POLYMERIZED LIPOSOMES TARGETED TO M CELLS AND USEFUL FOR ORAL OR MUCOSAL DRUG DELIVERY

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1. INTRODUCTION

The present invention relates to targeted polymerized liposomes for oral and/or mucosal delivery of vaccines, allergens and therapeutics. In particular, the present invention relates to polymerized liposomes which have been modified on their surface to contain a molecule or ligand which targets the polymerized liposome to a specific site or cell type in order to optimize the immune response to the encapsulated antigen or the efficacy of the encapsulated therapeutic. More particularly, the present invention relates to the use of polymerized liposomes modified to contain a carbohydrate or lectin on their surface to deliver vaccines to mucosal epithelium. The present invention further relates to the synthesis, preparation and use of the modified polymerized liposomes of the present invention as, or in, pharmaceutical compositions for oral delivery of drugs and vaccines.

2. BACKGROUND OF THE INVENTION

2.1. DRUG DELIVERY

Drug delivery takes a variety of forms, depending on the agent to be delivered and the administration route. The most convenient way to administer drugs into the body is by oral administration. However, many drugs, in particular proteins and peptides, are poorly absorbed and unstable during passage through gastrointestinal (G-I) tract. The administration of these drugs is generally performed through parenteral injection.

Although oral vaccination is more convenient, vaccines are generally given through injection. This is particularly true with killed or peptidic vaccines, because of their low absorbability and instability in the G-I tract. A problem with systemic immunization is that it may not effectively induce mucosal immune responses, particularly production of IgA, that are important as the first defense barrier to invaded microorganisms. For this reason, it would be beneficial to provide oral vaccination, if the problems of low absorbability and instability could be overcome.

Controlled release systems for drug delivery are often designed to administer drugs to specific areas of the body. In the gastrointestinal tract it is important that the drug not be eliminated before it has had a chance to exert a localized effect or to pass into the bloodstream.

Enteric coated formulations have been widely used for many years to protect drugs administered orally, as well as to delay release. Several microsphere formulations have been proposed as a means for oral drug delivery. For example, PCT/US90/0643 and PCT/US90/06433 by Enzytech discloses the use of a hydrophobic protein, such as zein, to form microparticles; U.S. Pat. No. 4,976,968 to Steiner et al. discloses the use of "proteinoids" to form microparticles; and European Patent Application 0,333,523 by the UAB Research Foundation and Southern Research Institute discloses the use of synthetic polymers such as polylactic acid-glycolic acid to form in microspheres.

Particles less than ten microns in diameter, such as the microparticles of EPA 0,333,523, can be taken up by cells in specialized areas, such as Peyer's patches and other intestinal mucosal lymphoid aggregates, located in the intestine, especially in the ileum, into the lymphatic circulation. Entrapping a drug or antigen in a microparticulate system can protect the drug or antigen from acidic and enzymatic degradation, yet still allow the drug or antigen to be administered orally, where they are taken up by the specialized uptake systems, and release the entrapped material in a sustained manner or are processed by phagocytic cells such as macrophages. When the entrapped material is a drug, elimination of the first-pass effect (metabolism by the liver) is highly advantageous.

2.2. LIPOSOMES

Liposomes have been proposed for use as an oral drug delivery system, for example, by Patel and Ryman, *FEBS Letters* 62(1), 60–63 (1976). Liposomes are typically less than 10 microns in diameter, and, if they were stable to passage through the G-I tract, may be absorbed through Peyer's patches. Liposomes also have some features that should be advantageous for a particulate system for oral drug or antigen delivery. The phospholipid bilayer membrane of liposomes separates and protects entrapped materials in the inner aqueous core from the outside. Both water-soluble and -insoluble substances can be entrapped in different compartments, the aqueous core and bilayer membrane, respectively, of the same liposome. Chemical and physical interaction of these substances can be eliminated because the substances are in these different compartments. Further, liposomes are easy to prepare. However, liposomes are physically and chemically unstable, and rapidly leak entrapped material and degrade the vesicle structure. Without fortifying the liposomes, they are not good candidates for oral drug or antigen delivery.

Several methods have been tried to fortify liposomes. Some methods involved intercalating cholesterol into the bilayer membrane or generating the liposomes in the presence of polysaccharides. These methods are not useful in making liposome for oral delivery since during oral delivery liposomes are exposed to an acidic pH in the stomach and bile salts and phospholipases in intestine. These conditions break down the cholesterol and polysaccharide in the liposomes.

Investigators have explored the improved stability of polymerized liposomes, however in the area of drug delivery their ultimate utility remains uncertain (Regen, 1987 in Liposomes From Biophysics to Therapeutics, edit. Ostro, Marcel Dekker, N.Y.). Polymerized liposomes have been developed in attempts to improve oral delivery of encapsulated drugs (Chen et al. WO 9503035). The ability of liposomes derivatized with wheat germ agglutinin to better survive the G-I tract has also been investigated (Chen et al., 1995, Proceed. Internat. Symp. Control. Rel. Bioact. Mater. 22; Chen et al., 1995 Proc. 3rd U.S. Japan Symposium on Drug Delivery).

However, to the inventors' knowledge, to date the utility of conventional liposomes for oral delivery is still questionable. Similarly, whether polymerized liposomes are more advantageous than conventional or unpolymerized liposomes for oral drug delivery is still unclear since improved stability alone may not be sufficient for oral drug delivery, particularly oral vaccination. Thus, there remains a need for drug and antigen delivery devices that can survive the harsh conditions in the G-I tract, and effectively deliver the drug, antigen or any other therapeutic.

3. SUMMARY OF THE INVENTION

The present invention encompasses polymerized liposomes which have been modified, preferably on their