The Cancer Treatment by Using Liposome as Drug Delivery Systems and Its Applications: An Extensive Review

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REVIEW ARTICLE

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ABSTRACT

Cancer is a leading cause of death in many countries around the world. However, the efficacy of current standard treatments for a variety of cancers is suboptimal. In the development of cancer chemotherapy, besides the discovery of new anticancer drugs, a variety of nanocarrier systems for the delivery of previously developed and new chemotherapeutic drugs have currently been explored. Liposome is one of the most studied nanocarrier systems because of its biodegradability, simple preparation method, high efficacy and low toxicity. To make the best use of this vehicle, a number of multifunctionalized liposomal formulations have been investigated. This review will be including the development of liposomes for cancer therapy, liposomal formulation of various anticancer drugs that are commercially available, recent progress in liposome technology for the treatment of cancer, and the next generation of lipid-based nanoparticles., recent progress in liposome technology for the treatment of cancer, and the next generation of lipid-based nanoparticles.

Keywords: Cancer treatment, liposomes, Drug delivery system

Introduction

Currently available chemotherapy is hampered by a lack in tumor specificity and resulting toxicity. Small and long-circulating liposomes can preferentially deliver chemotherapeutic drugs to tumors upon extravasation from tumor vasculature. Although clinically used liposomal formulations demonstrated significant reduction in toxicity, enhancement of therapeutic activity has not fully met expectations. Tumors that stay in one spot and demonstrate limited growth is generally considered to be benign. When a tumor successfully spreads to other parts of the body and grows, invading and destroying other healthy tissues, it is said to have metastasized. This process itself is called metastasis, and the result is a serious condition that is very difficult to treat. In 2019, cancer claimed the lives of about 7.6 million people in the world. Low drug bioavailability from liposomal formulations and limited tumor accumulation remain major challenges to further improve therapeutic activity of liposomal chemotherapy. However, delivery systems have been developed to exploit a feature of tumor micro physiology often referred to as the 'enhanced permeability and retention' effect. (1) This effect is a consequence of the dysregulated nature of tumor angiogenesis, which characteristically involves structural and physiologic defects leading to hyperpermeability. Macromolecular agents with highly restricted volumes of distribution and the capacity for greatly prolonged circulation will preferentially extravasate from these abnormal vessels and accumulate in tumor tissue. The figure 1 indicates the structure of liposomes.

Liposomes, as carrier systems, have been explored more than any than other system as a result of their various forms. Phospholipid bilayers membranes can generate sphere structure with internal hydrophilic

compartment through introducing phospholipids in water solution; these structures are called liposomes. About four decades ago, Bangham and co-workers defined liposomes as vesicles with small size and spherical shapes that can be generated from phospholipids, cholesterols, non-toxic surfactants and even membrane protein. Investigations of this group resulted in regarding liposomes as delivery systems, which are characterized by carrying a variety of compounds in the core section. (2) These structures can encapsulate and deliver both hydrophilic and hydrophobic substances afflictively. Two important advantages of liposomes, in drug delivery of living organisms, are biocompatibility and biodegradability, which are due to lipid characteristics. (3) Different types of lipids and amphiphiles can act as liposomes. Furthermore, polymers can be used for the synthesis of polymerosomes as new drug/gene carriers.

Types of liposomes and its preparation

There are several approaches for preparation of liposomes, which include the use of mechanical procedures, organic solvents, or through the removal of detergent from phospholipid/detergent micelle mixtures. In liposome preparation, types and amounts of phospholipid, the ionic and charge properties of aqueous medium, as well as time hydrations, are important factors that determine the final liposome structure.

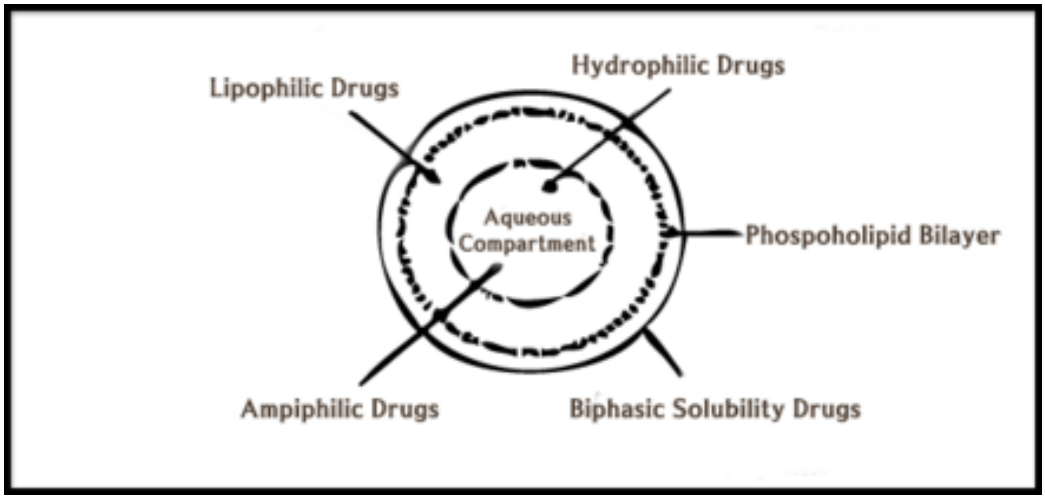

Figure 1. Liposome structure

Multilamellar vesicles preparation

The Multilamellar vesicles are very simplest in production in comparison to all other liposomes.

