Contribution ID: **30** Type: **Oral**

Fate of self-assembled lipid nanoparticles in a biomimetic medium

Wednesday, 4 June 2025 15:30 (15 minutes)

For two decades, pharmaceutical industries have developed a growing interest towards nanoparticles (NPs). The combination of pharmaceutical activity and nanoscale formulation offers many advantages such as better targeting and reduced toxicity of the drug, improvement of the pharmacokinetic to cite a few. However, the limited knowledge regarding some of their physicochemical characteristics following their administration in the body poses a barrier to their safe use. Despite the abundance of publications in the field over the past years, only a limited number of nanoparticles have received marketing authorization (1).

In this context, we propose to study a particular case of "soft" NPs formed by self-assembly in water of the squalene-Leucine-enkephalin (SQ-LENK) prodrugs. These amphiphilic nanomedicines are intended to alleviate pain in patients after intravenous administration without causing side effects (2). Indeed, these SQ-LENK NPs constitute a great alternative to other opioids like morphine since they displayed an important analgesic activity in vivo with a longer lasting effect. Moreover, it was observed that unlike morphine, they act on peripheral opioid receptors thus avoiding the central nervous system, commonly implicated in the occurrence of addiction phenomena (3).

Following previous studies on the influence of different linkers between squalene and enkephalin on the NP stability (4), this study aims to characterize the behavior of SQ-LENK NPs in a biomimetic environment. To replicate physiological conditions, the NPs were examined in various buffer solutions across a range of concentrations, resulting in different pH and ionic strength values. A combination of SAXS/WAXS and SANS techniques was then employed to investigate the evolution of the internal structure, size, shape and self-assembly state of SQ-LENK NPs in these buffered media.

The analysis finally revealed an equilibrium between SQ-LENK NPs, micelles and monomers (SQ-LENK bioconjugates composing the NP) depending on the buffer concentration. As a first result, the relative proportion of each compound in the suspension appears to be primarily governed by the pH. Variability in self-assembly can significantly impact the pharmacokinetics of these prodrugs, thereby influencing their therapeutic efficacy. Consequently, precise characterization of size distribution, morphology, and the nature of the self-assembled structures is essential for effectively controlling the activity of such NP formulations.

For now on, ongoing studies are focused on investigating the interactions between blood proteins and SQ-LENK NPs in buffered media in order to be one step closer to the biological media.

References:
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Session Classification: Contributed talks