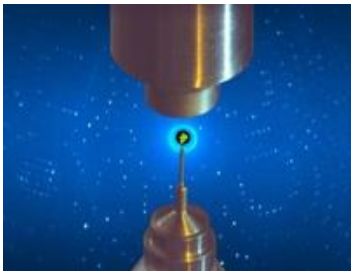

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Structural characterization of mRNA - lipid nanoparticle upon pH changes: a SANS study

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Therapeutic treatments based on the production of proteins by delivering messenger RNA (mRNA) represent a versatile approach. Lipid nanoparticles (LNPs) are promising vehicles for mRNA delivery and are formed by a cationic ionizable lipid (CIL), DSPC, cholesterol (Chol) and a pegylated (PEG) lipid. Even though some LNPs for small interference RNA (siRNA) delivery were recently FDA approved, and vaccines against SARS-CoV-2 based on mRNA-LNPs have been developed and given emergency approval in the last months, there are still concerns about the safety profile of LNPs. In addition, it is not clear how to improve their efficacy following endocytosis. It is suggested that there is a pH change from 7.4 in the extracellular region, to 6.5 in early endosomes, 5.5 in late endosomes and 4.5 in lysozomes. Moreover, the release of siRNA from LNPs occurs within 5-15 min of endocytosis, which implies that LNPs must be designed to escape early endosome compartments at pH 6.5. A good understanding of the physical and chemical characteristics of the LNPs under study is necessary to progress from pre-clinical testing.
We employed small angle neutron scattering (SANS) to investigate the LNP structure and the distribution of components in the LNPs at pH values mimicking the endosomal compartment for 3 different LNP compositions. For the 3 formulations, the LNP core-shell structure was disrupted suggesting that a redistribution of the components occurs upon lowering the pH.

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