Abstract

Cochleates are cylindrical phospholipid particles with a tightly-packed and dehydrated lamellar bilayer structure. They are formed through a complex pathway initiated by addition of Ca2+ to acidic phospholipid bilayers where aggregation and fusion of the lipid bilayers in the end lead to the cylindrically shaped particles. Based on a high physical and chemical stability caused by the Ca2+-PL interaction and the unique structure, cochleates have been proposed as drug delivery system for oral and parenteral drug delivery as encapsulated drug molecules should be protected in the stable structure until release.

The purpose of the thesis was to evaluate cochleates as parenteral depot formulations. Initially, the formation pathway of cochleates were investigated to obtain more homogenous cochleate formulations by changing the mixing conditions of the formulations. The formation of nonaggregated cylindrical particles at low lipid concentration indicated that the cochleate formation process could be controlled, however, formation speed was also greatly reduced. Additionally, under certain conditions, small rounded non-aggregated particles of 100 nm size could be prepared, which could be interesting for intravenous injection.

To evaluate the use of cheaper raw materials, the preparation of cochleates from acidic phospholipid mixtures derived from soybean lecithin were investigated. The lipid of highest purity (96% PS, 4% PA) formed small and compact cochleates, but the less pure lipids formed larger particles with less ordered and rigid lamellar bilayer structures. Due to the lipids being less pure, it was proposed that for complete formation of a more ordered structure, a higher amount of calcium could be required. Overall, the results indicated that the less pure lipids could be good alternatives to the expensive purified or synthetic phospholipids.

To investigate the possibility of industrial processes in the preparation of cochleates, a scalable mixing device was used to prepare cochleates at increasingly larger batch sizes (2 ml to 40 ml). Through extensive characterization of the cochleates, the batches were found to be similar despite the larger size indicating the feasibility of upscaling the preparation method. Freeze-drying of the cochleates was feasible and did not require any lyoprotectant, however mannitol in the lyophilizates increased the dispersibility.

Finally, the in vivo performance of cochleates were investigated by determining the biocompatibility of cochleate formulations after subcutaneous administration, and the cochleates were found to be well-tolerated. The in vivo release of two lipophilic fluorescent dyes after subcutaneous injection resulted in either fast or sustained release, indicating that sustained release might only be obtainable with certain drug compounds.