Bioadhesive hydrogel for intra-articular delivery of lipid and mesoporous silica nanoparticles for osteoarthritis treatment

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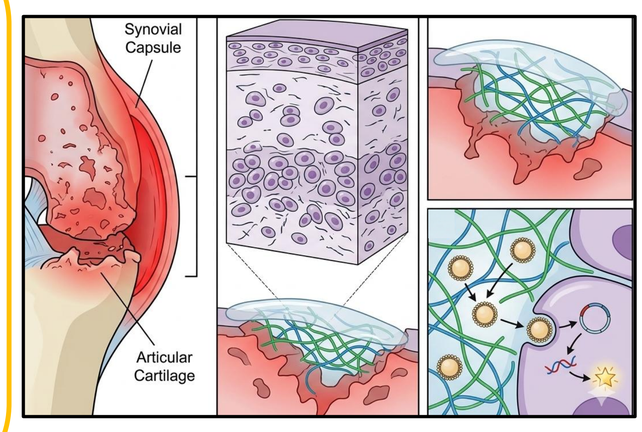
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INTRODUCTION

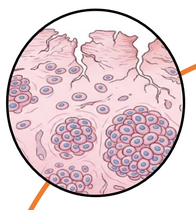
Osteoarticular pathologies, particularly osteoarthritis (OA), represent a significant global health and economic burden. [1] OA is characterized by a multifactorial etiology that disrupts cartilage homeostasis, leading to progressive tissue degradation. [2] These conditions are notoriously difficult to treat due to the avascular nature and limited regenerative capacity of cartilage, as well as the rapid synovial clearance of intra-articular therapies. [3]

The synergy between materials science and gene therapy holds great potential for regenerative medicine, the clinical translation of gene therapy is often hindered by poor cellular delivery and low tissue retention. Nanoparticles such as lipid nanoparticles and silica nanoparticles can address these delivery barriers. [4,5] However, to overcome inherent tissue constraints and current system limitations, an injectable and retentive delivery platform, as a hydrogel, is required. [6] This work describes the development of a bioadhesive, dopamine-functionalized oxidized hyaluronic acid/fibrin (DOPA-OHA/Fibrin) hydrogel. This composite system is designed to act as a reservoir for the high-efficiency intra-articular delivery of nanoparticles, facilitating localized and sustained gene transfer to chondrocytes.



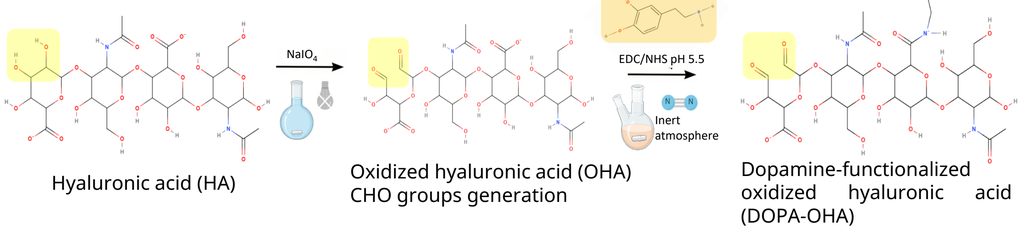
OBJECTIVE

This work focuses on the development of a bioadhesive dopamine-functionalized oxidized hyaluronic acid/fibrin hydrogel designed to enable high-efficiency intra-articular delivery of lipid nanoparticles. The aim of the work is to enhance gene transfer to chondrocytes.



Dopamine-functionalized oxidized hyaluronic acid/fibrin (DOPA-OHA/Fibrin) hydrogel

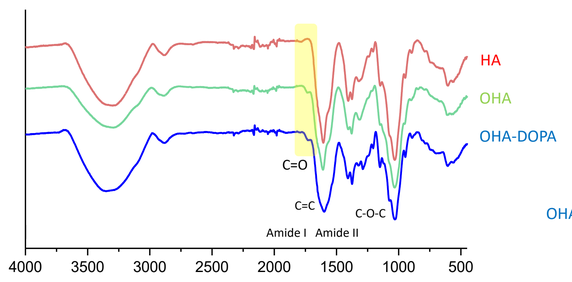
Oxidation of hyaluronic acid to form aldehyde groups and activation of the acid for dopamine functionalization:

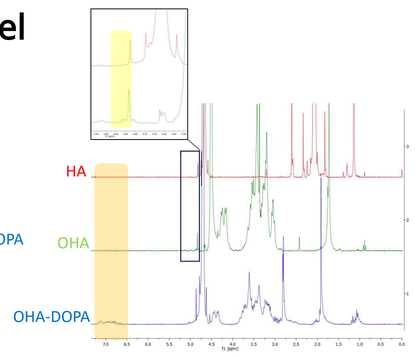


Hyaluronic acid (HA)

Oxidized hyaluronic acid (OHA)
CHO groups generation

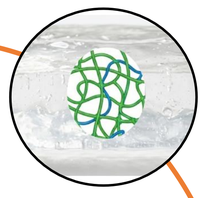
Dopamine-functionalized oxidized hyaluronic acid (DOPA-OHA)





