HARNESSING HYDROGEL INTERACTIONS WITH FUNCTIONAL POLYMERIC NANOPARTICLES FOR SUSTAINED CO-DELIVERY OF THERAPEUTICS

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CONTEXT

Hydrogel composites are promising materials for biomedical applications, including drug delivery and cancer therapy. Embedding nanomaterials within the hydrogel matrix overcomes their intrinsic limitations (poor mechanical strength, burst release, excessive hydrophilicity) and addresses the drawbacks of common drug delivery systems such as polymeric nanoparticles (NPs)[1-2]. Although NPs enable targeted and multivalent therapy, they face rapid clearance, premature degradation, and low bioavailability[3]. Incorporating NPs into the hydrogel network (NPs-hydrogel composite) yields tailored system, with improved drug retention and sustained, controlled release[1].

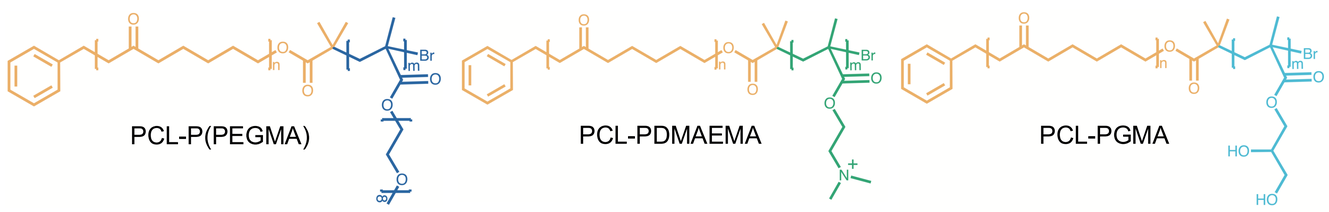
AIM OF THE WORK

This work presents a hybrid system combining a hydrogel matrix with custom-designed polymeric NPs bearing distinct surface moieties for the co-delivery of therapeutics with diverse physicochemical properties. Dexamethasone (DEX) was selected for its anti-inflammatory activity to be encapsulated into the NPs core, while Bovine Serum Albumine (BSA) mimicked high molecular weight, hydrophilic therepeutic agents inserted into the hydrogel matrix. The platform offers a versatile strategy for sustained and controlled multi-drug release for advanced medical applications, with anti inflammatory effect on cells.

1 POLYMERS AND NANOPARTICLES DESIGN

Amphiphilic block copolymers were synthesized via:

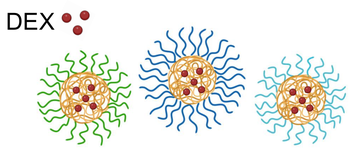
1. **Ring Opening Polymerization** of the hydrophobic macroinitiator: Poly(ε-caprolactone) – **PCL**
2. **Atom Transfer Radical Polymerization** of the functional hydrophilic blocks:
   - Poly(poly(ethylene glycol methacrylate)) – **P(PEGMA)**
   - Poly(dimethylaminoethyl methacrylate) – **PDMAEMA**
   - Poly(glycerol methacrylate) – **PGMA**



Polymers	$M_{n,SEC}$ [kDa]	Đ [-]
PCL_{30}-$P(PEGMA_{27})$	17.1	1.1
PCL_{30}-$PGMA_{29}$	8.5	1.2
PCL_{30}-$PDMAEMA_{32}$	8.8	1.1

SEC analysis confirmed polymers predetermined MW and narrow chains dispersity

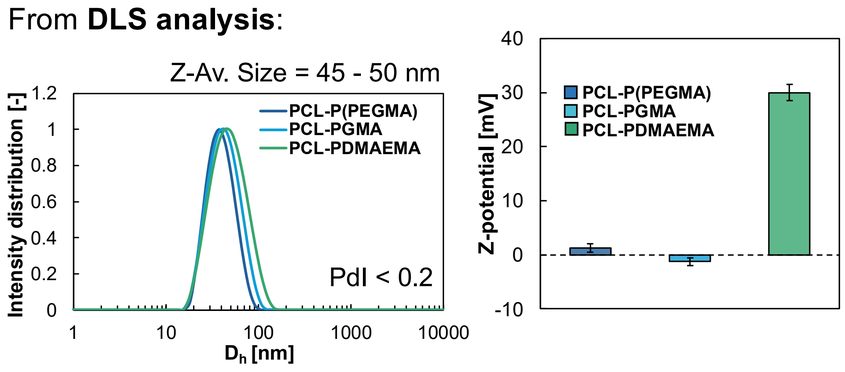
DEX-loaded NPs with **core-shell structure** were formulated via nanoprecipitation-solvent evaporation



