Progress of Liposome as Drug Carriers

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Abstract. Drug delivery has always been a hot topic of concern for researchers. A good drug delivery system can not only enhance the efficacy of drugs, but also reduce their side effects. Liposome, a microscopic spherical particle similar to bio-membrane, is an ideal drug carrier being used during recent years for its biocompatibility, which has changed the traditional administration method. This article analyze different examples, refers to multiple literature and provides an overview of the birth and development of liposomes, as well as their latest types and applications. Through the research of many literatures, liposome carriers are now applied in many areas, such as cancer, antibacterial drug, wound healing and so on. It is clearly sure that with new polymer materials and different formulations, liposome carriers can handle the treatment of a sea of diseases.

Keywords: liposome carrier, drug delivery, polymer material, formulation.

1. Introduction

Drug delivery systems, the concept that first appeared in the early 1970s, in biopharmaceuticals have a great promoting effect on the field of medicine by enhancing the efficiency and efficacy of therapeutic intervention. One of the key innovations in this area is the development of targeted drug delivery systems, making it possible to deliver drugs in a controlled manner to specific parts of the body where drugs are needed most. Liposome is one of the very popular carriers in this technology. The concept of liposome (once called “bangosomes”) was first proposed by Bangham et al [1]. in 1965 when they established a model for biofilms. As a closed vesicle with an aqueous phase in the middle and a phospholipid bilayer on one side, liposome has a strong amphiphilicity which enables liposome to transport both lipophilic and hydrophilic drugs. To overcome the potential immune responses caused by foreign proteins involved in therapy which directly inject enzymes into patients, as well as the unpredictability of directing a given protein to specific tissues, in 1971, by G. Gregoriadis and Brenda E. Ryman, liposome was firstly applied to drug delivery and the result showed that liposome could not only direct enzymes and drugs to the liver and spleen, but remain intact during the circulation [2]. After the success of the first application of liposome, G. Gregoriadis et al. continued their experiments to verify the feasibility of liposomes as drug carriers. The result shows that entrapment largely controls the clearance of drugs in plasma and their distribution in tissues [3]. Because of the contributions made by pioneers like G. Gregoriadis, scientists began to use liposome as carriers in drug delivery systems. As time passed by, to adapt to different situation, scientists have developed several types of liposomes.

2. Liposome

According to the composition and modification methods, liposome can be classified into the following categories.

2.1. Classical Liposome

Classical liposome, including single-compartment liposome and multicompartmental liposome, is a basic liposome with almost no modification. It is also one of the mainstream types of liposomes.

2.2. "Stealth" Liposome

"Stealth" liposome, the so called "second-generation liposome", is a type of long-circulating liposomes aimed to extend the circulation time of lipid delivery in the body. Depending on the studies by CJ Drummond et al., it shows that aqueous surfactant systems have a positive influence on the longevity of liposome in circulation [4]. Being modified with polyethylene glycol, "stealth" liposome has the ability to create hydrated membranes on its surface. The extended hydrophilic long chains have higher hydrophilicity and spatial resistance, which increase liposome stability and decreasing reticuloendothelial system recognition and uptake. As a result, the circulation time is extended. Besides, "stealth" liposome will have better targeting properties by modifying the terminal PEG molecules

2.3. Cationic Liposome

Cationic liposome (CTL), usually being composed of cationic lipid, is an ideal carrier in drug delivery systems for siRNA transportation through electrostatic interactions. It is now tried to be applied to the treatment of breast cancer by Mingyuan Li et al [5].

2.4. Magnetic Liposome

Magnetic liposome is a kind of liposome combined with magnetic materials, which has a more powerful function in targeting and controllability. Nowadays, magnetic liposome-hydrogel composite is playing a significant role in biomedicine.

2.5. Immunoliposome

Immunoliposomes (IL), referred to liposomes modified by monoclonal antibody fragments, can specifically bind to target cell surface antigens or receptors. It was used by Enrique Barrajón-Catalán et al, to help Trastuzumab target HER2[6].

2.6. pH Sensitive Liposome

pH sensitive liposome, consisting of lipids that are sensitive to pH values as membrane materials, only release drugs when the pH values reach certain range. Rajan Swami et al, develop Docetaxel loaded pH-sensitive SIRT1 shRNA complexed lipoplex to improve the therapeutic effect of breast cancer [7].

2.7. Heat-Sensitive Liposome

Heat-sensitive liposome is composed of lipids with a phase transition temperature higher that body temperature. When experiencing a temperature higher than its melting phase transition limitation, its phase will change from a solid gel to a liquid-crystalline phase, which makes its release of drugs sensitive to environmental temperature. Referred to the recent research, William H. Sauer et al, have proven that animals treated with heat-sensitive liposome had enhanced radiofrequency lesion durability, and that longer-lasting and higher-power radiofrequency treatments had a more noticeable cardiotoxic effect [8].

