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Physico-chemical characterization of ferrocifen loaded lipid nanocapsules: different drug delivery systems depending on succinimido-ferrociphenol structure

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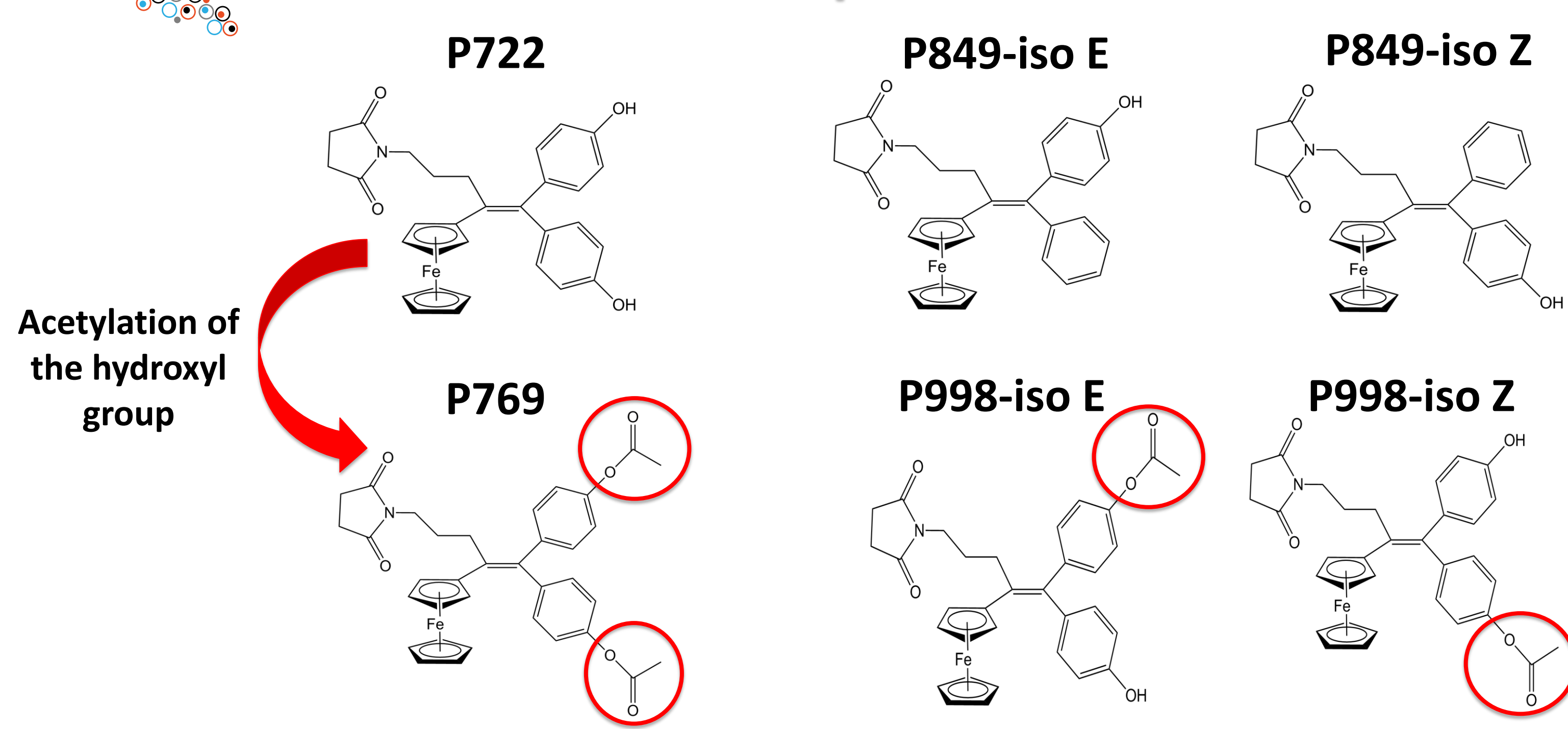
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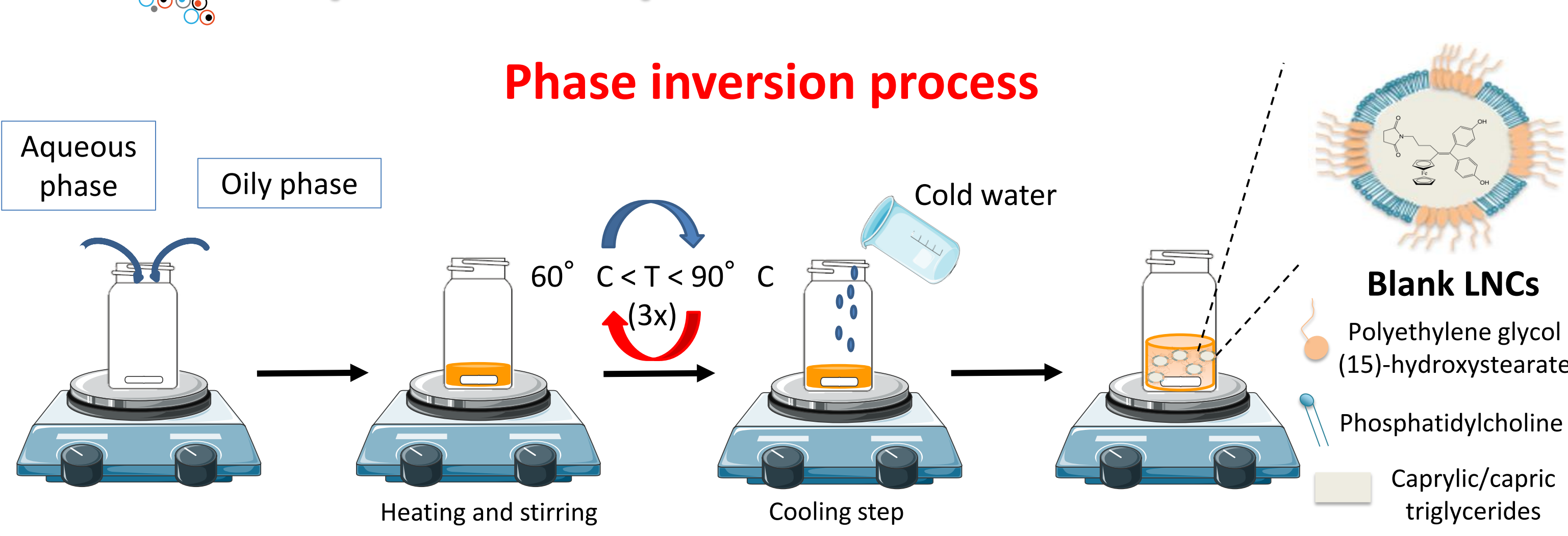
Introduction and objectives

