Optimization of an NLC-loaded hydrogel for fenretinide and YARA local codelivery

Isabella Draszesski Malagó [a, b]; Vanessa Franco Carvalho Dartora [a]; Luciana Biagini Lopes [b], Alyssa Panitch [a]

[a] Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University – USA

[b] Department of Pharmacology, Institute of Biomedical Sciences, University of São Paulo – Brazil

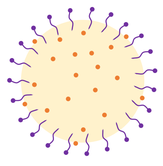
isabella.malago@bme.gatech.edu/isabelladmalago@usp.br

Introduction

We have designed a multifunctional system for the simultaneous local delivery of lipophilic and hydrophilic compounds to the mammary tissue, aiming at breast cancer chemoprevention, consisting of a nanostructured lipid carrier (NLC)-loaded *in situ* forming hydrogel. The lipophilic drug is fenretinide (Fen), a well-tolerated breast cancer preventive with limited use due to low bioavailability (1,2); the hydrophilic molecule is YARA, a MAPKAP kinase-2 inhibiting peptide (3). Here, we present results on optimizing the NLCs for hydrogel incorporation.

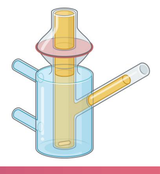
Methods

1. NLC characterization

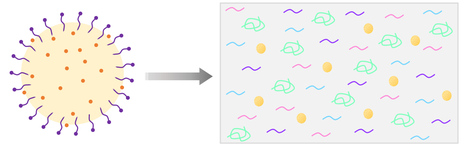


- Cryoprotectant selection based on size and PDI
- Aqueous phase selection based on rheology
- Transmission electron microscopy (TEM)

2. Fenretinide in vitro release

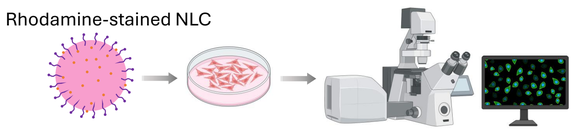


3. NLC incorporation into hydrogel and hydrogel characterization



- Rheology
- Scanning electron microscopy (SEM)

4. NLC cellular uptake by confocal microscopy



Results

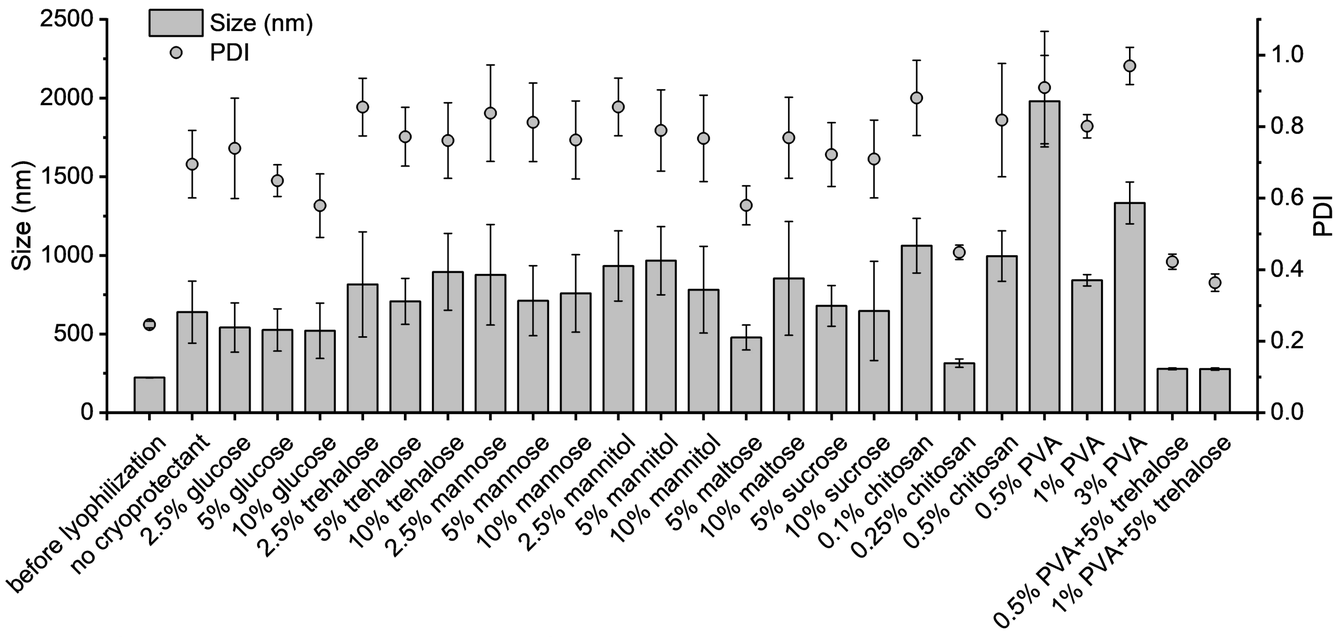


Figure 1 . Size (left axis) and PDI (right axis) of NLCs containing a range of cryoprotectants after lyophilization and reconstitution in PBS. For comparison, data for the NLC before lyophilization is also presented. Mean ± SD; n = 3.

