Hyaluronic acid-based hydrogel loaded with phloretin and triamcinolone acetonide-encapsulated PLGA nanoparticles for intraarticular osteoarthritis therapy

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Background

Osteoarthritis (OA) is a prevalent degenerative joint disease characterized by chronic inflammation, cartilage breakdown, and progressive loss of joint function. Key mediators such as IL-1β drive the overexpression of inflammatory cytokines (iNOS, IL-6…) and catabolic enzymes (MMPs), accelerating tissue degradation. Nanotechnology-based drug delivery systems, particularly **Poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NPs)**, offer controlled and sustained release of therapeutic agents, improving drug stability and bioavailability. Combining synthetic antiinflammatory drugs like **triamcinolone acetonide (TA)** with natural compounds such as **phloretin (PHL)** may enhance efficacy through a **synergistic therapeutic effect**. Incorporating these NPs into **hyaluronic acid (HA)** hydrogels can further improve joint residence time while maintaining suitable viscoelastic properties. **This strategy** represents a promising approach to simultaneously target inflammation and cartilage degradation, addressing key limitations of current OA treatments.

Graphical abstract and methodology

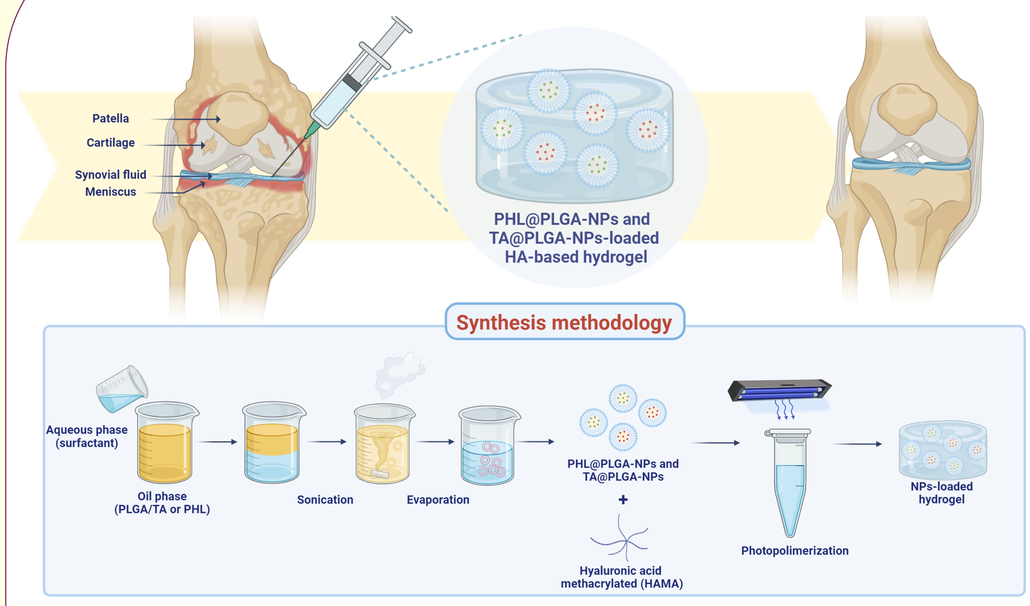
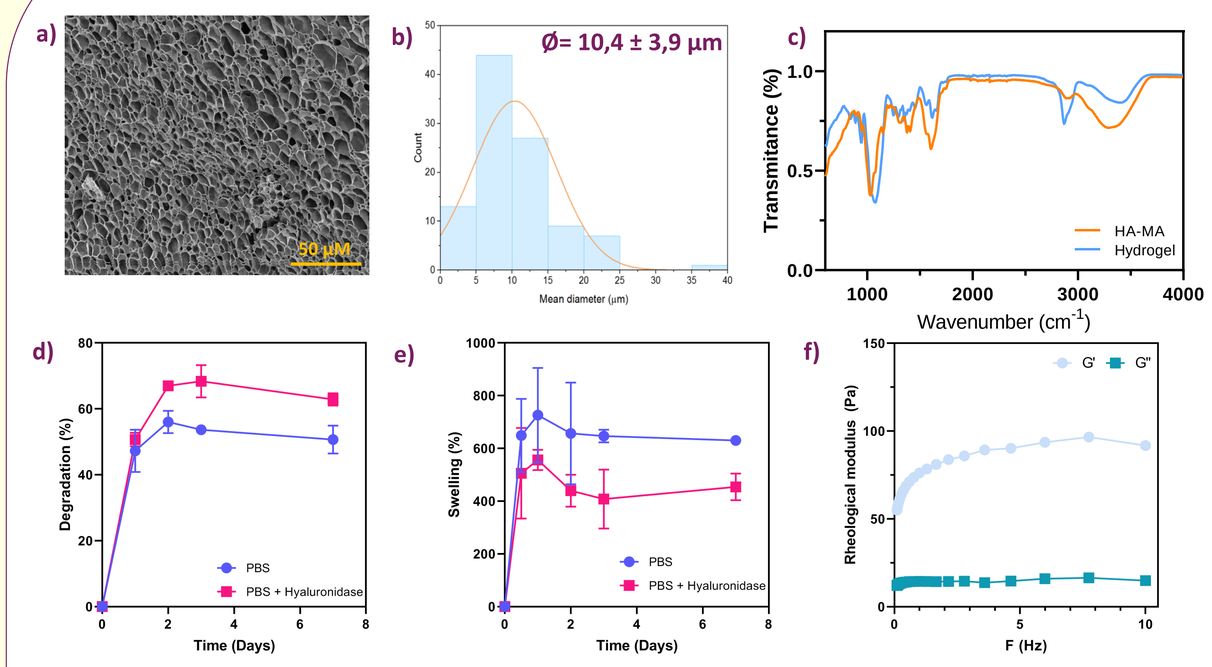


