Sustainability and Veterinary Health

Biopolymer-based strategies toward heavy metal removal and neurodegenerative diseases management

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CONTROLLED RELEASE SOCIETY
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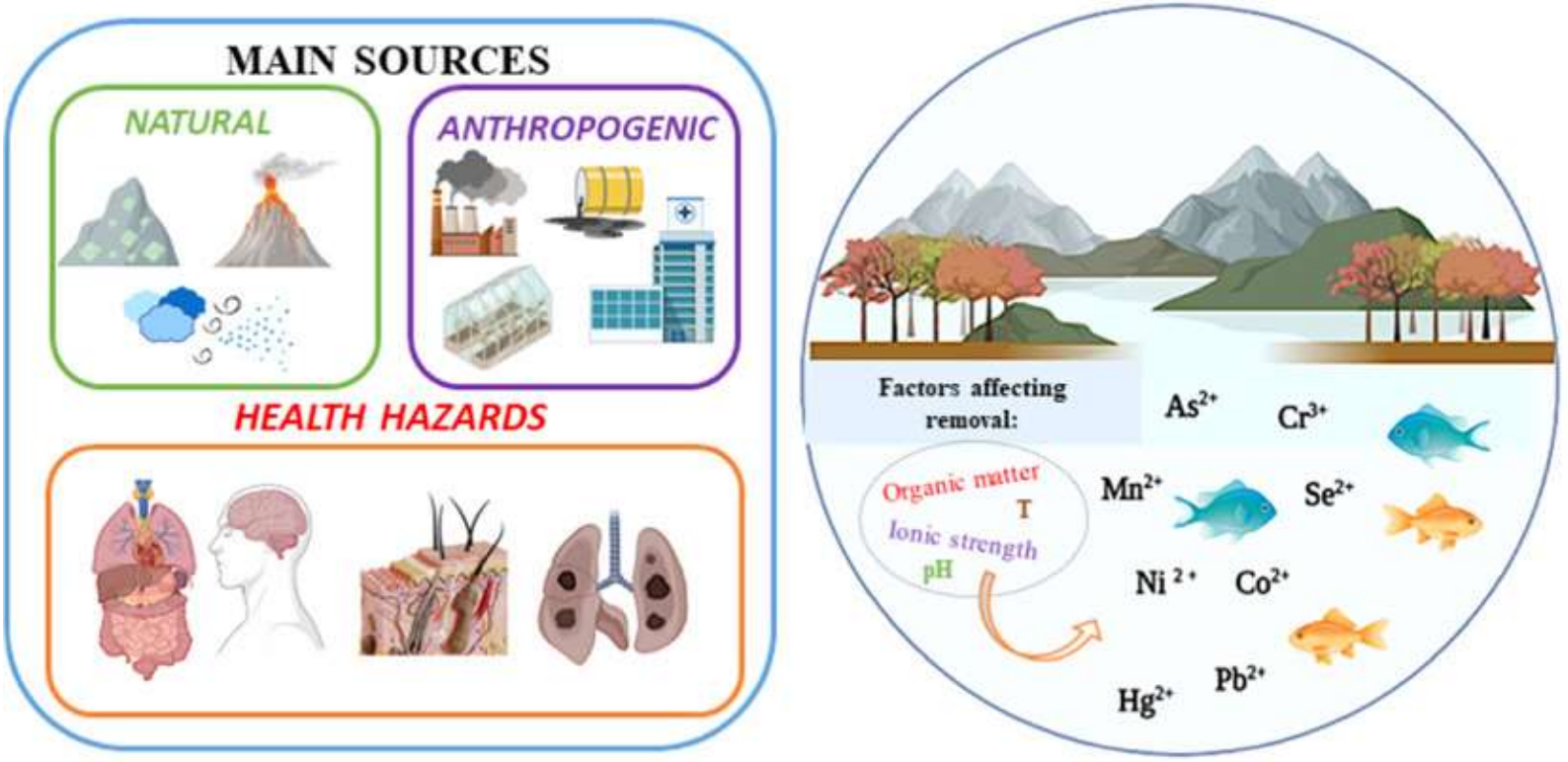
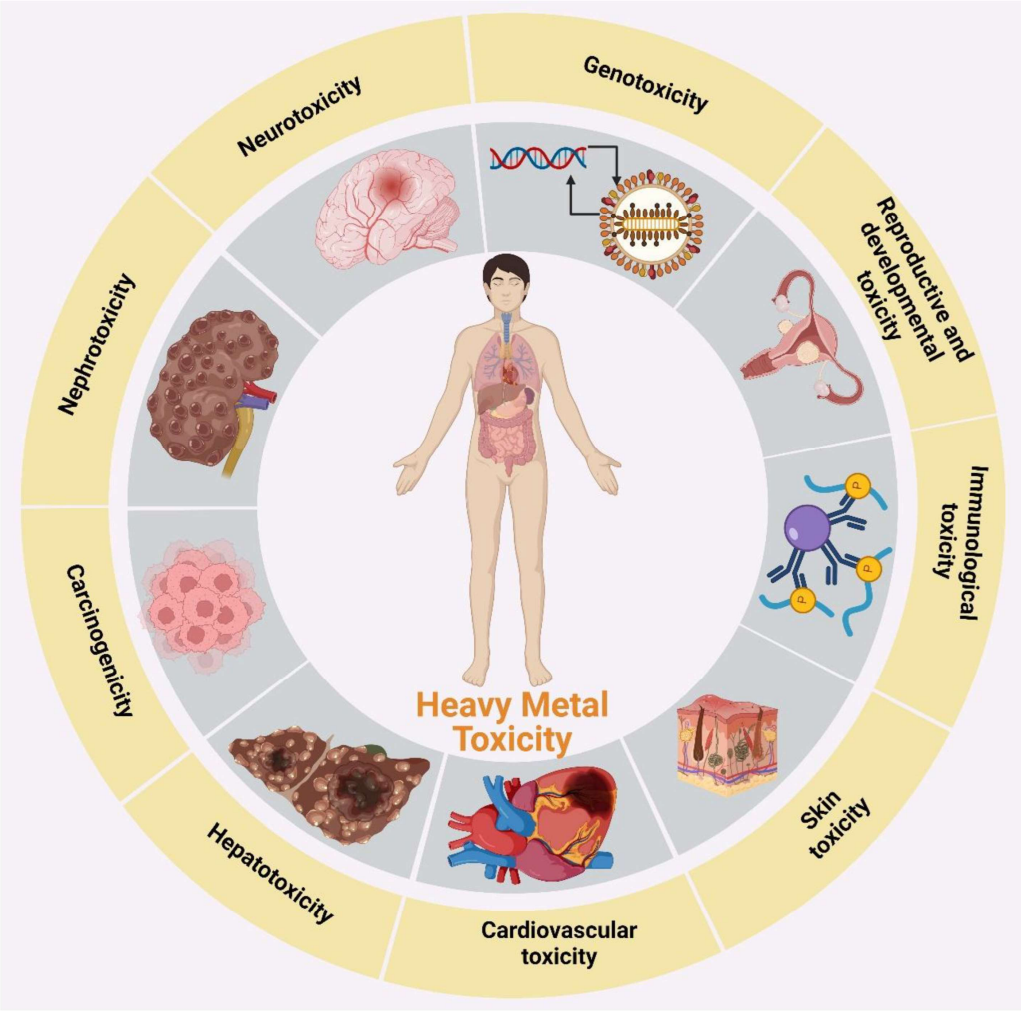
THE FUTURE OF DELIVERY SCIENCE

