrimack pharma is MM-302, which encapsulates doxorubicin.

MM-302: is developed and designed for selective reach of drug into tumor cells while without harming healthy tissues. MM-302 contains a very novel antibody-drug conjugate on the surface which specifically targets cancer cells overexpressing the HER2 receptor. Currently, MM-302 is being evaluated and optimized in phase I clinical trials for its potency to treat advanced metastatic HER2-positive breast cancer (Geretti *et al*. 2015).

MBP-426: It is formulation containing transferrin receptor targeted liposome which is a formulation of oxaliplatin designed by Mebiopharm. MBP-426 is being evaluated and optimized in phase II clinical trial for the treatment of patients affected with gastric cancer (Suzuki *et al*. 2008; Goldberg *et al*. 2013).

Lipoplatin: It is the liposomal formulation containing cisplatin designed by Regulon Inc. and currently, it is being evaluated and optimized in phase III clinical trial for the patients with non-small cell lung cancer (Fantini *et al*. 2011).

Another liposomal formulation Stimuvax is developed and designed as anti-MUC1 cancer vaccine by Oncothyreon to treat non-small cell lung cancer and presently it is in the phase III clinical trial (Bradbury and Shepherd 2008; Fantini *et al*. 2011; Broglio *et al*. 2014).

ThermoDox (Celsion): It is the thermo sensitive liposomal formulation of doxorubicin which is under phase III clinical trial to treat the patients with primary hepatocellular carcinoma, in phase II for refractory chest wall breast cancer and colorectal liver metastasis (Poon and Borys 2011; Staruch *et al*. 2011).

CONCLUSION

Liposomes have revolutionized and most advance cancer therapy which have broad clinical applications. Advancements in liposomal vesicle design and development have achieved both controlled drug release and targeted drug delivery (disease-specific localisation). Liposomes overcome the limitations of conventional chemotherapy by improving the bioavailability and stability of the drug molecules and minimizing side effects by site-specific targeted delivery of the drugs. Liposomes were the first nanotechnology-based drug delivery systems approved for the clinical applications because of their biocompatibility and biodegradability like features. Some liposome-based drug delivery systems are already in the market and many more are undergoing research and clinical trials. In this context, the encapsulation of anticancer drugs in a liposomal system offers safe platforms for the targeted delivery of anticancer drugs for cancer treatment. So far, liposomes have established themselves in nanocarriers-based drug delivery systems as evident by the successful clinical applications of liposomal formulations in anti-cancer therapy.There are different liposomal formulation of drug some are already used for the treatment of cancer however there are many drug which are under the clinical phase trials.

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