The resistance to the current chemotherapeutic drugs has obliged the scientific community to seek innovative strategies (molecules, nanoparticles or gel). In the late 1990s, Jaouen's team synthesized a new class of **bio-organometallic molecules** called **ferrocifens** [1]. However, their high lipophilic nature requires a formulation stage before being administered *in vivo*. **Lipid nanocapsules (LNCs)**, developed in 2001 [2], have shown their ability to successfully encapsulated ferrocifens. In last decades, ferrocifen loaded LNCs have demonstrated anticancer properties on multidrug-resistant cancers (glioblastoma, metastatic melanoma, breast cancer) on mice models [3]. The most recent family of ferrocifens (**the succinimido-ferrociphenols**) seems to be the most efficient on several resistant cancer cell lines, with IC₅₀ in the nanomolar range [4]. As LNCs are composed of an oily core (caprylic/capric triglycerides), playing with the lipophilicity of the succinimido-ferrociphenols can be interesting to improve the drug loading in LNCs. In the present work, 50 nm LNCs loaded with six different succinimido-ferrociphenols were formulated. For each ferrocifen, the maximal drug loading was determined. Interestingly, the encapsulation of two ferrocifens led to the formation of **gels**: it is unprecedented. In order to understand this phenomenon, tensiometry measurements were performed to determine a potential influence of the ferrocifen position in the LNCs.