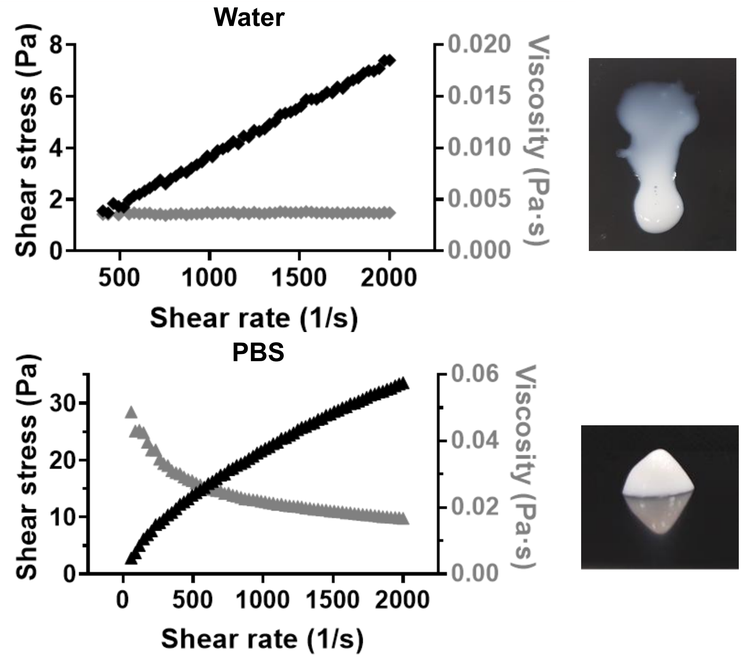


Figure 2. Influence of the aqueous phase (water or PBS) on NLC rheological behavior and viscosity. Malagó, 2026 (4).

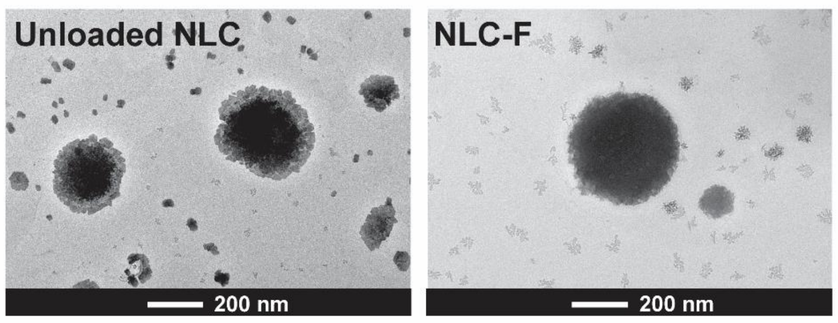


Figure 3. NLC TEM images (unloaded and fenretinide-loaded). Malagó, 2026 (4).

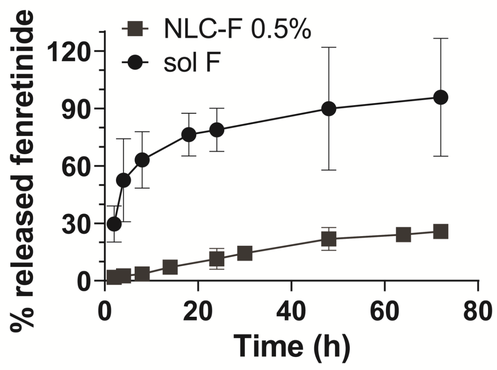
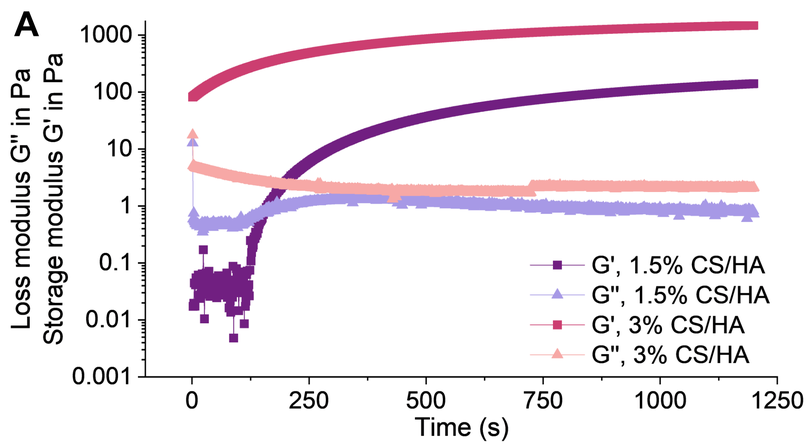