In this method, stages of liposome generation are used as organic solvent for dissolving of lipid and drying of the resulted mixture. Combination of lipids such as egg lecithin, cholesterol and phosphatidyl glycerol in a molar ratio of 0.9:1.0:0.1 are used respectively. Chloroform or a mixture of chloroform and methanol in a typical ratio of 2:1 are used respectively. Firstly, each lipid component is dissolved in the organic solvent separately, followed by mixing in the suitable proportion with the other solubilized lipids to ensure and uniform distribution of the lipids in mixture. Afterwards, nitrogen stream is used to generate a film from the mixture in test tube. Also, in order to remove any last traces of organic solvent, the film of lipid is allowed to dry completely in an evacuated chamber for a minimum of 4-6 hours. (4)

Unilamellar vesicles preparation

The unilamellar vesicle is the most popular type of liposomes. Its liposome structure allows for an even distribution of trapped agents within a single internal aqueous compartment. There are several methods for preparation of these structures including ultrasonication, extrusion through polycarbonate filters, freeze-thawing, ethanol

injection, detergent method and preparation of sterile large unilamellar vesicles. Bhatia et al (2015) used mixture of different small unilamellar vesicles (SUVs) populations for obtain ternary GUV with uniform property. (5)

Giant Unilamellar

Liposomes Preparation There are many methods in the preparation of giant liposomes based on utilizing only distilled water, nonelectrolyte or zwitterions. There is an increase in attraction between membranes caused by the presence of ions imparting a net charge, and thereby inhibiting the separation of the membrane sheets during the rehydration and swelling process. Recently, researchers have demonstrated preparation of giant liposomes, using physiological strength buffers. There are several methods for preparation of these systems including electroformation, giant liposomes prepared in rapid preparation, using physiological buffer for preparation of giant unilamellar liposomes and osmotic shock technique. Also, Karamdad and coworkers (2015) used new method of a microfluidic for GUV preparation and mechanical characterization. (6)

Drug Delivery System

The art of drug delivery can be defined as the approach of physical, chemical and biological sciences to furnish physiological administration of therapeutic molecules for health benefits. (7) When the pharmacologically effective drugs administered for the treatment of disease endeavor physicochemical and physiological barriers at disease sites, their therapeutic potency is prominently abridged. Hence, improving the physicochemical properties of medicaments and overcoming the physiological barriers for the entry of drug to be delivered into the disease site for efficient therapeutic activity is one of the major concerns of the present day medicine. (8) The limitations of physiochemical and physiological properties finally hinder the therapeutic potential of the administered dosage forms that result in poor clinical performances in the treatment of diseases. These restrictions and shortcomings can be overcome by a controlled drug delivery system where the drug is delivered directly to the site of action capacitated to surpass the effects of physiochemical and physiological barriers, thereby, improving the efficiency of drug delivery. This advanced form of therapy is particularly important when there are conflicts between the doses, the amount of drug required for therapeutic effects and unwanted side effects. (9)

Liposomes as Drug Delivery System

Liposomes are spherical vesicles composed of lipid bilayer arranged around a central aqueous core. They can be composed of natural constituents such as phospholipids and may mimic naturally occurring cell membranes. Liposomes have the ability to incorporate lipophilic and amphiphilic drugs within their phospholipid membrane or they can encapsulate hydrophilic compounds within the aqueous core. Liposome formulations can therefore increase safety and efficiency in reaching the site of action.

The applicability of drugs is always a compromise between their therapeutic effect and side effects. Like allother carrier systems, the use of liposomes in drug delivery has advantages and disadvantages. The amphiphilic character of the liposomes, with the hydrophobic bilayer and the hydrophilic inner core, enables solubilization or encapsulation of both hydrophobic and hydrophilic drugs. The most active drugs against breast cancer are currently the anthracyclines and taxanes (paclitaxel and docetaxel). (10) Strategies for the delivery of taxanes are under active investigation to increase tumor exposure and/or to reduce adverse effects such as neurotoxicity, edema, asthenia, and alopecia. (10,11) Other applications for delivery systems in breast cancer include approved chemotherapy drugs such as vinca alkaloids, platinums, and camptothecins. In each case, it is possible that delivery systems such as liposomes or polymers could improve pharmacokinetics, could increase tumor accumulation, and/or could reduce limiting toxicities. While delivery systems for standard anticancer compounds may increase their clinical utility, there is also intense interest in developing

delivery strategies for novel anticancer agents that cannot be used by themselves as drugs. Delivery systems can potentially overcome many common pharmacologic problems such as those involving solubility, in vivo stability, pharmacokinetics, tumor uptake, and toxicity. The increasing repertoire of sophisticated delivery systems may thus allow new classes of potent anticancer agents to reach clinical application. This includes not only drug delivery, but also liposome-derived systems for nucleic acid-based agents, such as antisense oligonucleotides and gene therapy constructs. (12)