1. Succinimido-ferrociphenol structure



2. Lipid nanocapsule formulation



3. Encapsulation efficiency and dispersity

The concentration in ferrocifen is expressed in mg/g of lipophilic molecules (ferrocifen + caprylic/capric triglycerides + polyethylene glycol (15)-hydroxystearate + phosphatidylcholine)

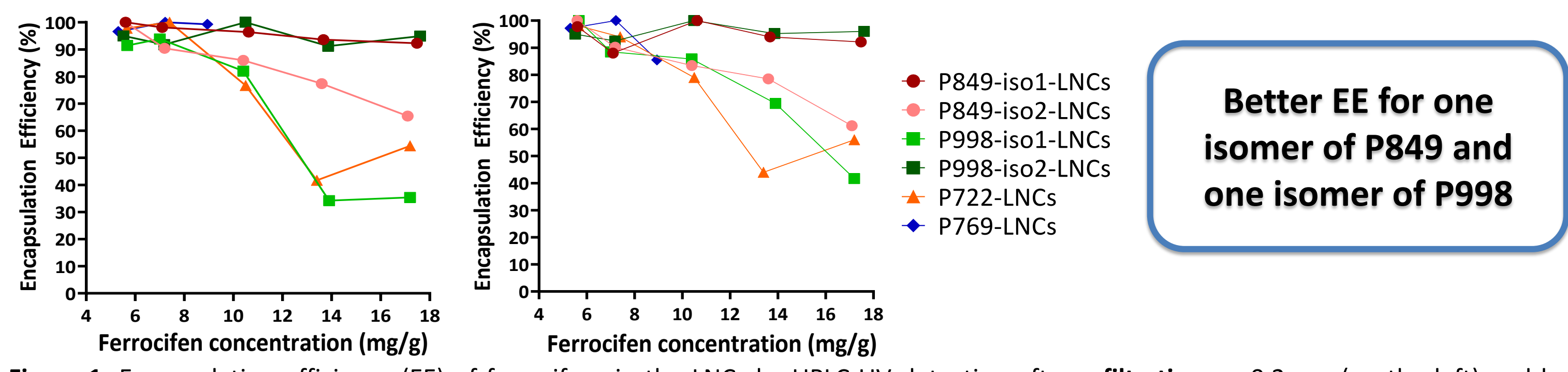


Figure 1: Encapsulation efficiency (EE) of ferrocifens in the LNCs by UPLC-UV detection after a filtration on 0.2 µm (on the left) and by sedimentation (on the right).

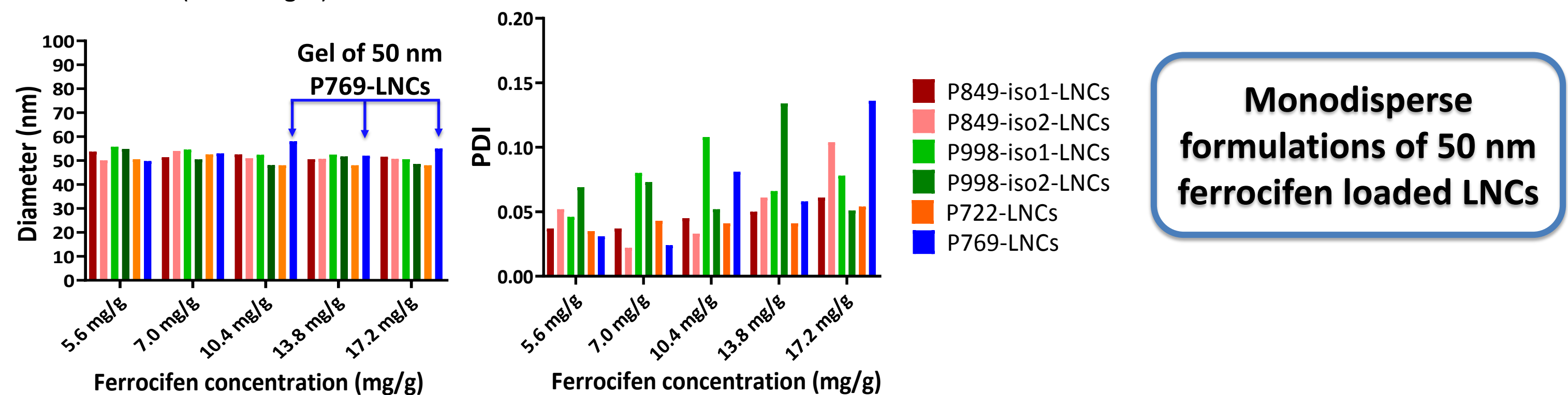


Figure 2: Diameter (on the left) and polydispersity index (PDI) (on the right) of ferrocifens loaded LNCs, obtained by DLS.