From **HPLC analysis**:

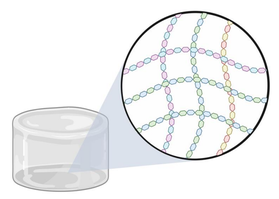
- ✓ Encapsulation efficiency = 40%
- ✓ Drug loading = 3.5%

From **DLS analysis**:

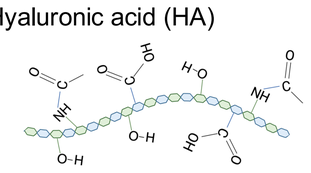


2 NPs-HYDROGEL COMPOSITE FORMULATION

Hydrogels were prepared via a microwave-assisted **polycondensation** reaction

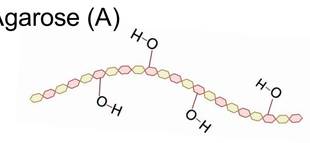


Hyaluronic acid (HA)

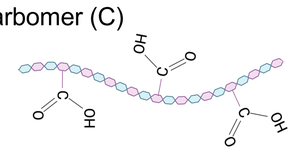


Component	w/w [%]
Agarose	20
Carbomer	7
Hyaluronic acid	73

Agarose (A)



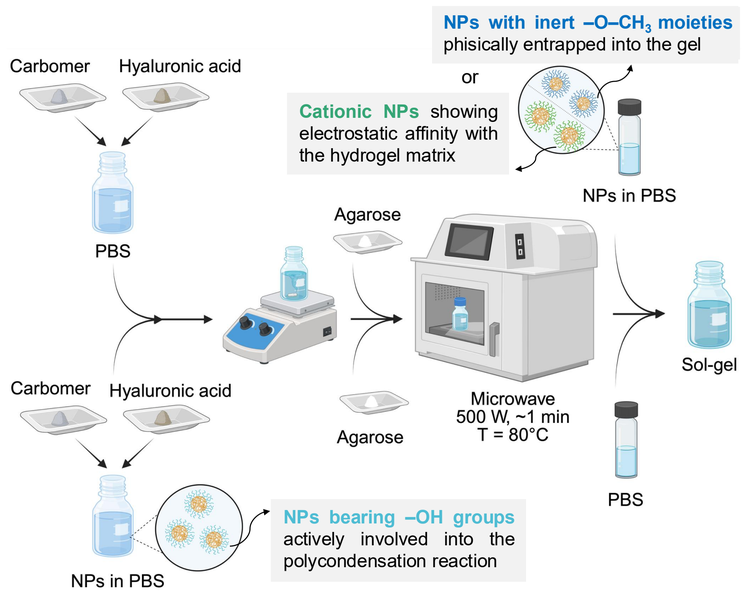
Carbomer (C)

