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Amphiphilic pH-responsive core-shell nanoparticles can increase the performances of cellulose-based drug delivery systems

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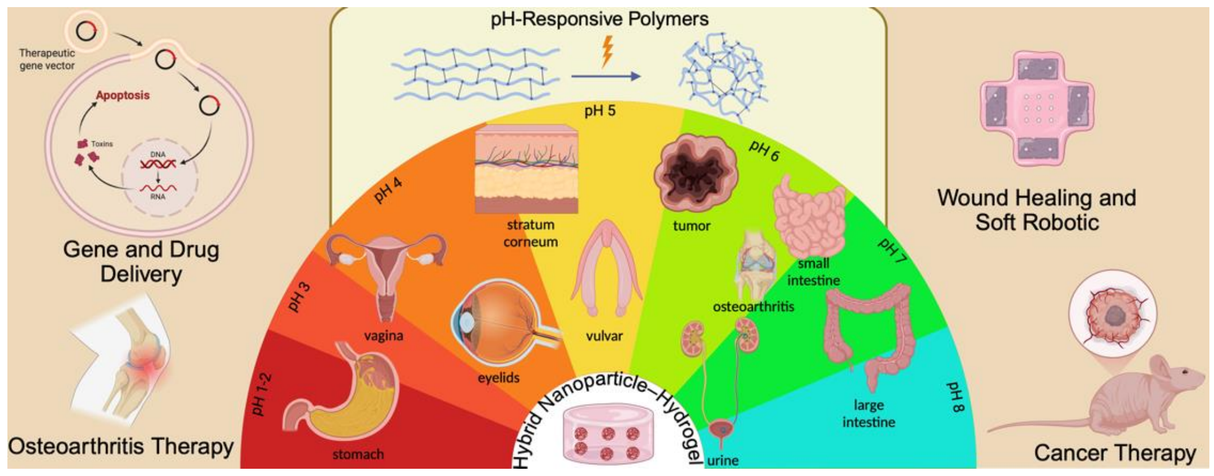
INTRODUCTION & AIM

pH-responsive polymeric systems are increasingly explored as smart materials for targeted drug delivery, since many tissues and pathological sites naturally exhibit characteristic pH variations.