Figure 4. Fenretinide in vitro release from the NLC. Data expressed as percentage of fenretinide released, in relation to the total amount, as a function of time (mean ± SD; n = 3). Malagó, 2026 (4).



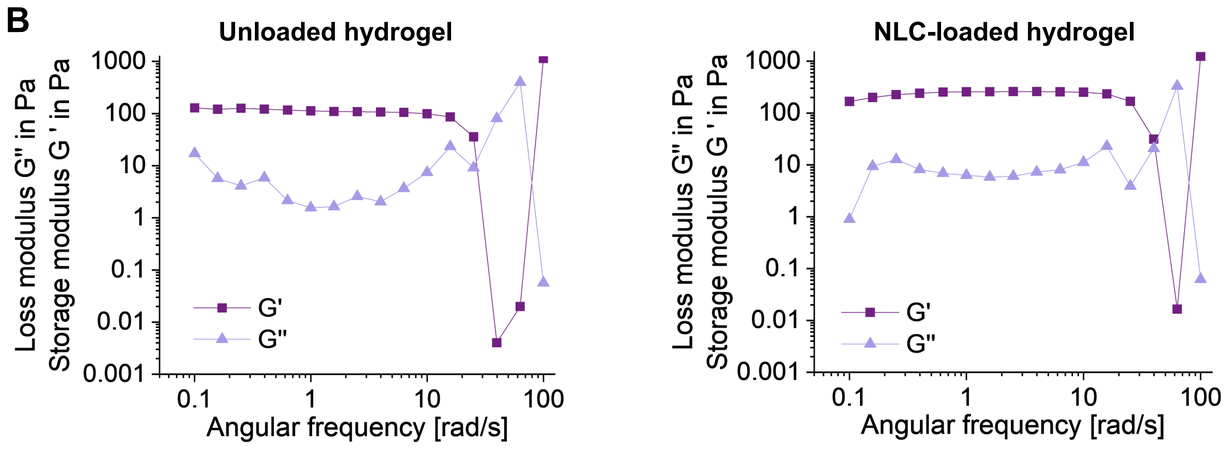


Figure 5. Rheological study of the hydrogels. **(A)** Study of the crossover point between the storage and loss moduli in hydrogels composed by 1.5% or 3% total CS/HA. **(B)** Frequency sweep of unloaded and NLC-loaded hydrogels composed by 1.5% CS/HA at a constant shear strain of 0.5%

