Unraveling the microfluidic assembly kinetics of lipid nanoparticles under laminar flow conditions: an in situ Time-resolved SAXS study

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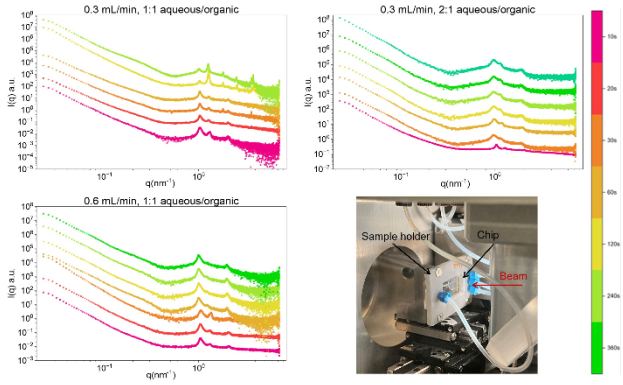
The development of effective drug delivery systems for therapeutics and diagnostics is a challenging matter at the forefront of nanomedicine. Lipid-based nanocarriers (LNPs) currently represent the emergent technology to achieve functional delivery with controlled and targeted drug release and enhanced intracellular uptake [1]. Advances in the development of precision microfluidic devices allow high-throughput screening and optimization of synthetic parameters (i.e. chip geometry, flow velocity and ratios) and lipid/polymer compositions. Thus, highly reproducible nanovectors with desired structural and surface properties can be obtained. However, a lack remains of systematic investigation of fundamental processes, i.e. mechanism and kinetic of assembly in conditions that closely mimic microfluidic assembly. These latter constitute crucial knowledge to control assembly in laminar flow conditions and aggregate stability, since the transient and metastable states influence the final equilibrium states. Moreover, knowledge of relevant synthetic parameters to obtain specific structural and dynamic properties is fundamental to optimizing nanosystem development. In this work, microfluidic-synthetized LNPs were designed and optimized by employing varied molar fractions of lipid components and polymer coatings, and the structural evolution occurring during microfluidic mixing with a laminar flow was investigated with high spatiotemporal resolution. Static and Time-resolved synchrotron SAXS measurements using an *in situ* microfluidic setup showed that the supramolecular assembly and dynamics depend not only on lipid composition, but on total flow velocity and aqueous/organic flow ratios as well (Figure 1). Supramolecular and kinetic characterization was complemented by Dynamic Light Scattering and Zeta potential measurements. The fundamental understanding of the mechanism and kinetics of assembly of these systems is essential to control aggregation and stability, and correlate structural and dynamic properties to carrier functionality [2].

Keywords:
Lipid nanoparticles, Time-resolved SAXS, microfluidics, in situ kinetics



Dependence of assembly kinetics of LNPs according to total flows (mL/min) and flow rate ratios with colour-coded time evolution; (bottom right panel) custom chip setup on P12 beamline of EMBL Hamburg.

References:

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