Miscibility of Glycerol Diether Bolalipids with Phospholipids for the Application as Oral Drug Delivery Systems

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Introduction and Aims:

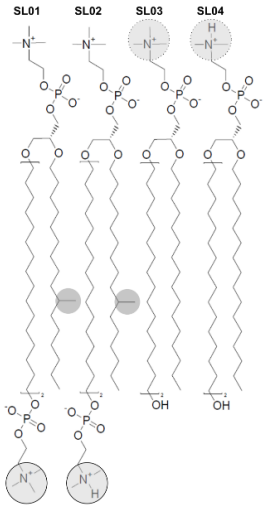
The aim of our research is to develop a liposomal formulation for oral use. For this purpose, we use synthetic analogues of membrane lipids of certain archaea to stabilize classical liposomes. The chemical structure of these bolalipids makes it possible for the archaea to live under harsh conditions such as high temperatures and low pH values. Since the extraction of archaeal lipids is expensive and time consuming, our group synthetizes and investigates analogues of natural occurring bolalipids.

Methods

We mainly use DSC and TEM for the characterization of the aggregation behavior of pure bolalipids and the miscibility of them with classical bilayer-forming phospholipids. Extrusion is used for the production of unilamellar liposomes. By means of DLS, we determine the particle size, particle size distribution, and storage stability of liposomes.

Results

The miscibility of four bolalipids (SL01-SL04) with DPPC as well as the aggregation behavior of these lipid mixtures were investigated. All four bolalipids are asymmetric glycerol diether bolalipids with a long C32 alkyl chain etherified to the *sn*-3 position of a glycerol unit and with either a hexadecyl or a racemic 10-methylhexadecyl residue bound to the *sn*-2 position. SL02 and SL04 have dimethylphosphoethanolamine headgroup that is differently charged depending on pH value. The mixing experiments of SL01 with DPPC showed the formation of different coexisting bolalipid-rich or DPPC-rich phases. TEM pictures revealed the aggregation into sheet-like structures. An ideal miscibility and the formation of closed vesicles consisting of both lipids was not observed. SL02/DPPC mixtures aggregates into liposomes or sheet-like structures depending on the pH value. At pH 5 and 7, the formation of sheets and large vesicular structures was observed. At pH 10 the lipid mixture SL02/DPPC formed liposomes, which were more stable with increasing amount of bolalipid. The bolalipids SL03 and SL04 in mixture with DPPC showed phase separation in the DSC experiments and the formation of large sheet-like structures in the TEM images.



Conclusions

The four investigated glycerol diether bolalipids showed only a limited miscibility with DPPC in the tested mixing ratios. In most cases, coexisting of either phosphocholine-rich or bolalipid-rich phases was observed. The bolalipid SL02 showed pH dependent liposome formation at pH 10. These liposomes were more storage-stable with increasing amount of bolalipid. Although liposome formation at pH 10 is an interesting physicochemical behavior, it is not applicable for *in vivo*.

Keywords

Bolalipids, Lipids, Lipid Mixtures, Liposomes, Drug Delivery