Fate of self-assembled squalene nanoparticles in a biomimetic medium assessed by scattering techniques

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ABSTRACT

Over the last 20 years, pharmaceutical industries gained interest towards therapeutic nanoparticles (NPs) so-called nanomedicines. The NP formulations demonstrated enhanced properties compared to the drug alone such as improved targeting, reduced toxicity, and enhanced pharmacokinetics. However, there is still a lack of data and understanding of the physicochemical properties of such compounds in particular after their injection in biological media leading to numerous failures in clinical trials[1].

In this context, we proposed to study a particular case of “soft” NPs composed of a pro-drug which consists of a squalene (SQ) linked through an amide bond to Leucine-enkephaline (LENK). Feng et al. demonstrated that LENK-SQ NPs produced an analgesic effect comparable in duration to that of morphine, unlike LENK alone[2-4]. Moreover, contrary to the opioids currently used as painkillers, LENK allows to get rid of the development of an addiction over time by acting on peripherally localized receptors rather than central nervous system opioid receptors.

In this study, we characterized the assembly state of LENK-SQ bioconjugates in a biomimetic environment using physicochemical techniques focusing on small/wide angle X-ray scattering (SAXS/WAXS on SWING at SOLEIL) and small angle neutron scattering (SANS on D22 and SAM at ILL). Taking benefit of the BioSAXS sample changer, we were able to evidence and characterize the micellization of the bioconjugate in conditions that mimic physiological conditions of blood in terms of pH and ionic strength. The influence of different buffers was assessed across a range of concentrations, resulting in various pH and ionic strength conditions in the final suspension. These results were put into perspective with SANS analyses.

The study revealed an equilibrium between LENK-SQ bioconjugates, LENK-SQ NPs and micelles, which depended on buffer concentration[5]. Consequently, the relative proportion of each species appears to be primarily governed by the pH, highlighting its critical role in the relationship between drug efficacy and morphology of self-assembled bioconjugates. These findings provide key insights into how the physicochemical environment can influence NP formation and, ultimately, therapeutic performance.

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