Since there are lots of types of liposome carriers and each of them has a great influence on drug delivery, it is necessary to have a review on these liposome carriers with a view to provide reference for studies of drug delivery systems.

3. Application

3.1. Cancer Diseases

Cancer is one of the biggest health problems around the world. Moreover, in the past few decades, a sea of people from different countries have been proven to have a higher risk of developing early-onset cancers. Nowadays, the most commonly used methods for tumor treatment include surgical

treatment, radiotherapeutics, chemotherapy, interventional therapy, immunotherapy and molecular targeted therapy. Among them, drug delivery system is a great auxiliary tool to help drug target tumor cells. Liposome is one of the most popular carriers for its targeting, biocompatibility and biosafety.

Liposomal paclitaxel is one of the earliest applied internationally marketed injectable liposomal drugs. It is often used in therapy of ovarian cancer and breast cancer. According to the studies by Zhao Bi et al., patients with breast cancer receiving liposomal paclitaxel therapy have an evident higher apCR (63.5%) than the group receiving PTX therapy (24.6%) and docetaxel therapy (34.8%). Moreover, the research also shows that compared to the PTX and docetaxel groups, the liposomal paclitaxel group saw a considerably decreased incidence of neutropenia (grade III–IV) and peripheral neurotoxicity (grade I–II) [9].

Liposomal doxorubicin is another popular anti-cancer agent which overcomes the deficiency of classical doxorubicin in biosafety. To eliminate the side effects caused by accumulation of doxorubicin, heat-sensitive liposomes and pH-sensitive liposomes are used to encapsulate doxorubicin to deliver it to the tumor. However, the traditional heat-sensitive liposome has its limitations on the drug release speed and amount. In this circumstance, Lyso-Thermosensitive Liposome, being eliminated one fatty acid chain by hydrolysis [10].

Quaternized N, O-oleoyl chitosan (QCS), a polysaccharide that has been quaternized and modified, is synthesized by scientists to added in liposomes to develop an anticancer drug nanocarrier against cervical cancer [11]. As a cationic liposome, Lip-QCS possesses adhesion characteristics, and since QCS creates cationic charges on the liposome surface, it also improves cell attachment.

In addition to stimulating capillary growth and dividing host capillaries and small vein endothelial cells, tumor cells can also create tumor angiogenesis factors and supply ample nutrition for tumors. Given that, a popular therapy is to destroy these capillaries. Suman Dandamudi et al. add MAG-C(magnetite) to liposome without changing the cationic charge potential [12]. Both endothelium and cancer cells are capable of absorbing the acquired MAG-C cationic liposomes, and the retention rate of magnetic cationic liposomes against tumors is increased when external magnets are applied.

In order to improve the anti-tumor effects of its modified nucleic acid aptamers, Hamdi Nsairat et al. loaded small interfering RNA (siRNA) into liposomes [13] for the treatment of triple-negative breast cancer and precisely bound riboprobes as targeting ligands.

In some extreme cases, liposomes are a good choice as carriers. Glioblastoma multiforme (GBM) is a brain tumor that is very aggressive and malignant. It is challenging to remove all tumor tissue without seriously harming the brain in the cases of surgery and radiation. Using boron neutron capture therapy (BNCT), cancerous cells can be specially destroyed while healthy cells are kept intact. According to studies of Bin Feng et al., anti-epidermal growth factor receptor (EGFR) antibodies bound to the liposomes have an effective influence on delivering 10B to glioma cells in BNCT [14].

3.2. Antimicrobial Drug Carrier

Microbial pathogens remain one of the most serious global health concerns. Given that ineffective delivery might result in subpar therapeutic results, liposome carrier is one popular approach to solving this problem, which serves as antimicrobial drug carriers that can increase antibiotic concentrations at the infection site, improve drug uptake, increase bactericidal efficacy, and reduce the toxicity of potentially toxic antimicrobial agents.

Shikonin (SH) is an effective medicine to heal infections caused by methicillin-resistant S. aureus (MRSA). Scientists make SH-liposome through film formation method to improve therapy efficacy. It shows that the SH-liposome can not only damage the integrity of the bacterial cell wall and membrane, but also encourage burn wound and reduce inflammation by controlling the I-KBα/NFKB-p65 pathway [15].

In a similar situation of S. aureus infection, Seyed et al. find that PEG-Lip-NF (nafcillin) has an influence on preventing weight loss of infected mice [16], as a result the virulence of MSSA bacterial is down.

