Lipid nanocapsule-loaded polymer-free hydrogels: a new generation of implants to control drug sustained releases

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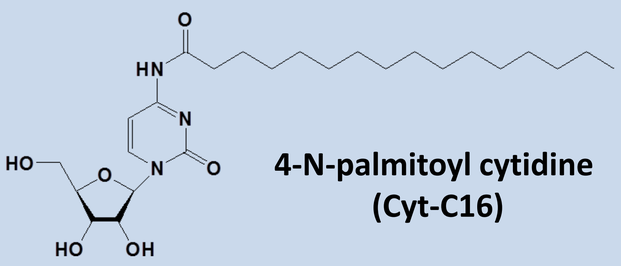
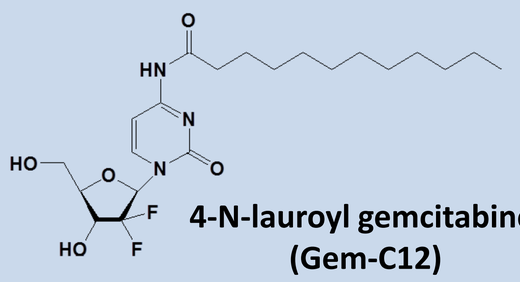
INTRODUCTION

New drug delivery systems were designed as nanoparticle-loaded hydrogels. These attractive pharmaceutical systems combine the gel advantages: local administration and/or a drug sustained release, and nanoparticle properties: stealthiness, targeting and decreased toxicity. Nevertheless, even using biodegradable polymer to design the gel matrix, implants can always be found at the injection site long time after administration. This research focuses on the development of lipid nanocapsule (LNCs)-based hydrogels without the use of polymer, and the drug release profiles from the hydrogel and their modulation correlated to hydrogel characteristics.

SYNTHESIS OF CROSS-LINKING AGENTS

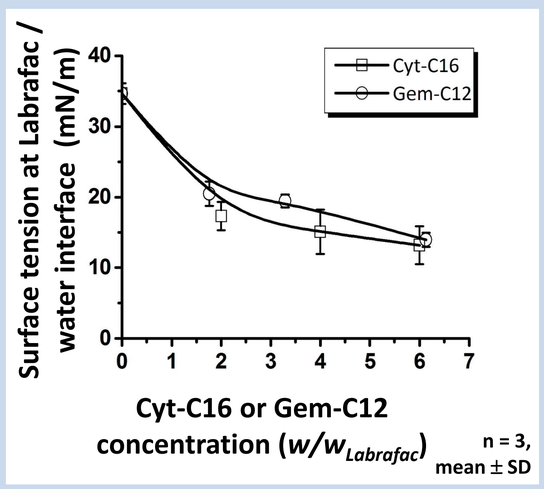


4-N-palmitoyl cytidine (Cyt-C16)



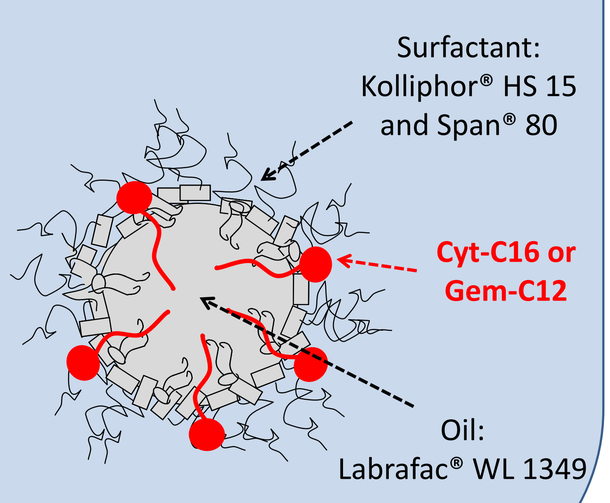
4-N-lauroyl gemcitabine (Gem-C12)

The two aliphatic-modified cytidine and gemcitabine exhibit amphiphilic properties, at oil/water interface. They are positioned at the surface of lipid nanocapsules (LNCs), formulated using a phase inversion process.[1,2,3]