4. Rheological studies of ferrocifen LNC gel

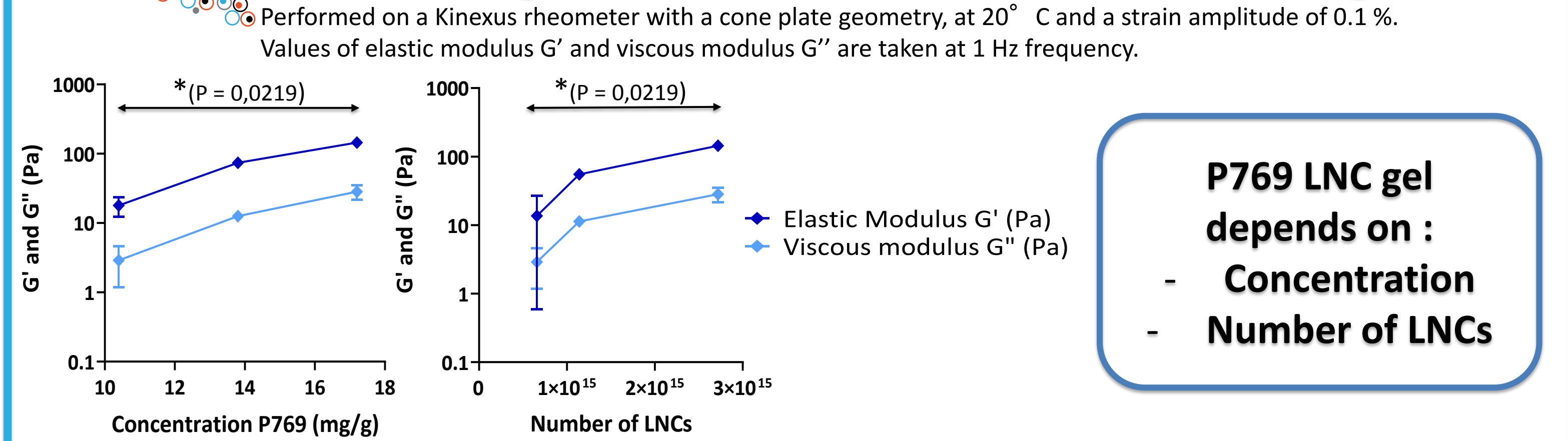
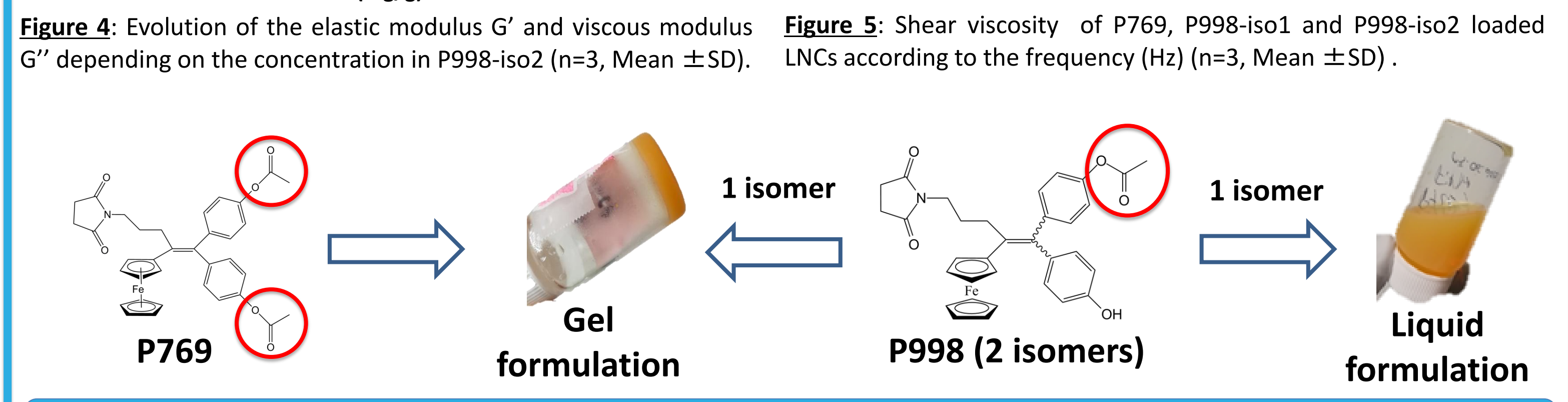
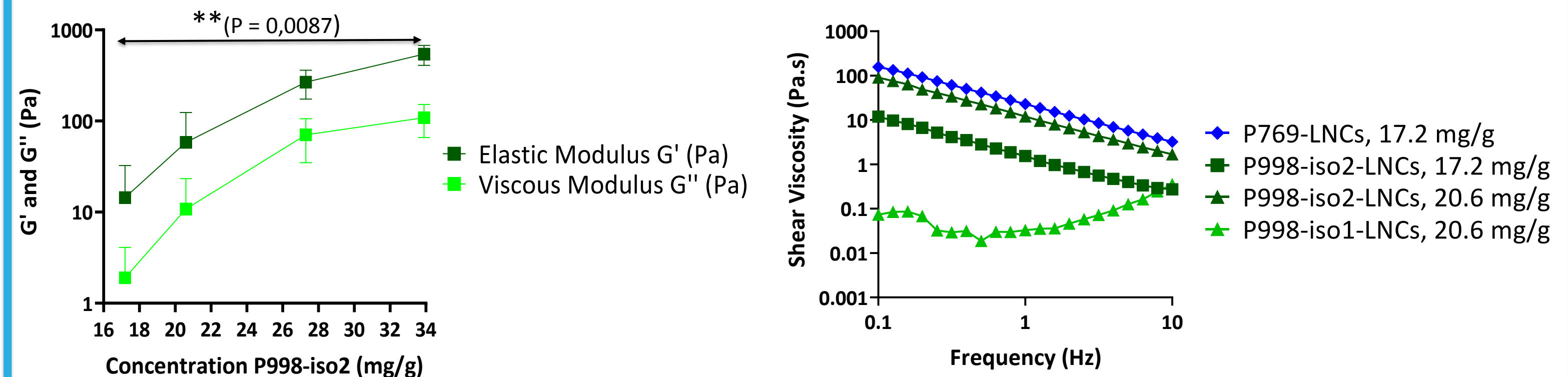