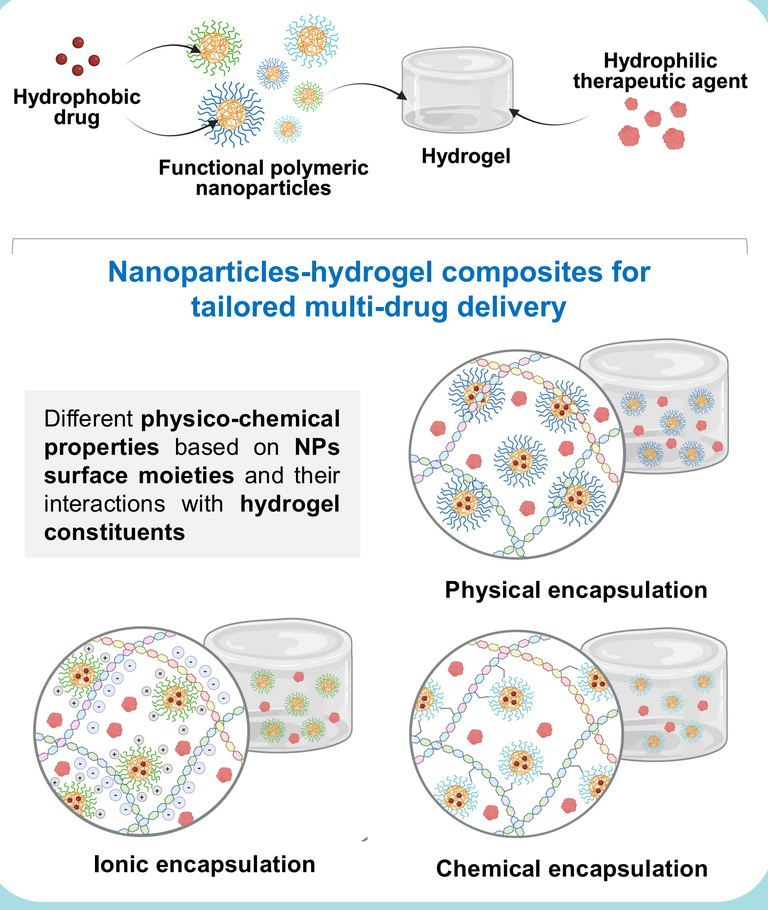


BSA was **encapsulated** by mixing it with the hydrogel polymeric constituents before gelation

NPs were **incorporated** according to the interactions established between their **shell functional groups** and the **hydrogel matrix**:

- Phisical encapsulation – **PCL-P(PEGMA)**
- Electrostatic interactions – **PCL-PDMAEMA**
- Chemical linkages – **PCL-PGMA**



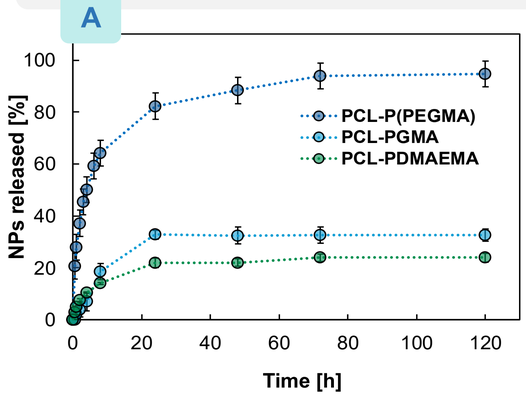


3 NPs, DEX AND BSA RELEASE KINETICS

NPs, DEX and BSA release tests from NPs-hydrogel composite were perfomed in PBS at 37°C, pH 7.4 under sink conditions

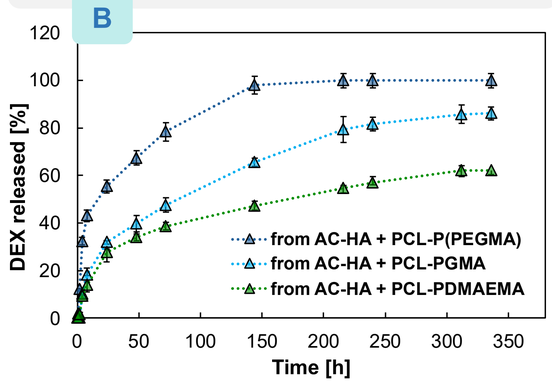
NPs-hydrogel interactions (physical, ionic, chemical) effect on **NPs kinetic release profile**

A



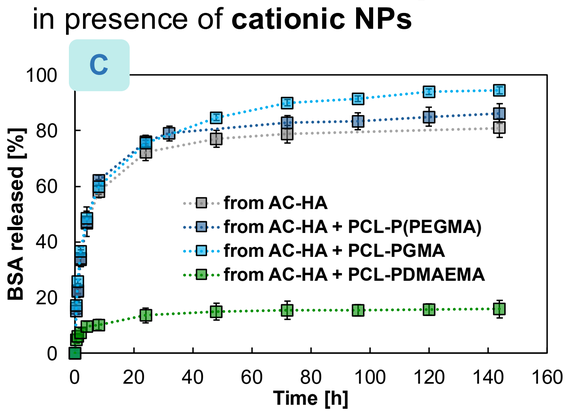
Effect of the **encapsulation method and NPs interaction** on **DEX kinetic release profile**

