Chapter 6
The Use of Liposomes in Enzymes and Drug Design: Liposomes Drug Delivery System

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ABSTRACT

Liposomes are phospholipid vesicles that share many of membranes properties. Liposomes can be easily prepared in a range of sizes. They are able to improve the unfavorable properties of many free drugs such as increasing the amount of drugs delivered to various diseased sites in addition to decreasing the drug toxicities. Encapsulation of enzymes and food ingredients, as well as antioxidants in liposomes also received a lot of awareness. Moreover, an increase for drugs delivered to various diseased tissues was achieved by encapsulating drugs in the liposomes. The topics of encapsulation of enzymes and food ingredients as well as antioxidants in liposomes were highly investigated.

INTRODUCTION

Liposomes are lipid bilayers enclosing aqueous solution in their core. Liposomes can either be passively or actively targeted to diseased tissues whose abnormal vasculature enables the liposomal accumulation. Inserting hydrophilic biomolecules such as polyethylene glycol within the liposomal bilayers was found to increase their stability in blood circulation and consequently raise their treatment efficacy. Liposomes vary in their sizes and can incorporate antioxidants, nutrients, enzymes or pharmaceutical drugs. Through encapsulation of various medications in liposomes, a decrease in their nonspecific toxicities and an increase in the amount delivered to the required location can be achieved. Medications encapsulated inside highly stable liposomal formulations are sequestered and require to be released so that the diseased sites receive appropriate doses of these medications. The main objective of this chapter is to elucidate the role of liposomes in enhancing the effectiveness of therapeutic agents including enzymes. The importance of liposomes in improving the limitations of drugs will also be clarified.

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BACKGROUND

Liposomes are phospholipid vesicles first described by Bangham and his coworkers who showed that aqueous suspensions of phospholipids shared many of the structural and functional properties of membranes (Bangham, Standish, & Watkins, 1965). Liposomes can be prepared by dehydrating phospholipids dissolved in organic solvent. A thin phospholipid film is then obtained producing multilamellar vesicles upon its rehydration. Extrusion is a popular method of unilamellar liposomes preparation where several passes of multilamellar liposomal suspension through small polycarbonate filter membranes yields particles having a diameter near the pore size of the filter used. Consequently, the extrusion method enables the preparation of liposomes in a range of sizes (Hope, Bally, Webb, & Cullis, 1985).

Liposomes were recommended as drug delivery systems to improve the unfavorable properties of many free drugs such as the low stability, poor solubility, rapid metabolism or inappropriate biodistribution. The amphiphilic property of phospholipids enables the liposomes to carry either hydrophilic drugs in their aqueous core or hydrophobic drugs in the lipid bilayer (Leonetti, Scarsella, Semple, Molinari, D'Angelo, Stoppacciaro, Biroccio, & Zupi, 2004). Blood can be distributed to all tissues via the vasculature, which is affected and changed during the disease process. It was evidenced that inflammation results in an early phase of vasodilation followed by increased vessel permeability. Moreover, many of the drug delivery approaches in cancer therapy take advantage of the unique pathophysiology of tumor vasculature. That is, the enhanced permeability of tumor blood vessels and the decreased rate of clearance caused by the lack of functional lymphatic vessels resulted in the increased accumulation of macromolecules in tumors after intravenous administration (Claesson-Welsh, 2015).

1. Steric Stabilization of Liposomes

Most liposomes failed to stay in blood circulation for a few hours, owing to the opsonic activity of the plasma components and to the liposome removal by the cells of the mononuclear-phagocytic systems (Blume & Cevc, 1990). A change in liposome composition by incorporating a negatively charged glycolipid, such as monosialoganglioside produced a steric surface barrier suppressing the elimination of liposomes from the blood by the phagocytes (Gabizon & Papahadjopoulos, 1988). Stealth liposomes containing 10% distearoylphosphatidylethanolamine-conjugated poly-(ethylene glycol5000) (DSPE-PEG5000) stayed in blood and avoided liver and spleen for many hours. It was also assumed that PEG attracted water to the liposomes surface, presenting a barrier to the adherence of protein opsonins. The hydrophilic barrier also retarded disintegration of the liposomes through exchange and/or transfer of liposomal phospholipids to high density lipoproteins (Allen, 1998).

2. Targeted Delivery of Liposomes

A lot of work has been done on liposome targeting in order to achieve tissue or cell specific liposome uptake (Allen & Cullis, 2013). Specific accumulation of liposomal substances in the diseased sites was achieved by attaching of targeting agents to the liposomes. Epidermal growth factor was used as a tumor seeking agent because of its overexpression in many tumor cells (Chaidarun, Eggo, Sheppard, & Stewart, 1994). On the other hand, *in vivo*- tissue distribution of folate-targeted liposomes injected intravenously into mice bearing folate receptor-overexpressing tumors indicated the binding of those liposomes to the folate receptor in the tumor cell (Gabizon, Horowitz, Goren, Tzemach, Shmeeda, & Zalipsky, 2003). As