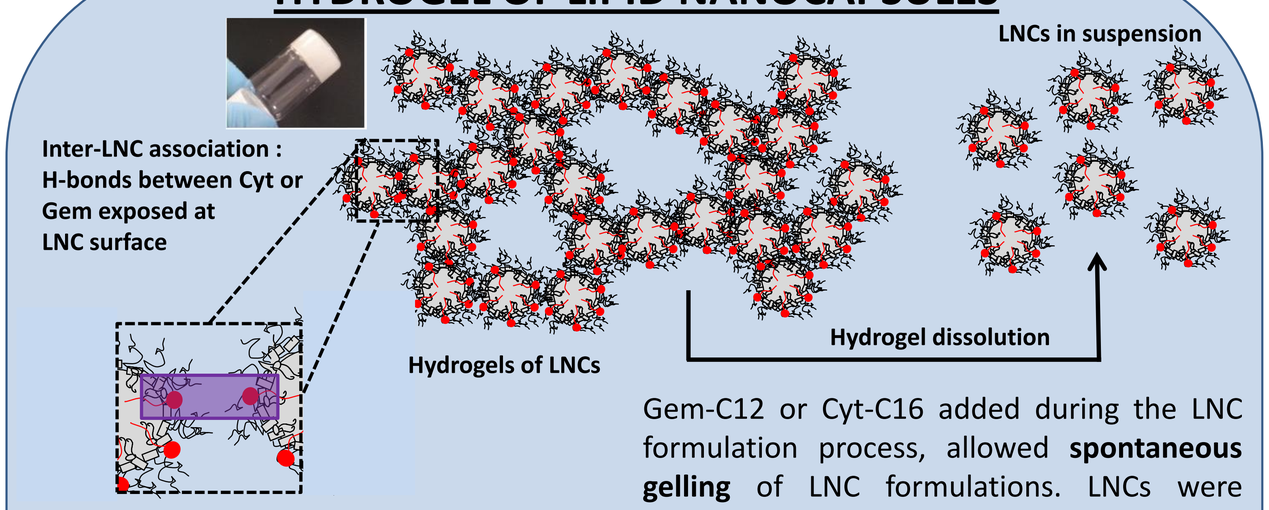
n = 3, mean ± SD

Drop tensiometer (Teclis Scientific)

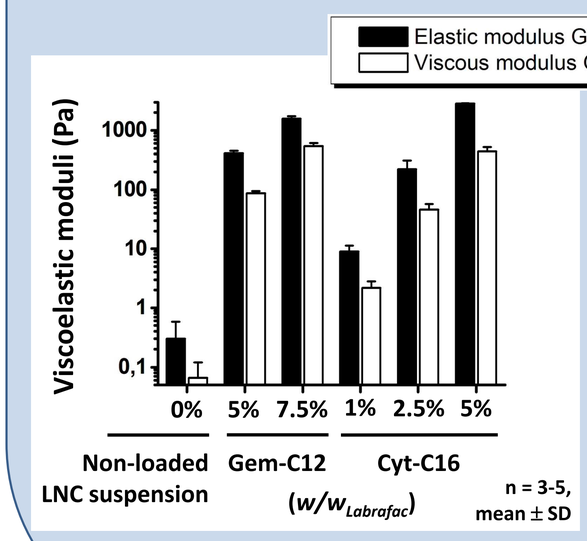


lipid nanocapsules (LNCs)

HYDROGEL OF LIPID NANOCAPSULES

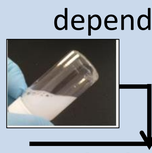


Gem-C12 or Cyt-C16 added during the LNC formulation process, allowed **spontaneous gelling** of LNC formulations. LNCs were associated in a **three-dimensional network due to H-bond interaction** between Gem or Cyt moieties at LNC surfaces leading to formation of **polymer-free hydrogels**. Viscoelastic properties of the hydrogels depend on Gem-C12 or Cyt-C16 loading.[2,3]



n = 3-5, mean ± SD

Kinexus® (Malvern Instruments S.A.)



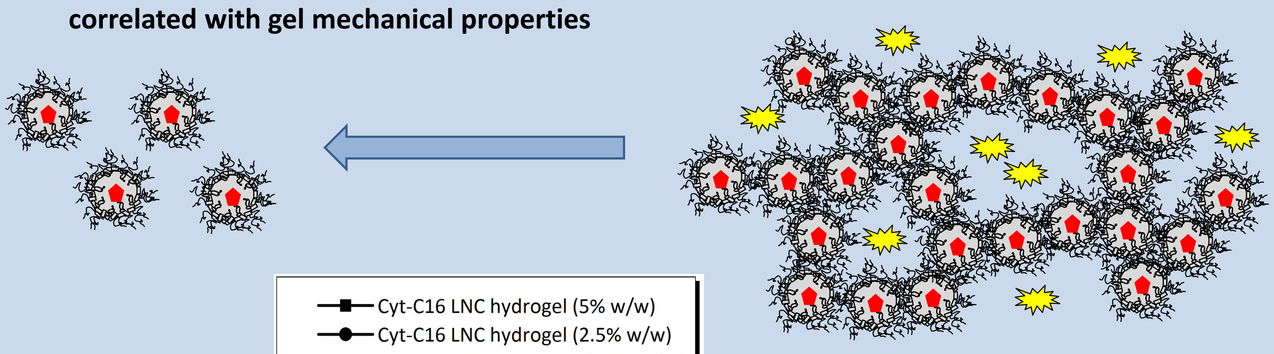
	Z-ave (nm)	PdI
Non-loaded LNCs	56 ± 2	0.06 ± 0.03
Hydrogel of Cyt-C16-LNCs after dissolution	51 ± 3	0.06 ± 0.04
Hydrogel of Gem-C12-LNCs after dissolution	55 ± 2	0.05 ± 0.01