Figure 3: Evolution of the elastic modulus G' and viscous modulus G'' depending on the concentration in P769 (on the left) and on the number of LNCs in the formulation (on the right, values obtained with a concentration in P769 of 17.2 mg/g) (n=3, Mean ± SD).



5. Position of ferrocifens: in/on the LNCs ?

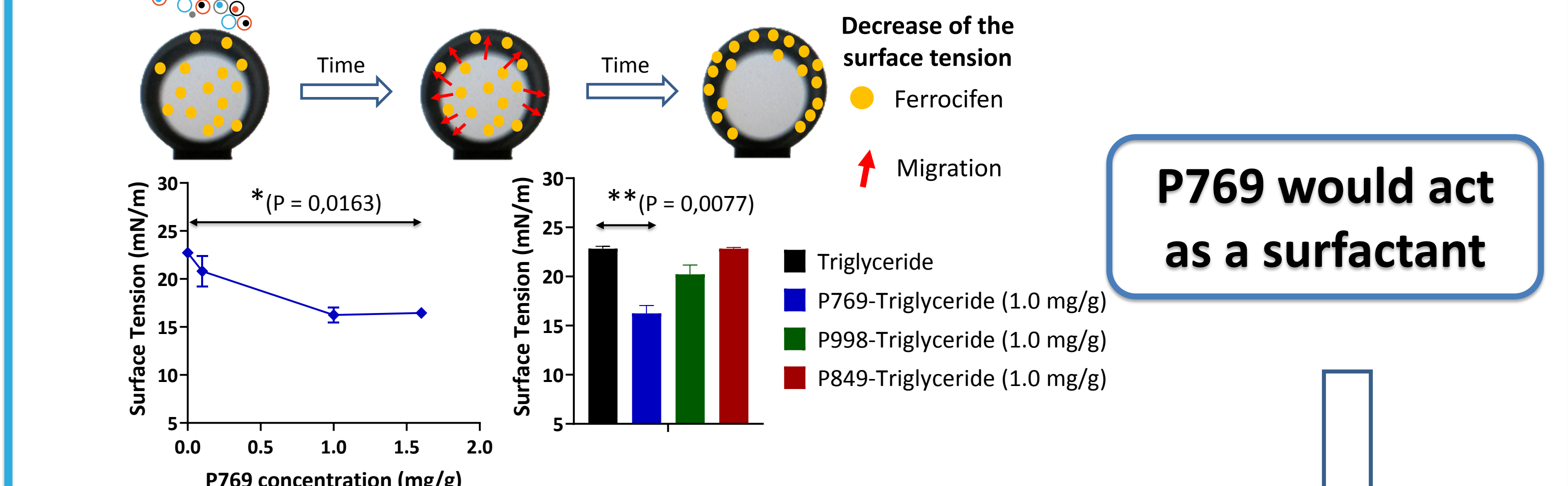


Figure 7: Surface tension of a caprylic/capric triglyceride drop (10 µL) with or without ferrocifen, in a water phase, recorded in time by using a video camera connected to a microcomputer, at 20.8 ± 0.3° C (n = 3 or 4, Mean ± SD).

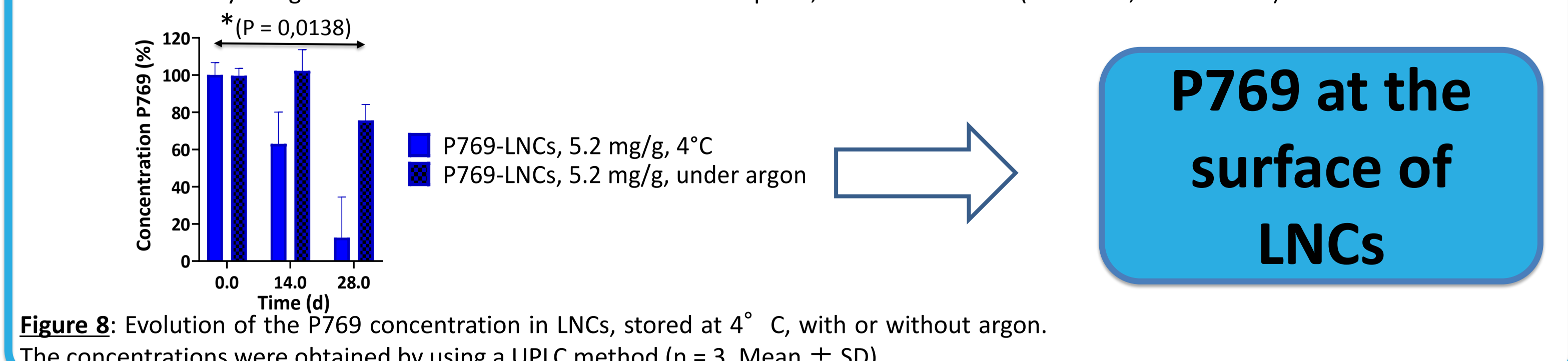


Figure 8: Evolution of the P769 concentration in LNCs, stored at 4° C, with or without argon. The concentrations were obtained by using a UPLC method (n = 3, Mean ± SD).

Conclusion

As expected, the encapsulation of the succinimido-mono-ferrociphenols (P849) and succinimido-monoacetyl-ferrociphenols (P998) resulted in higher drug loading than the P722. However, for the first time with ferrocifens, a **gel** made of **LNCs** was obtained with **P769** and with one isomer of **P998**. The position of the **acetyl group** on the succinimido-ferrociphenols seems to have an importance in the gelification process observed. The **position** of P769 at the surface of LNCs, could be an explanation to this phenomena. Interestingly, these unexpected results could lead to two treatment strategies: one liquid formulation for systemic administration and a gel for a local administration.

References:

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