Along with their good solubilization power, a relatively easy preparation and a rich selection of physicochemical properties have made liposomes attractive drug carrier systems. Efficient drug delivery systems based on liposomes need to possess a large number of special qualities. First, good colloidal, chemical and biological stability is required. The fact that liposomes are nonequilibrium structures does not necessarily mean that they are unsuitable for drug delivery. On the contrary, a colloidally stable nonequilibrium structure is less sensitive to external changes than equilibrium structures, such as micelles. Hence, colloidally stable liposomes often work well in pharmaceutical applications. Biological stability includes control over the rate of clearance of liposomes from the circulatory system or compartments of the body, if the drug has been administered locally. The rate of clearance is dose dependent and varies according to the size and surface charge of the liposomes. Early studies using conventional liposomes revealed that the clearance was too rapid for an effective *in vivo* drug delivery. In contrast to a sustained release, liposomes also have to be able to release the encapsulated drug, which might not be as easy as it sounds, and, they should preferably also be targeted. (13)

Liposomes in cancer therapy

Liposomes are used for drug delivery in cancer therapy due to their unique properties. They have the distinct advantages of being non-toxic and degradable in the body because of their naturally occurring lipids as main content. Liposomes have also a unique ability to entrap both hydrophilic and lipophilic drugs to its compartment and lead to a controlled release effect. Drug entrapment in the liposomes has also shown reduced drug toxicity due to minimized uptake in other tissues such as heart, kidneys and gut, beside their ability to protect the entrapped drugs from degradation in the blood stream. Their most important properties are the ability to accumulate in the tumors by passive targeting due to the enhanced permeability and retention effect (EPR). The EPR effect is due to the differences between the vasculature in tumors and healthy tissues. Because of the angiogenesis, the blood vessels in tumor are leakier and have less perfect cellular packing leading to bigger gaps between the cells. Furthermore, the lymphatic system which is responsible for removing substances such as liposomes or other nanoparticles from the tissues is marginally expressed compared to normal tissue. By utilizing the EPR effect, small liposomes (< 70 nm) are able to escape vasculature within tumors and accumulate there via passive targeting effect.

Liposomes have been successfully used in cancer therapy. Although, the application of liposomes in the field of cancer therapeutics has been extensively studied and deserves a broad assessment but this is outside the scope of this review. However, the most successful applications of liposomes in cancer therapeutics are discussed here. A number of different liposomal formulations of anti-cancer agents have been shown to deliver the drug at the site of solid tumors with minimum toxicity as compared to free drug. (14-16)

Currently, there are a many products in the market and in clinical development for use as anti-cancer drug delivery vehicle. Doxil, a PEGylated liposomal formulation, is the first liposomal product that was approved by the FDA for the treatment of kaposi's sarcoma in AIDS patients (17-19). Doxil (US), or Caelyx (outside-US) is a PEGylated liposomal formulation encapsulating anticancer drug doxorubicin commercialized by Johnson & Johnson. In 2011, an imbalance between the demand and supply of Doxil was observed as

the manufacturing unit was shut down temporarily due to some quality control issues. (20,21) To address the Doxil shortage in USA, FDA allowed temporary importation of LipoDox. LipoDox is the same liposomal formulation as Doxil in USA and made in India by Sun Pharma and in 2013, FDA approved the first generic version of Doxil, made by Sun Pharma.

Lipoplatin is the liposomal formulation of cisplatin designed by Regulon Inc. and currently, it is being evaluated in phase III clinical trial for the patients with non-small cell lung cancer. (22) Another liposomal formulation Stimuvax is designed as anti-MUC1 cancer vaccine by Oncothyreon to treat non-small cell lung cancer and presently is in phase III clinical trial. (23-25). The thermo sensitive liposomal formulation of doxorubicin, called ThermoDox (Celsion) 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. (26, 27)

Conclusion

In study of various literature and study work we found and concluded that liposomes as anticancer for use in targeted cancer therapy have solely been investigated in the pre-clinical setting. Obtained results certainly provide a promise that in the future this drug carrier system could achieve more specific and less toxic clinical delivery of a wide variation of anticancer drugs in cancers such as glioblastoma multiform, where currently available therapy lacks efficiency. However, for liposome-based anticancer therapy to display maximal effect and minimal side effects, it requires identification of specific target molecules and appropriate drugs to be delivered.

Liposomes have revolutionized cancer therapy by their broad clinical applications. 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. 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. Thus, based on the molecular characteristics of the different cell populations within a specific tumor, Immuno-liposomes that target a highly expressed molecule and contain a drug of anticipated effect can be prepared specifically for the chosen target cell population. In the clinical setting, this allows application of highly “personalized”, multi targeted Immuno liposomes for the single patient.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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