n = 7-20, mean ± SD

Zetasizer® Nano S (Malvern Instruments S.A.)

RELEASE PROFILES

Sustained release of LNCs (loaded with lipophilic drug model), correlated with gel mechanical properties



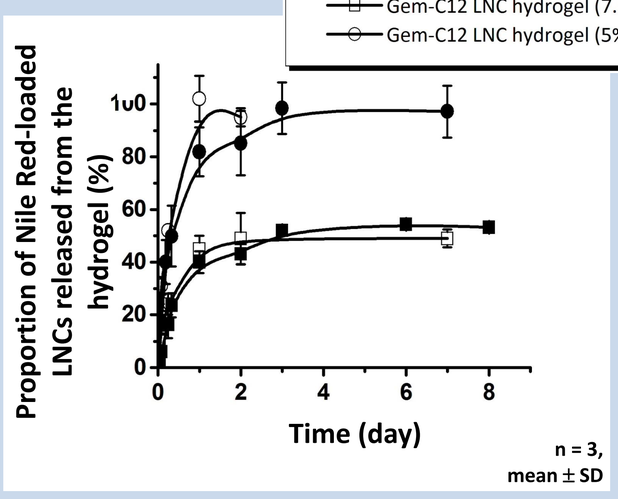
Rapid release of hydrophilic drug model, gel mechanical property-independent

Protocol

300µL of hydrogel and 5.7 mL of artificial extracellular matrix (37°C, no stirring).[3,4]

Lipophilic drug model : Nile Red, loaded in LNCs[2,3,5]

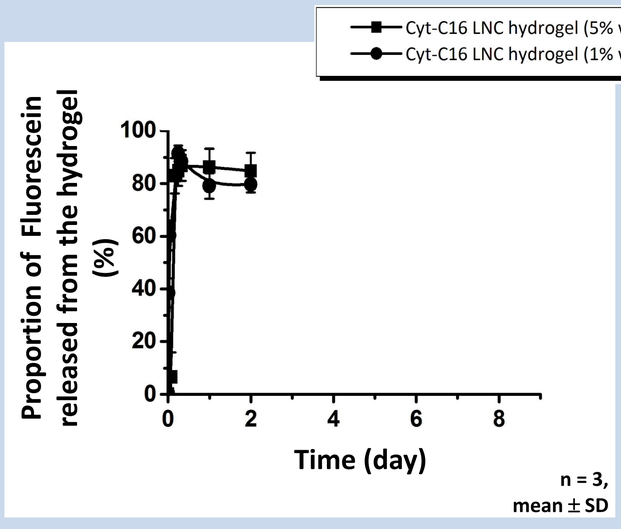
Hydrophilic drug model : fluorescein, solubilized in hydrogel solvent



n = 3, mean ± SD

Fluoroscan Ascent® (Labsystems S.A .)

In the hydrogel, lipophilic drugs were encapsulated in LNCs and hydrophilic ones were loaded in medium around the LNC network. The **LNC (and lipophilic drug) release profiles are controlled by mechanical properties of the hydrogels** (slower release profiles correlated with higher mechanical properties). There is **no correlation between hydrophilic drug release profiles and hydrogel viscoelastic properties** (due to drug diffusion). Whatever the hydrogel characteristics, **total LNC release profiles were achieved and hydrogels were totally solubilized leading to LNC suspensions.**[2,3]



n = 3, mean ± SD

Fluoroscan Ascent® (Labsystems S.A .)

CONCLUSION

New generation of nanoparticle-loaded hydrogels: LNC-based, polymer-free hydrogels is promising as implants for health application. Once the LNC release is completed, no gel matrix remains at the injection site, minimizing the additional toxicity due to the persistence of polymeric implant. Drug sustained release profiles can be controlled by the mechanical properties of the hydrogels and will be tailor-made, depending on the therapeutic strategies.

REFERENCES

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2) Moysan E. *et al.*, Soft Matter, 2014, 10, 1767
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4) Kinnunen H. *et al.*, J. Control Release, 2015, 214, 94
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