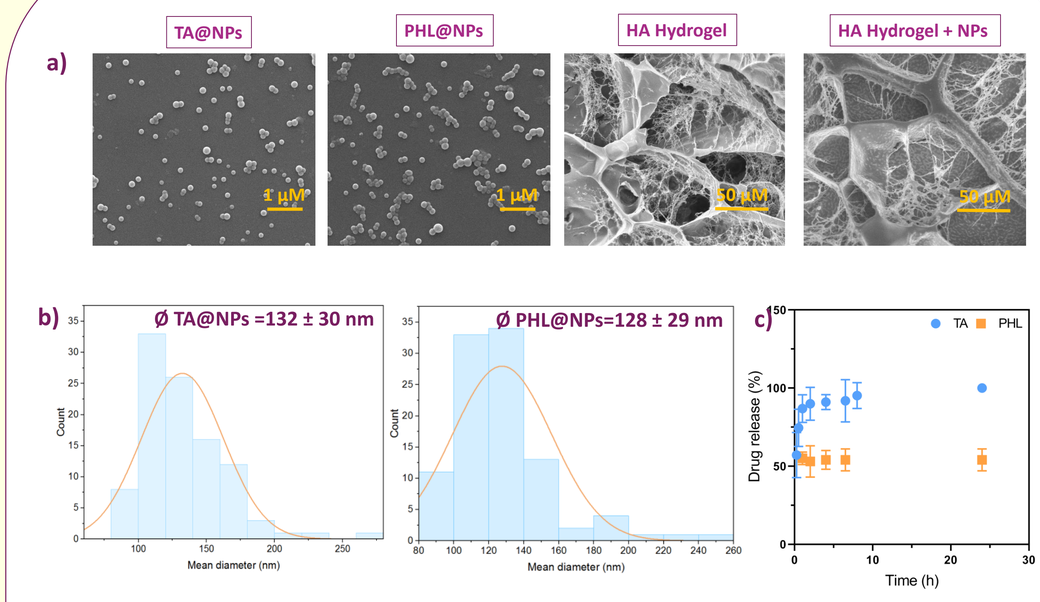
Figure 1. Schematic illustration of the preparation of PLGA nanoparticle-loaded methacrylated hyaluronic acid (HAMA) hydrogel and its intraarticular injection for osteoarthritis therapy.

