The same nucleoside crosslinking agent to develop hydrogel and organogel platforms

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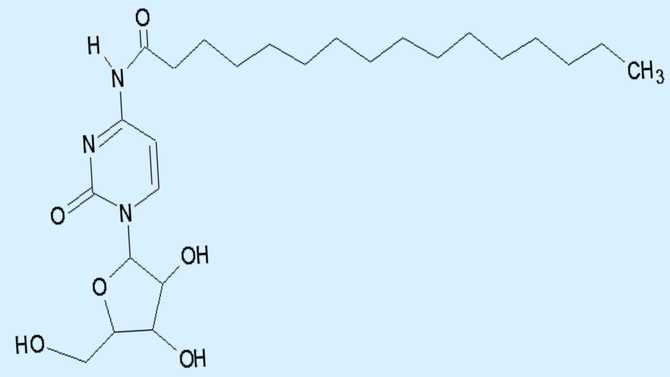
- Gels are attractive pharmaceutical systems to develop local administration and/or drug sustained release therapy.
- Nanoparticle-loaded gels combine the gel advantages with the nanoparticle properties: stealthiness, targeting site, decreased toxicity and protection of the encapsulated drug from degradation.
- Previously, the formulation of gemcitabine-loaded lipid nanocapsules (LNCs) formed an unexpected and spontaneous gelling [1].
- This hydrogel was due to H-bond interactions between gemcitabine moieties exposed at the LNC surface.
- The subcutaneous administration of this hydrogel in mice showed a sustained release of LNCs along with a progressive accumulation in lymph nodes, and allowed to combat mediastinal metastases issued from an orthotopic non-small-cell lung cancer model [2].

We decided to develop the same platform without the use of gemcitabine (highly toxic component), replacing it by an endogenous molecule with similar properties.

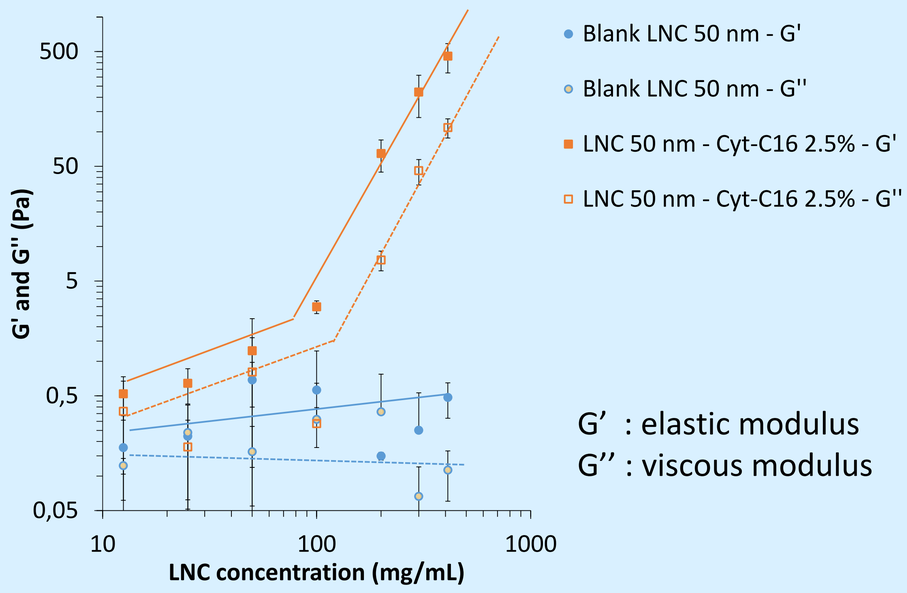


Palmitoyl cytidine (Cyt-C16)
Cytidine is an endogenous molecule and its structure is close to gemcitabine.

Hydrogel of LNCs

Rheological properties

A gel form could be obtained at a Cyt-C16 concentration of **1 or 2.5%** (w/w Labrafac®) and LNC concentration higher than **0.2 g/mL**, for LNC sizes from **50 to 100 nm.** For all the gels, phase transition temperatures were higher than the body temperature (> 70°C) (Kinexus® rheometer, Malvern Instruments S.A). (mean ± sd; n=3)

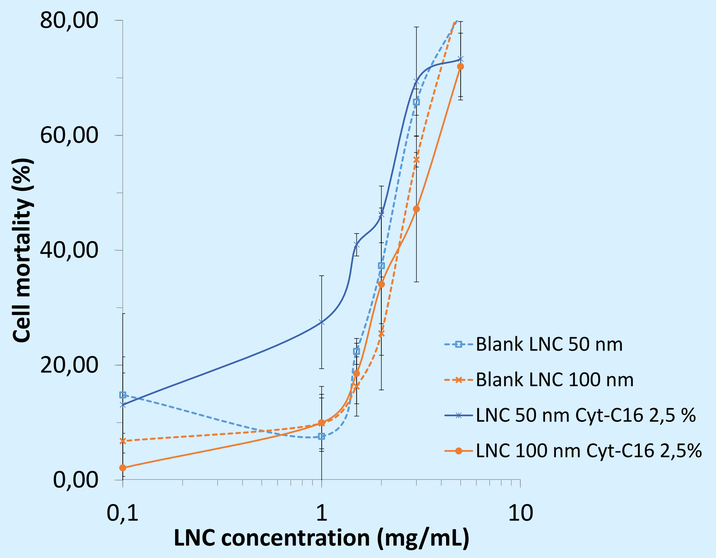


G’ : elastic modulus
G’’ : viscous modulus

An administration with a syringe does not alter the gel state of the formulation. Inclusion of urea, sodium chloride and ethanol (60 mol for 1 mol Cyt-C16) in the formulation to inhibit physical association, did not change the rheological properties of the hydrogel.