B



BSA was retained into the gel matrix in presence of **cationic NPs**

C

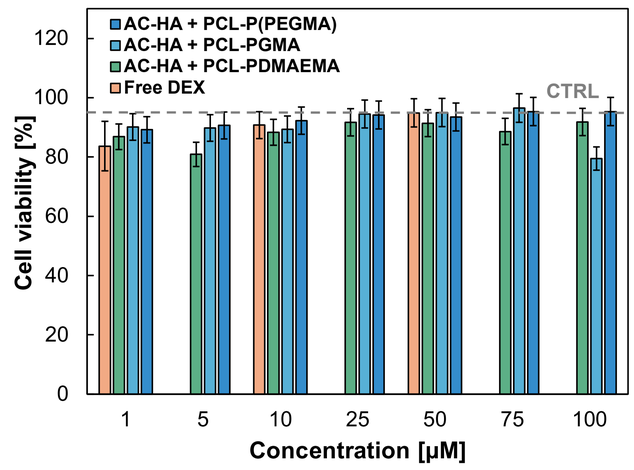


DEX was **sustainedly released** from the **NPs-hydrogel composite** with tunable kinetics at times, according to the NPs-hydrogel interactions

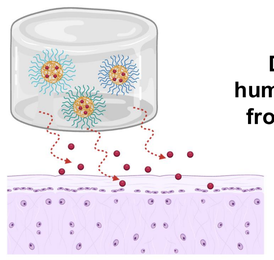
NPs-hydrogel system	t [days]	DEX [%]
PCL_{30}-$P(PEGMA_{27})$	6	100
PCL_{30}-$PGMA_{29}$	10	80
PCL_{30}-$PDMAEMA_{32}$	12	60

4 IN VITRO ANALYES

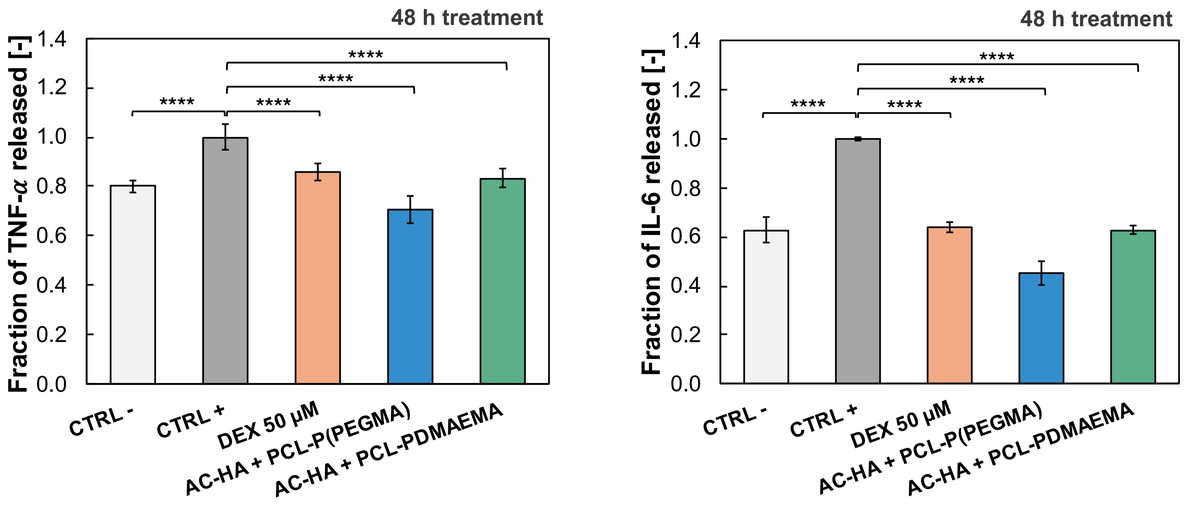
NPs-hydrogel effect was assessed in vitro using LIVE/DEAD assay



NPs-hydrogel demonstrated **negligible cytotoxic** effect on human chondrocytes



Inflamed human chondrocytes showed **reduced TNF-α and IL-6 expression** after 48 h treatment with NPs-hydrogel composites



CONCLUSIONS

NPs surface functionalities affect composite release performances: physical encapsulation induced rapid drug release, while ionic or covalent NPs–hydrogel interactions provide sustained profiles. The dual-compartment design enabled co-delivery of multiple drugs (with cationic NPs enhancing BSA retention) and additionally demonstrated anti inflammatory effect on cells.

REFERENCES

1. Molinelli, A. *et al. ChemNanoMat* 10, 2024
2. Lavrador, P. *et al. Adv. Funct. Mater.* 31, 2021
3. Porello, I. *et al. Eur. Polym. J.* 204, 2024