pH Dependence of the Structure of Drug-Free Lipid Nanoparticle Dispersions (LNPs)

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Lipid nanoparticle (LNP) dispersions have emerged as promising systems for drug delivery due to their ability to encapsulate and deliver a variety of therapeutic agents effectively [1]. The outer stabilizing shell of LNPs can be engineered to control the release of drugs [2]. Despite their potential, the precise mechanisms governing drug release and delivery remain not well understood. LNPs continue to be a subject of intense research, with a focus on optimizing their performance in drug delivery applications. A key feature of many LNPs is their responsiveness to environmental changes, particularly in pH. For instance, LNPs can release their encapsulated drugs in the acidic environment of endosomes. The current opinion is that the acidic pH triggers a phase transition in the core of the LNPs, destabilizing the LNP structure and leading to drug release into the cytoplasm of the target cells. In our research, we synthesized drug-free LNP dispersions using an antisolvent precipitation technique [3]. These dispersions were designed to mimic the drug-free version of the commercial Comirnaty formulation (Pfizer/BioNTech). To investigate the impact of pH on the structural properties of the LNPs, we performed simultaneous small angle X-ray (SAXS) and neutron scattering (SANS) measurements at the corresponding unique experimental setup at the D22 instrument of the Institut Laue-Langevin (ILL). These techniques provide information about particle swelling and phase transformations in the LNPs as a function of the pH (cf. Fig. 1). The systems were further characterized by in-situ measurements, conducted via a custom-made flow-through setup. These experiments revealed that the conformational changes triggered by pH variations were reversible which could be confirmed by microscopic observations. It has also been observed that pH variations during dialysis exhibit variable exchange rates (cf. Fig. 2). These differences may arise from multiple factors, including variations in buffer capacity and shifts in the apparent pKa, all of which will be systematically analyzed. The structural change triggered by pH variations is a critical feature of LNPs, suggesting that they can be engineered to release their contents in response to specific pH environments within the body. Moreover, the SAXS/SANS data, combined with photon correlation spectroscopy (PCS), allowed us to investigate the particle size distribution (PSD) and gain insights into the LNPs' behavior under different contrasts and pH conditions. By using an iterative SAXS/SANS/PCS approach, we identified a complex particle size distribution that provided valuable insights into the structural dynamics of LNPs [4]. These findings provide key insights for designing LNPs with improved control over drug release and targeting in future therapeutic applications.

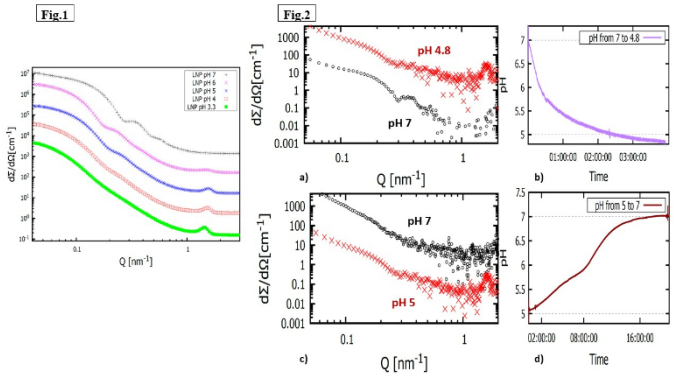

Fig.1: SANS measurements of LNPs synthesized at pH 3.3–7 (D22, ILL); curves at pH 4–7 are scaled (×10–×10000) for clarity. Fig.2: SAXS (a,c) and pH (b,d) measurements using a flow-through dialysis cell; selected curves are scaled (×100) for visualization.

References:

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