Novel pH-titratable stabilizer, SHEMS incorporated pH-sensitive liposome: Synthesis, characterization and in vitro study

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Abstract

Liposomes are being used to deliver drugs, oligonucleotides, enzymes and genes to therapeutic target site. Liposome-mediated delivery of biological active and therapeutic molecules has great advances in transition from the laboratoryto clinical trials. pH-sensitive liposome has been designed to release biological active molecules into cytosol or nuclear target site before approaching lysosomes. Therefore, pH-sensitive liposomes are able to escape a lysosomal degradation. Up to now, several amphiphile pH-titratable stabilizers have been studied such as PHC (palmitoylhomocyteine), OA (oleic acid), CHEMS (cholesteryl hemisuccinate), DOSG (dioleoylsuccinylglycerol) and DPSG (dipalmitoylsuccinylglycerol). Liposomes render pH-sensitive and thus release efficientlytheir active molecules in early endosomal stage because incorporated pH-titratable stabilizers are protonated and no longer maintain liposomal stability in acidic environments such as inner site of endosomes or lysosomes. Even though considerable progressive studies of pH-sensitive liposomes have been made, many elusive barriers to overcome the poor selectivity in bioavailability at specific target tissue, low loading efficiency and instability in the circulation are still remained. In this work, novel pH-titratable stabilizer, stigmasteryl hemisuccinate (SHEMS) was synthesized. Thus, SHEMS incorporated multi-lamellar vesicles (MLV) were prepared by thehydration method. Liposomes were composed of SHEMS and lipids with the appropriate mixing

ratio. A mean diameter of the prepared liposomes was measured by dynamic light scattering. Note that SHEMS can stabilize lipids such as dioleoylphosphatidylethanolamine (DOPE) at neutral pH. However, these liposomes become unstable due to the protonation of SHEMS at acidic pH and show fusogenic behaviors. pH-sensitive release profile of HPTS loaded SHEMS incorporated liposomes was evaluated for 15 hrs at either pH 7 or pH 3. To examine the intracellular deliveryof the SHEMS incorporated liposomes, cellular uptake of calcein loading liposomes into COS-7 cells was monitored by CLSM and FACS analysis. These results imply that the entrapment of biological active moleculesin a novel SHEMS incorporated pH-sensitive liposomes is particularly attractivefor therapeutic applications and pH-sensitive liposome, itself is promising for the efficient intracellular drug delivery carrier.

References

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