Hydrogel characterization



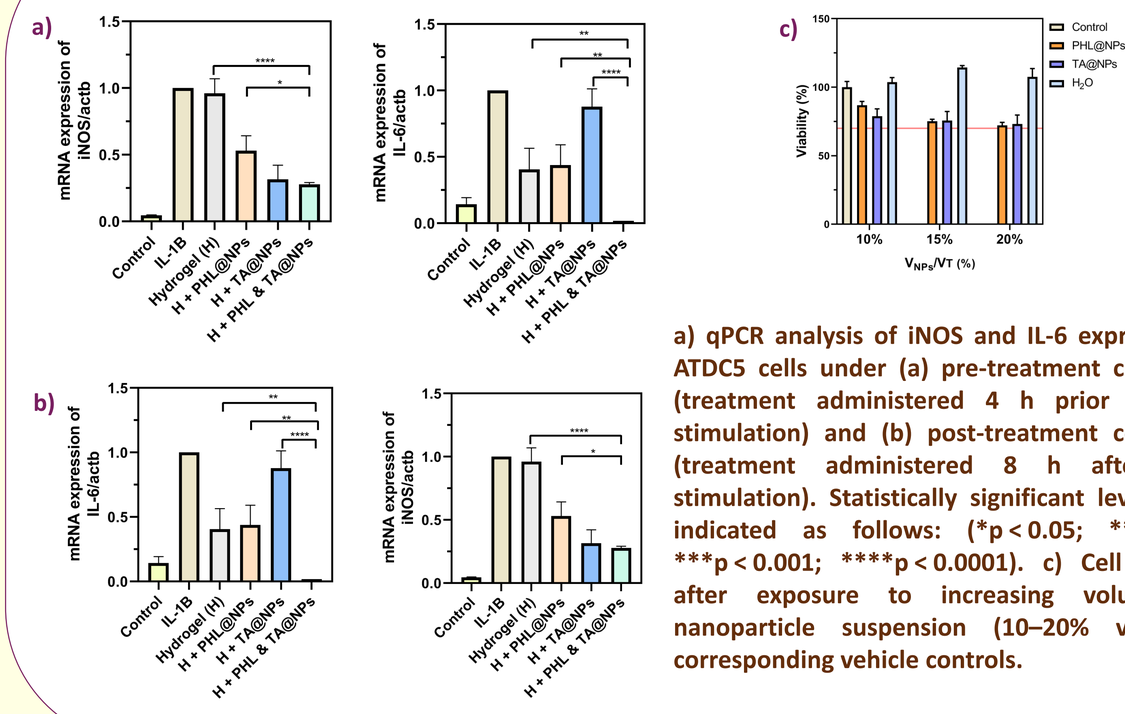
a) Cryo-SEM image of the hydrogel porous structure. b) Mean pore diameter and size distribution. c) Fourier transform infrared spectroscopy (FTIR) spectra of methacrylated hyaluronic acid and the formed hydrogel. d) Hydrogel degradation and e) hydrogel swelling. f) elastic (G') and viscous (G") moduli.

TA and PHL@NPs characterization



a) SEM images of TA@NPs, PHL@NPs, and the porous structure of the hydrogel without and with embedded NPs, respectively. b) Mean particle diameter and size distribution of TA@NPs and PHL@NPs, respectively. c) TA and PHL release in PBS at 37 °C.

Biological assays



a) qPCR analysis of iNOS and IL-6 expression in ATDC5 cells under (a) pre-treatment conditions (treatment administered 4 h prior to IL-1β stimulation) and (b) post-treatment conditions (treatment administered 8 h after IL-1β stimulation). Statistically significant levels were indicated as follows: (*p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001). c) Cell viability after exposure to increasing volumes of nanoparticle suspension (10–20% v/v) and corresponding vehicle controls.

Conclusions

- **A hyaluronic acid–based hydrogel and phloretin/triamcinolone acetonide-loaded nanoparticles were successfully synthesized, optimized, and integrated into a single platform, with drug loading (DL_{TA} = 1,01 ± 0,34 % and DL_{PHL}=1,87 ± 0,63 %) and encapsulation efficiency (EE_{TA}= 1,80 ± 0,46 % and EE_{PHL}= 2,64 ± 0,94 %) achieved for both formulations.**
- **The composite system combined viscosupplementation, attributed to the hyaluronic acid-based hydrogel, with physicochemical properties suitable for intraarticular delivery.**
- **Gene expression analysis demonstrated a reduction in inflammatory markers expression, including iNOS and IL6, compared with equivalent doses of the individual drugs.**
- **Notably, the nanoparticle-loaded hydrogel showed molecular anti-inflammatory effects, suggesting a potential synergistic interaction for osteoarthritis treatment.**

Acknoledgements

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