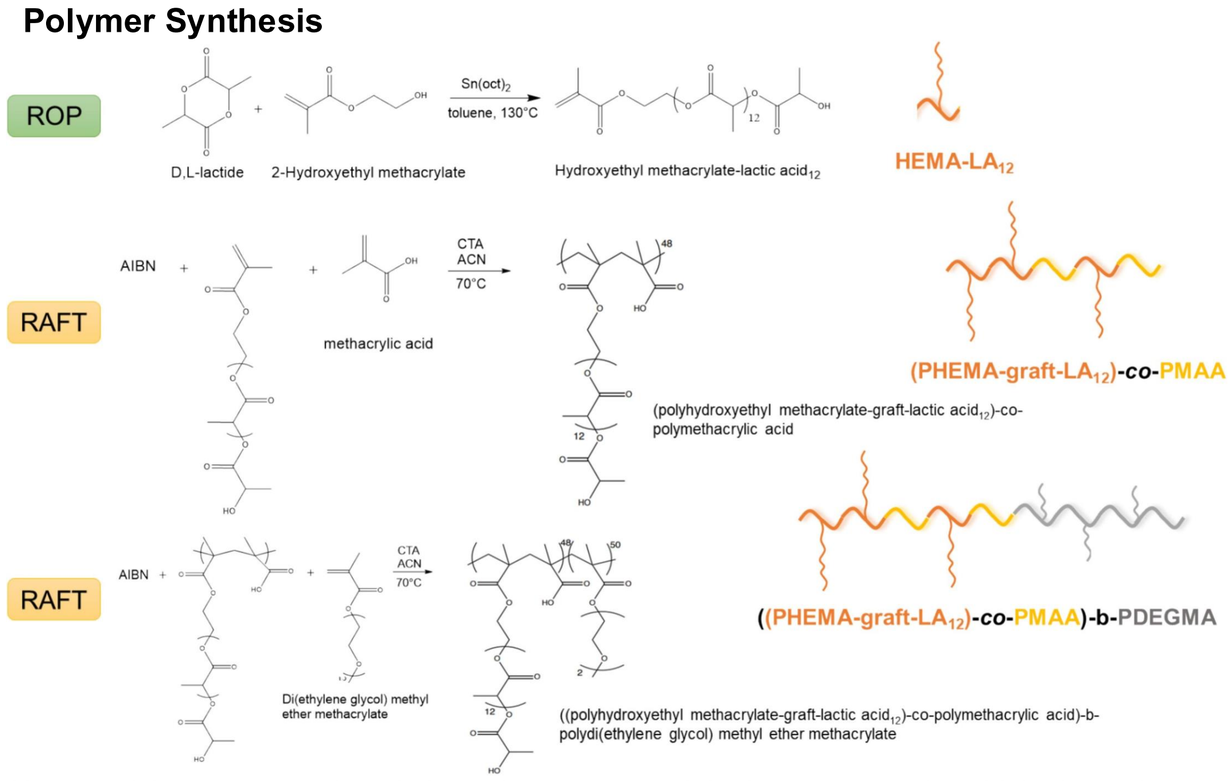


Nanoparticles and hydrogels are among the most versatile platforms within this field. Nanoparticles can stabilize and transport small hydrophobic drugs, while hydrogels ensure local retention and sustained release. However, each system alone has important limitations: nanoparticles tend to diffuse away from the injection site, and hydrogels struggle to efficiently load low-molecular-weight hydrophobic molecules. Combining the two into a single nanocomposite material can overcome these drawbacks. Embedding pH-responsive amphiphilic nanoparticles inside a hydrophobically modified HPMC-C_{12} network allows the system to take advantage of both the structural stability of the hydrogel and the environmental sensitivity of the nanoparticles. This integration enables a dual release mechanism, in which hydrophobic small molecules are released from the nanoparticles and larger biomolecules diffuse through the hydrogel matrix.

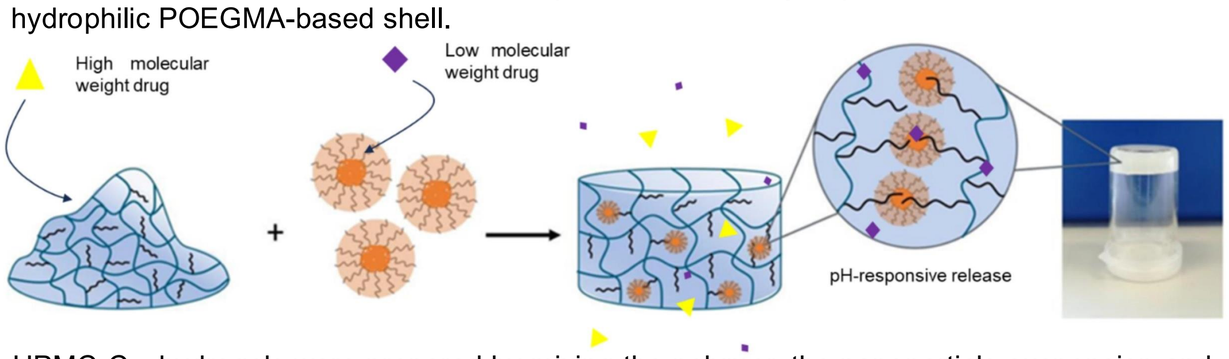
The **aim of this work** is to develop and characterize a pH-sensitive nanocomposite platform capable of achieving controlled, localized and complementary drug release, with the long-term goal of supporting advanced therapeutic strategies that benefit from the coordinated delivery of multiple classes of molecules.

METHOD

Polymer Synthesis

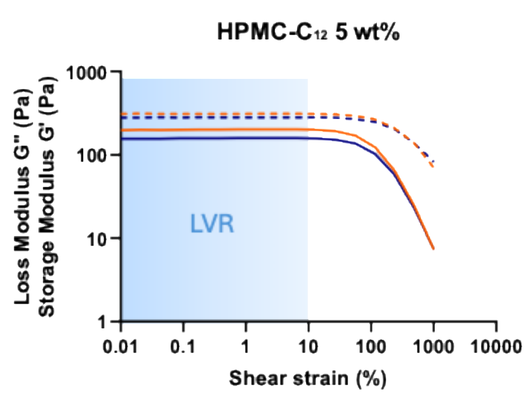


Nanoparticles were produced through a nanoprecipitation process, in which the polymer solution in ACN was dripped into water under magnetic stirring. This method enabled the formation of well-defined core-shell nanoparticles with a hydrophobic PLA-rich core and a hydrophilic POEGMA-based shell.



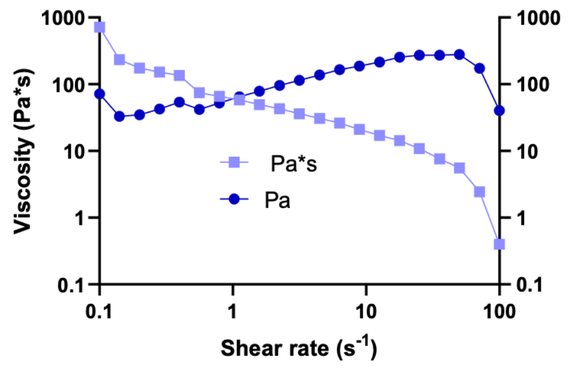
HPMC-C_{12} hydrogels were prepared by mixing the polymer, the nanoparticle suspension and PBS on a shaker at 1000 rpm for 48 hours. Different concentrations of HPMC-C_{12} and nanoparticles were tested to identify the formulations capable of forming stable and homogeneous nanocomposite hydrogels. The system was further evaluated for its codelivery performance, rheological behavior, injectability and therapeutic effect.