Antimicrobial also have a wide market in the food preservation area. People have started to use basil essential oil (BEO), capsulized by cationic liposome, as antimicrobial to preserve foods, which has an ideal effect for the protection of cationic liposome to maintain completeness of polymeric compound nanofiber structure [17].

Liposomal carrier also plays an important role in delivering some drugs through membranes that they cannot travel. Rhamnolipid-based liposome, used as the nanocarrier system, is considered to be able of helping ParELC3 travel through bacterial membranes [18] to inactivate bacterial topoisomerases.

Antibiotic resistance is a serious problem which happens in antibacterial therapies. For example, those bacterial strains, which have the antibiotic resistance to vancomycin, are hard to deal during clinical therapies. Researchers tried to use sulfonium-based antibacterial lipids as carriers to deliver antibiotics. The result highlights the value of the sulfonium-based lipid's synergistic effect with antibiotics, which indicates that the sulfonium-based lipid penetrated the bacterial membrane and boosted the antibiotics' cellular uptake [19].

3.3. Wound Healing

The healing process of refractory wound is especially long and long-term topical administration of drugs is essential to promote wound healing. However, many drugs applied to the wound healing have poor stability and permeability. Besides, these drugs are also prone to degradation or inactivation on the wound surface. Liposome is an ideal carrier to deliver these drugs for providing a stable physicochemical environment and playing the role of osmotic enhancement and slow release.

A wound on diabetics may cause symptoms such as difficulty in healing the wound, ulceration at the wound and triggering infections in the surrounding skin. It is meaningful to find an effective way to accelerate the healing process of diabetic wounds. According to the research, PVP/CS/TAX nanocomposite membranes do promote wound healing in mice [20]. Nevertheless, with the poor solubility in water, the TAX is not fully utilized. After that, Ding et al. encapsulate TAX using liposomal nanoparticles to increase its bioavailability [21]. With the help of liposome, TAX improves its slow-release effect and promote the healing in diabetic mice.

Artificial dermal substitute (ADS) is another method to cure the wound in diabetics. However, the disadvantage on precision and target limits the use of ADS. As a result, a gene liposome nanocomplex-loaded dermal substitute (GDS) is considered a probable solution, which ensures targeted delivery and slow release [22].

According to the latest research, a LYC-intercalated DPPC liposome (LT NPs) was used as vectors to load antibiotics (tobramycin, TOB), combined with HAMA hydrogel [23], to treat diabetic wound infection. This LT NPs with antioxidative and antibacterial properties could effectively suppress bacterial growth and alleviate ER stress, while promoting angiogenesis and cell migration.

3.4. mRNA Vaccine

mRNAs have a good application on genetic diseases therapeutics. mRNAs vaccines have been increasingly emphasized for their high immunogenic, stability and good safety profile. The mRNA vaccine delivery system with lipid carriers is characterized by precise targeting, good cell affinity and encapsulation.

COVID-19 is a serious public health crisis and vaccines are an important precautionary measure against this virus. In clinical trials, researchers found an effective drug delivery system based on RBD-encoding mRNA formulated in liposomes [24], which indicates the potential of various lipid nanoparticles (LNPs) in mRNA vaccine therapy. In this case, the RBD-encoding mRNA loaded in LNPs successfully expressed in vivo and produced the expected antibodies which effectively bind to the target virus antigen. This study reveals that liposome combined with nanotechnology has a promising future in medicine by delivering vaccines or other drugs to target location.

Subunit vaccines are a popular type of vaccine which contains only the antigenic portion of a pathogen (the antigen that can induce an immune response). Since this vaccine does not contain the

"live" component of the pathogen, there is no risk of introducing the disease, making it safer to use. However, it may require adjuvant and booster injections. Liposome encapsulation higher the vaccine's immunogenic, prevent vaccines from premature degradation and decide the type of the immune response [25].

Modifying the liposome is another approach to improve its ability of delivering mRNA. A research team demonstrates how persistent and improved mRNA distributed to cells in vitro is made possible by the condensing material for mRNA---cationic nanogels---into liposomes [26]. This modification eventually enhances the transfection efficiency and stability of mRNA in vitro, making a wider use of mRNA as therapeutics to be delivered through the whole body without considering producing strong toxic side effects.

4. Conclusion

This article mainly reviews most liposomes' category and key application areas of liposome as drug carriers. Characterized by its remarkable biocompatibility, high targeting and low toxic effects, liposome is widely used in drug delivery and shows a good prospect. Besides the single utilization of liposome, the combined use with nanotechnology, magnetic, and other modification techniques have more application space. Different types of liposome carriers can be constructed for different diseases. Various new formulation technologies have given new vitality to the field of liposomes. This review is aim to introduce the modern liposome technology to more profession relevant personnel. It is pretty sure that liposome carrier will continuously develop and be used with the continuous emergence of polymer materials.

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