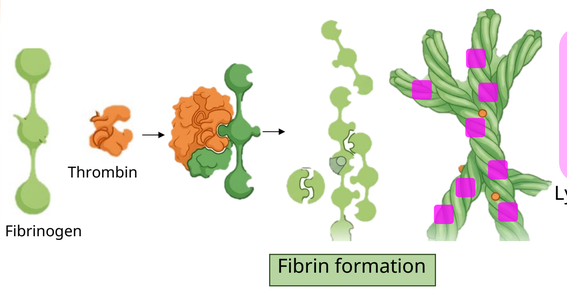
OHA synthesis:
FTIR: Aldehyde group absorption at 1730 cm^{-1} confirmed HA oxidation.
^1H NMR: Hemiacetal proton shifts (4.85–5.0 ppm) verified aldehyde formation.

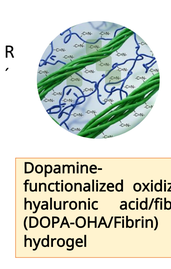
Dopamine functionalization:
Confirmed by catechol aromatic peaks at δ 7 ppm.



Dopamine-functionalized oxidized hyaluronic acid (DOPA-OHA)

The formation of fibrin from fibrinogen through thrombin activation. Fibrin contains lysine residues whose side chains provide amine groups. These NH_2 are essential for covalent cross-linking with the CHO of dopamine-oxidized hyaluronic acid via Schiff base formation.

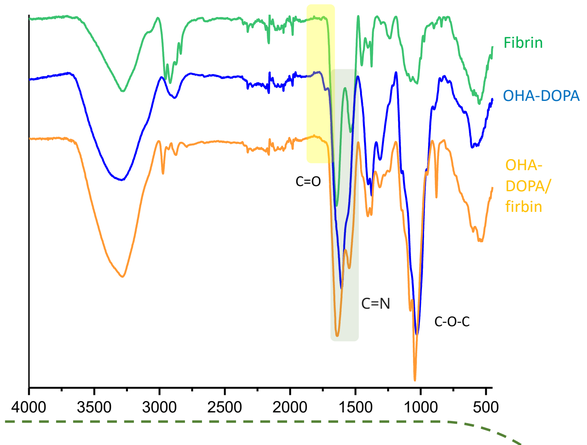


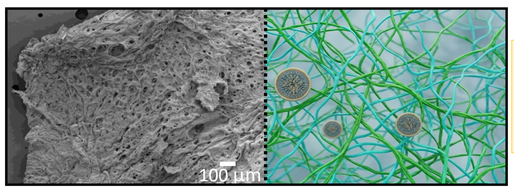


Dopamine-functionalized oxidized hyaluronic acid/fibrin (DOPA-OHA/Fibrin) hydrogel

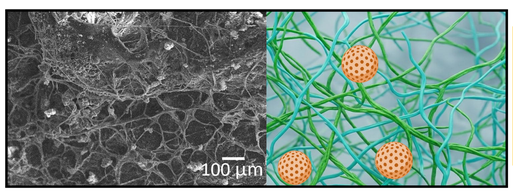
The covalent integration of both polymers via Schiff base formation was confirmed by:

- Aldehyde consumption: Disappearance of the 1720 cm^{-1} peak.
- Imine formation (C=N): Signal broadening at 1658 cm^{-1} (overlapping with amide bands).





Lipid Nanoparticles-loaded dopamine-functionalized oxidized hyaluronic acid/fibrin hydrogel

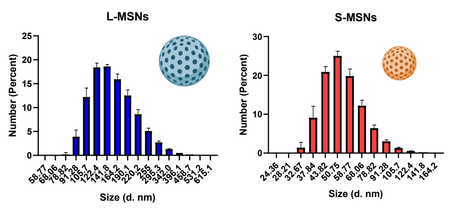


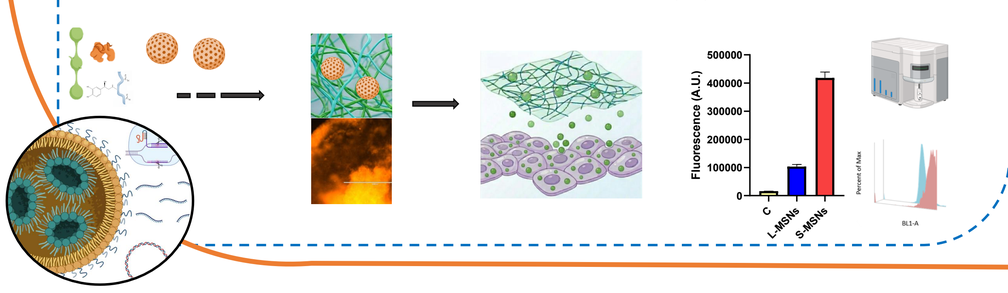
Mesoporous Silica Nanoparticles-loaded dopamine-functionalized oxidized hyaluronic acid/fibrin hydrogel

Mesoporous Silica Nanoparticles (MSNs)

Synthesis of small-sized MSNs with an internal fluorophore for tracking. MSNs were embedded during DOPA-OHA/Fibrin hydrogel cross-linking.