RESULTS & DISCUSSION

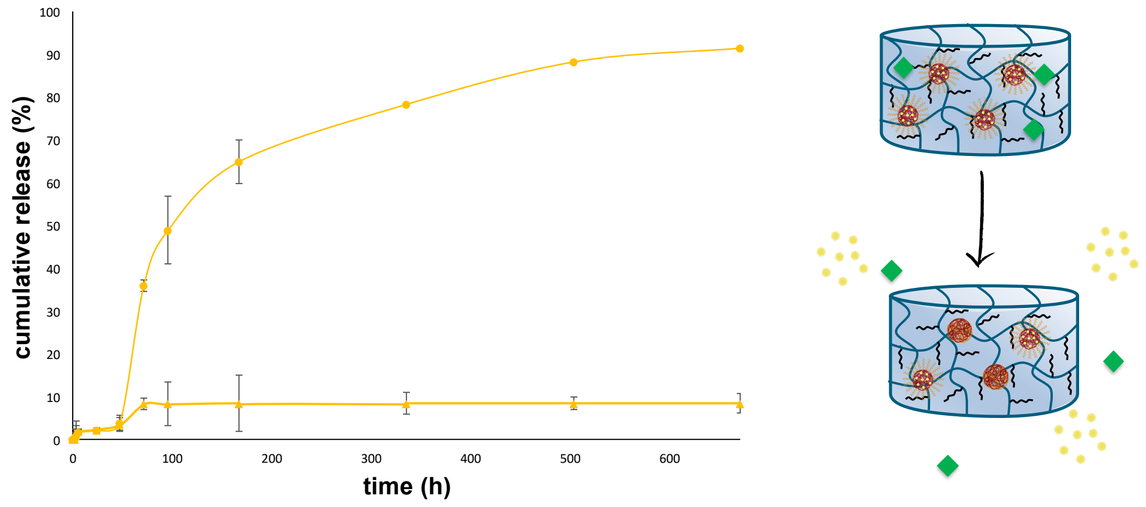


Amplitude sweep analysis confirmed a well-defined linear viscoelastic region for both samples, followed by a clear decrease in storage modulus beyond the critical strain, indicating the onset of network yielding.

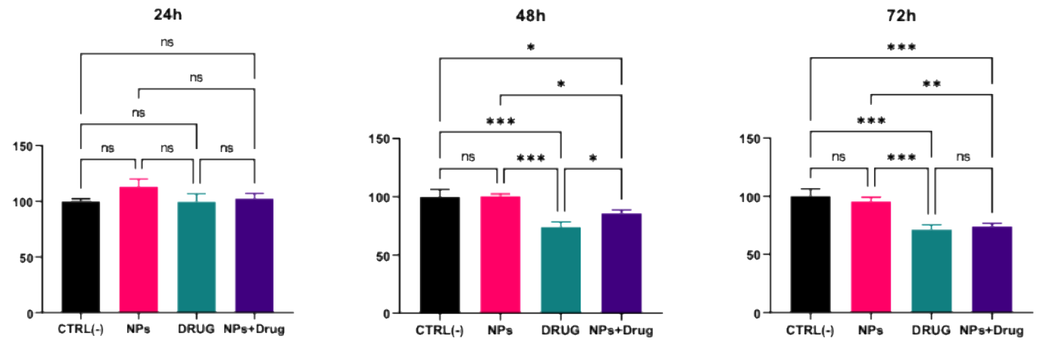
The nanocomposite hydrogel exhibited pronounced shear-thinning behavior, allowing a marked decrease in viscosity under increasing shear rate, confirming its suitability for syringe-based injection.



At pH 5.5 the system showed a sustained and progressive release exceeding 90 percent over time, whereas at pH 7.4 the release remained minimal, confirming the strong pH dependence of the delivery mechanism.



Nanoparticles showed high biocompatibility, maintaining cell viability close to 100% at all tested concentrations, confirming their safety for further therapeutic applications.



CONCLUSION

We report an injectable pH-responsive nanocomposite that integrates amphiphilic nanoparticles within an HPMC-C_{12} hydrogel to achieve coordinated release of two therapeutics. The system remains stable and retains both cargos at physiological pH, while acidic conditions trigger their selective and complementary liberation. This dual-delivery behaviour highlights a versatile platform capable of targeting acidic microenvironments with precise spatial and temporal control.

FUTURE WORK / REFERENCES

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2.Nunziata G. et al. pH-thermo dual-responsive polymeric nanoparticles for women's health: dual action against cervical and ovarian cancer cells. *ACS Appl. Mater. Interfaces* (2025).
3.Lacroce E. et al. Amphiphilic pH-responsive core–shell nanoparticles enhance the performance of cellulose-based drug delivery systems. *Int. J. Biol. Macromol.* 283 (2024) 137659.