HEAVY METAL WATER POLLUTION



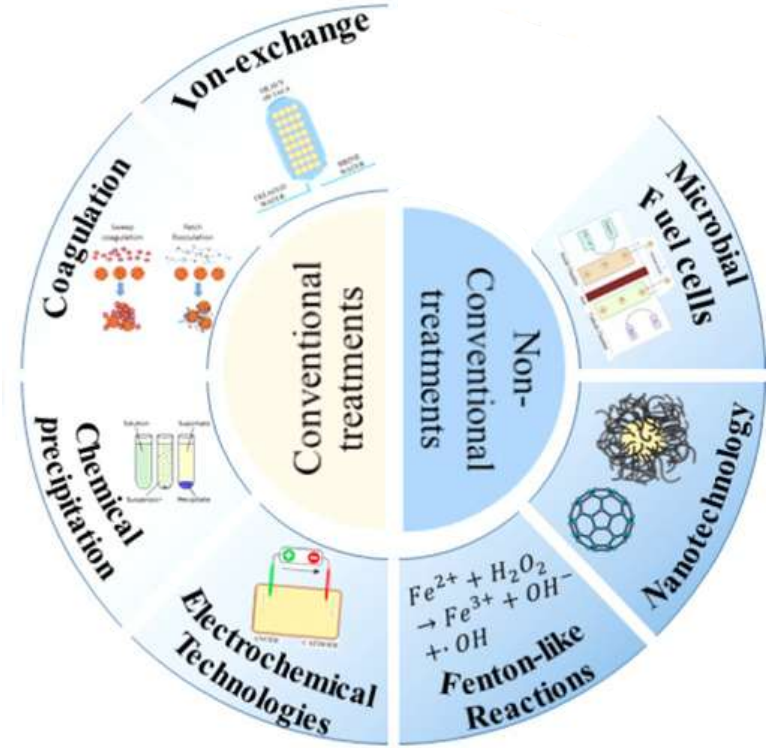
Guerrero VH *et al*, 2021

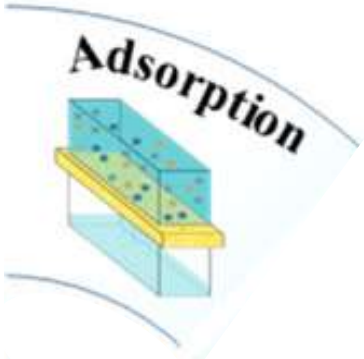
HEAVY METAL IMPACT ON HUMAN HEALTH



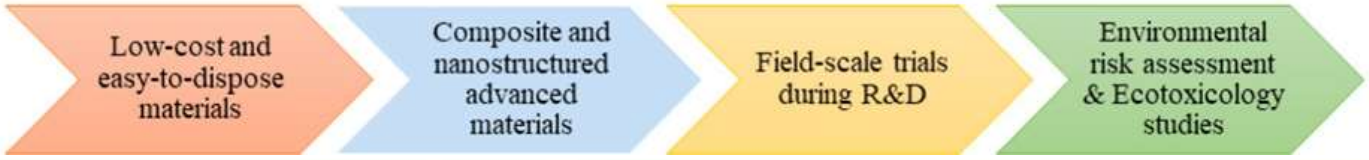
Mishra V *et al*, 2023

REMEDIATION



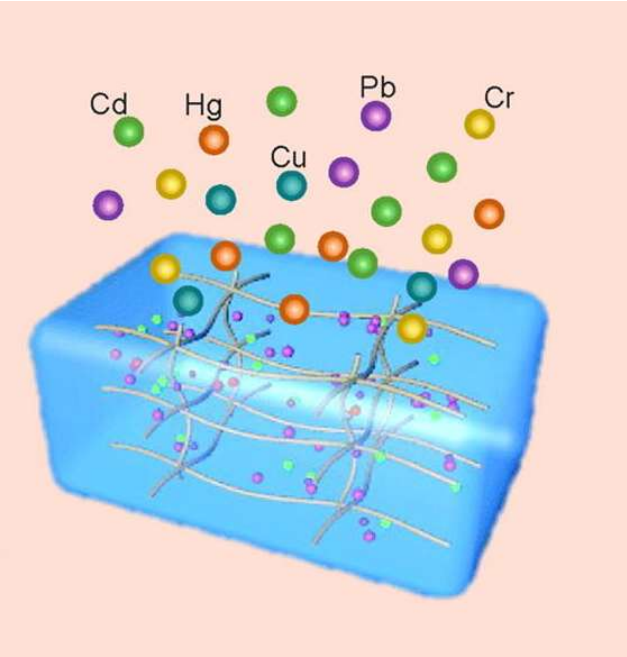


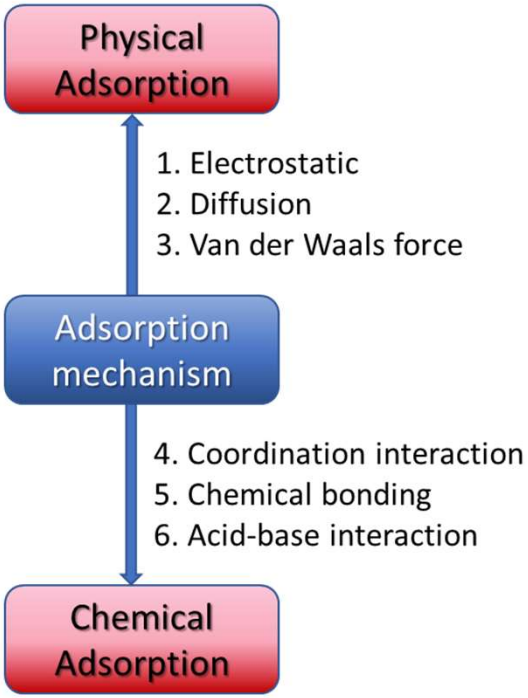
- high removal capacity
- low energy consumption
- low technical requirements for operation