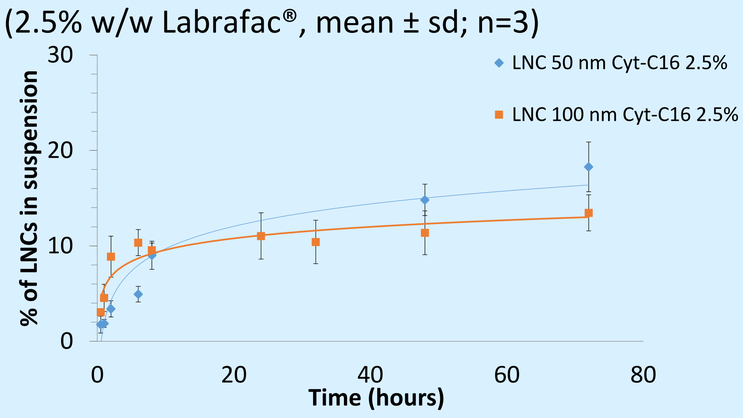
Cytotoxicity

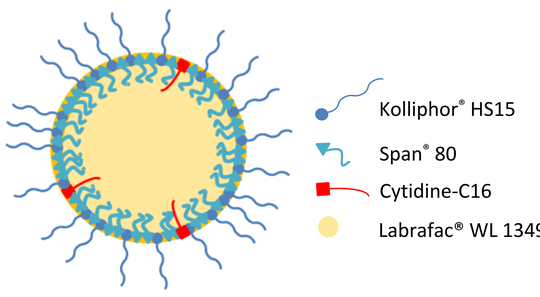
Cell mortality study on a macrophage cell line (derived from THP-1 cell line) confirmed the safety of Cyt-C16, comparing LNCs with and without Cyt-C16. (48h incubation, 37°C, MTT test, mean ± sd, n=3)



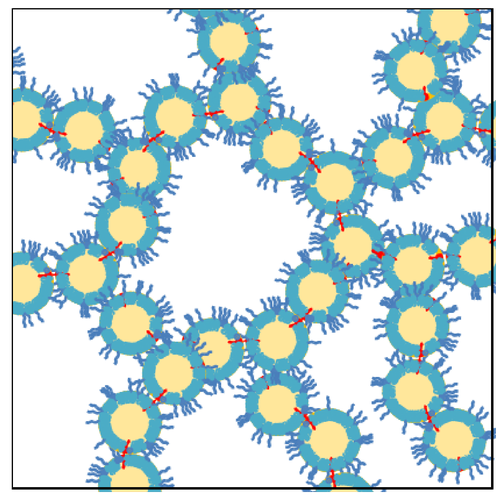
Release

The *in vitro* release of LNCs from hydrogel study was performed in artificial extracellular matrix (pH 7.4) at 37°C over 3 days. LNCs were labelled with nile red dye and followed by fluorescence. (2.5% w/w Labrafac®, mean ± sd; n=3)





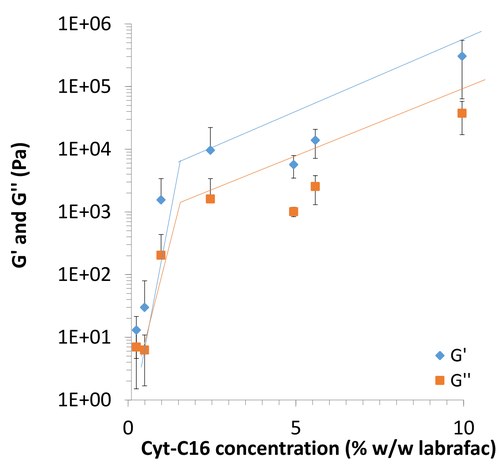
Cyt-C16 loaded LNC :
cytidine moieties are exposed at the surface. LNCs were produced by the classical phase inversion process [1].

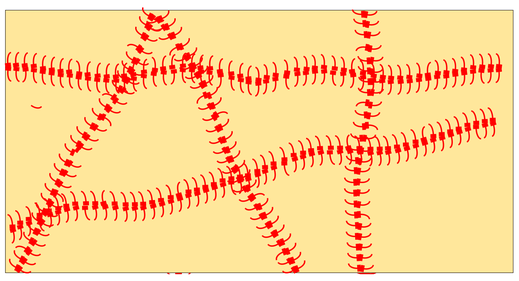


An hydrogel resulted from **H-bond interactions** between LNCs, forming a network in water similar to a tridimensional pearl necklace structure.

Organogel

Cyt-C16 was also able to form an organogel. The molecule was simply solubilized in an oil phase at high temperature and a gel was formed after cooling. Viscoelastic properties of the organogel were enhanced with increasing Cyt-C16 concentration (Kinexus® rheometer, Malvern Instruments S.A,). (mean ± sd; n=3)





Organogel was due to **interactions** between Cyt-C16, forming fiber network in oil.

Conclusion

Cyt-C16 is a very promising crosslinking agent to obtain two gel platforms with opposite properties. The LNC-based hydrogel could allow sustained release of lipophilic drug loaded nanocarriers after subcutaneous administration. Whereas, sustained release of hydrophilic components could be obtained from the organogel.

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