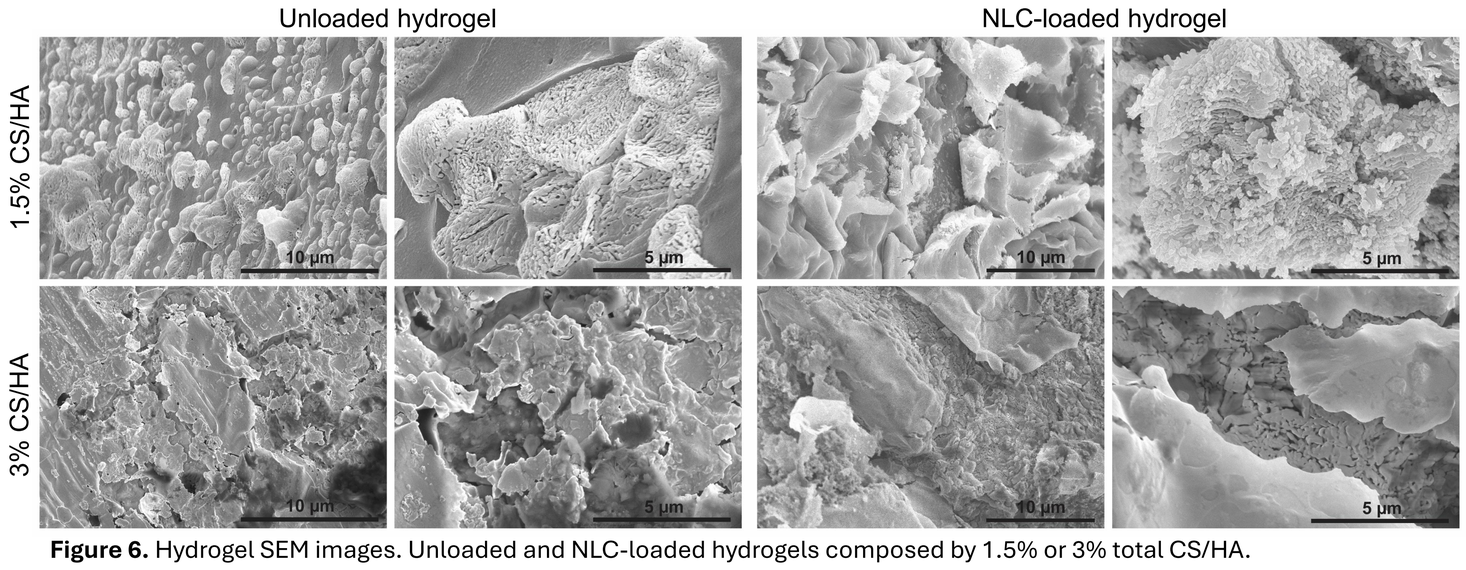


Figure 6. Hydrogel SEM images. Unloaded and NLC-loaded hydrogels composed by 1.5% or 3% total CS/HA.

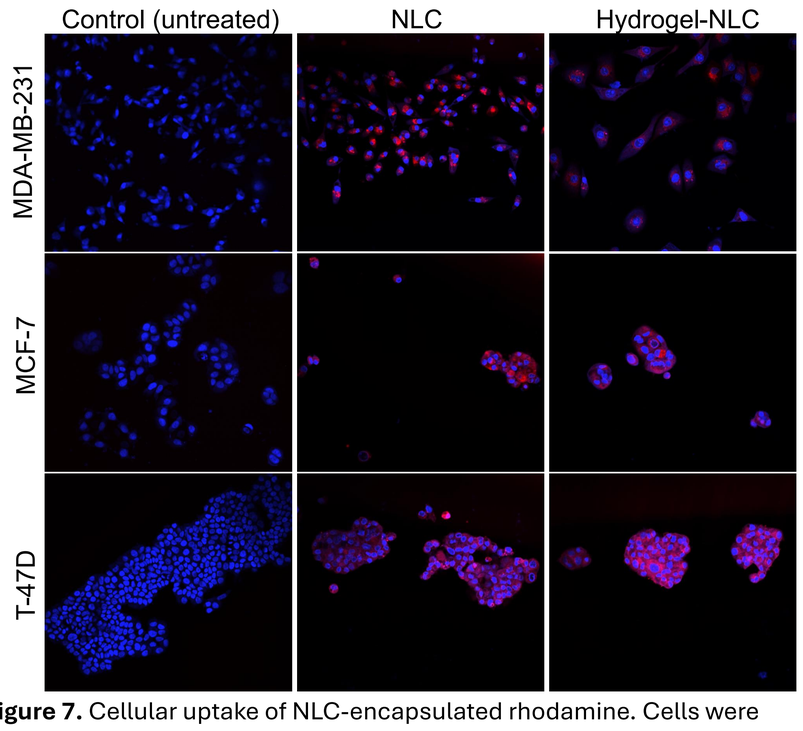


Figure 7. Cellular uptake of NLC-encapsulated rhodamine. Cells were incubated with the rhodamine-stained NLC dispersion or hydrogel-incorporated NLCs for 72 h. Blue: cell nuclei (Hoechst 33342); red: rhodamine B.

Conclusions/Implications

It was possible to select an NLC formulation with satisfactory physicochemical characteristics, capable of promoting fenretinide sustained release, and the combination of PVA and trehalose preserved colloidal stability upon lyophilization. Fenretinide-containing NLCs were successfully incorporated into the hydrogel without pronouncedly altering its structure or rheological behavior. Ongoing studies are investigating drug release from the hydrogel and the cellular effects of hydrogels containing both the NLCs and YARA.

Acknowledgements

Nanofarma
CAPES
CNPq
FAPESP
FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DE SÃO PAULO

References

1. Veronesi, U et al. Annals of oncology. 2006. v. 17, p.1065.
2. Alfei, S. & Zuccari, G. Pharmaceutics. 2024. v. 16, n. 5, p. 579.
3. Dartora, V. F. C. et al. Pharmaceutics. 2024. v. 16, n. 2, p. 231.
4. Malago, I. D. et al. Int J Pharm. 2026. v. 695, p. 126783.