The same nucleoside crosslinking agent to develop hydrogel and organogel platforms

Marion Pitorre1,2, Guillaume Bastiat1,2, Le Thuy Trang Pham1,2 and Jean-Pierre Benoit1,2

1 LUNAM, MINT, Angers, France; 2 INSERM, U1066, Angers

• 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.

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)

Cytoxicity

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 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)

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.

References