Effect of the helper lipid DOPE on endosomal membrane integrity

The zwitterionic helper lipid Dioleoylphospatidylethanolamine (DOPE) is usually incorporated with cationic lipid gene delivery vectors to improve their transfection efficiency by facilitating escape of the DNA from the endosomal compartment. In this study the effect of DOPE on the integrity of model early and late endosomal monolayers was investigated through Langmuir trough and neutron reflectivity experiments.

Mixtures of either neutral or neutral and anionic lipids representing early or late endosomal membranes respectively were dissolved in chloroform and spread on the surface of a Langmuir trough in MES buffer at pH 5 to mimic the endosomal environment then compressed to 30mN/m. Lipoplexes composed of the cationic lipid Dimethyldioctadecylammonium bromide (DDAB) or equimolar mixtures of DDAB:DOPE at 2:1 NP charge ratio were injected in the subphase and changes in surface pressure and neutron reflectivity were measured with time while holding constant area. Interestingly, injections of DDAB:DOPE lipoplexes resulted in a marked increase in surface pressure by up to 15mN/m to 45mN/m in both early and late endosomal models whereas injections of the same concentration of DDAB lipoplexes in the absence of DOPE did not result in a change in surface pressure. Simultaneous neutron reflectivity measurements, however, showed that DDAB in both formulations has been incorporated in both early and late endosomal membrane models within several minutes of injection. This difference in the two experimental techniques is thought to be due to DOPE's ability to form non-lamellar hexagonal phases when the cationic lipid undergoes charge neutralisation upon interaction with the endosomal anionic lipids.