Cellular internalization of the released MSNs was verified by flow cytometry to confirm their potential as a delivery vehicle.

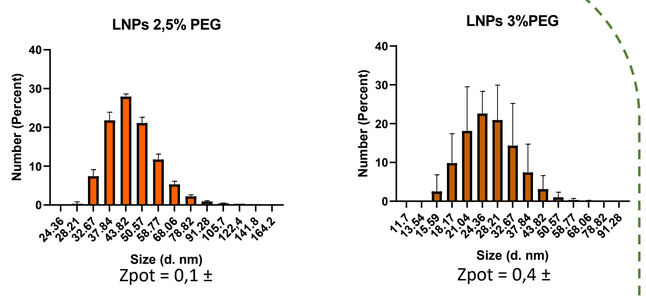




Lipid Nanoparticles (LNPs)

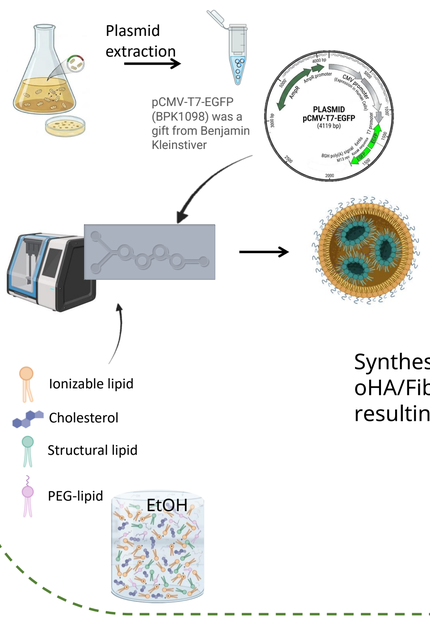
Optimization of the synthesis of LNPs with a hydrodynamic diameter of less than 50 nm. Since the size limits for penetration into deep layers of osteoarthritic cartilage have been established below this range.

Compostion: Ionizable lipid, Cholesterol, Structural lipid, PEG-lipid

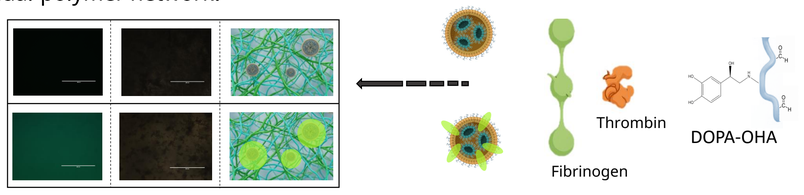


Zpot = 0,1 ±

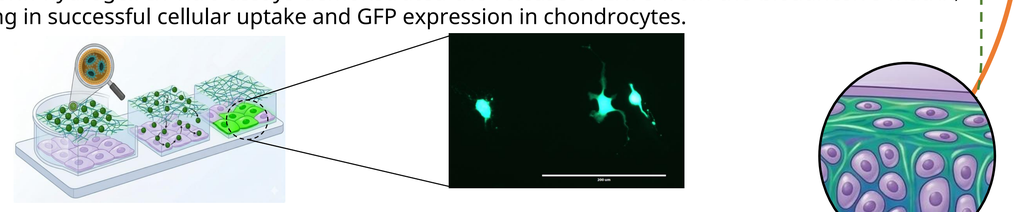
Zpot = 0,4 ±



Synthesis of the LNP-loaded DOPA-OHA/Fibrin hydrogel using LNPs formulated with fluorescently-labeled lipids. This approach allowed for the spatiotemporal monitoring of the nanoparticles, confirming their high retention and stability within the dual-polymer network.



Synthesis of pDNA-GFP encapsulated LNPs and their subsequent integration into the DOPA-oHA/Fibrin hydrogel. *In vitro* assays demonstrated the release of LNPs from the bioadhesive matrix, resulting in successful cellular uptake and GFP expression in chondrocytes.



CONCLUSIONS

Successful Hydrogel Synthesis: A bioadhesive hydrogel based on dopamine-functionalized oxidized hyaluronic acid and fibrin was successfully developed, showing efficient covalent cross-linking via Schiff base formation.

Nanoparticle Integration: Both Lipid Nanoparticles and Mesoporous Silica Nanoparticles were successfully synthesized with an optimized size distribution centered at 50 nm. The DOPA-OHA/Fibrin matrix acts as a versatile delivery reservoir.

Sustained Gene Delivery: *In vitro* assays confirmed that the hydrogel provides a sustained release of pDNA-loaded LNPs, leading to effective transfection and GFP expression in human cells.

Therapeutic Potential: The bioadhesive nature and controlled release profile make this composite hydrogel a promising platform for localized gene therapy in the treatment of osteoarthritis, overcoming current limitations in synovial retention.

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