- no major secondary pollution



Guerrero VH *et al*, 2021

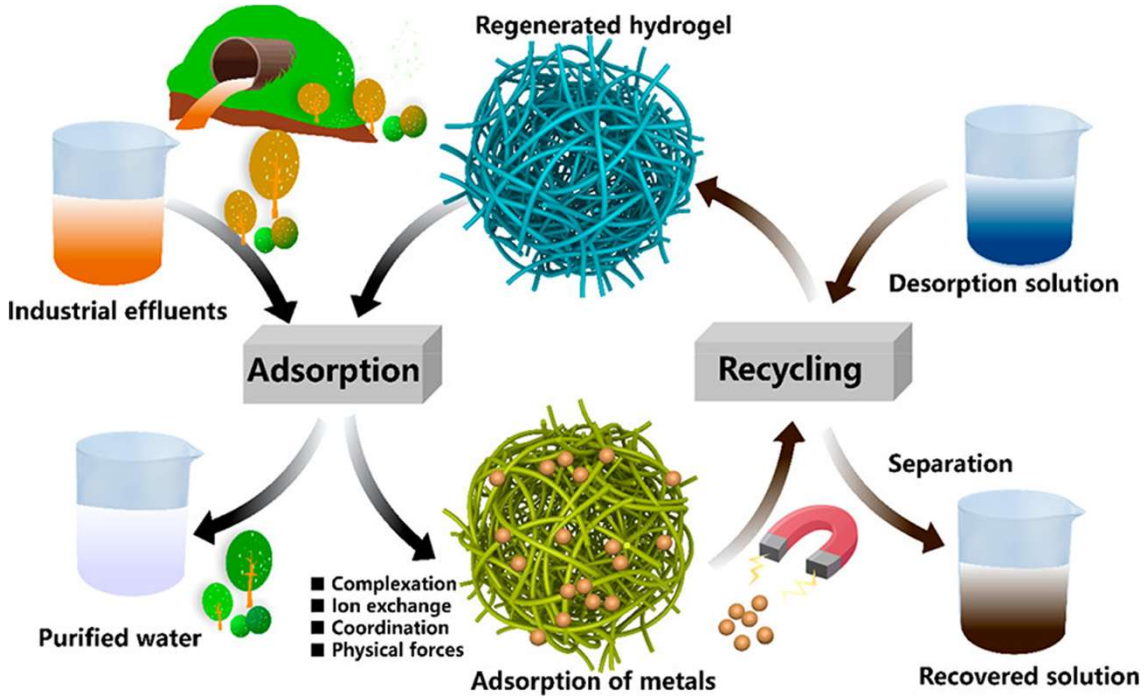
HEAVY METAL ADSORPTION





HYDROGELS

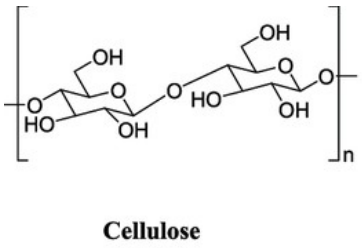
AIM OF THE WORK



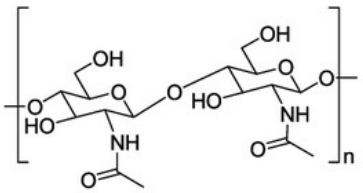
Design of **biopolymer-based hydrogels** with potential application in:

- Heavy metal environmental remediation
- Drug delivery systems for the simultaneous release of drugs and heavy metal homeostasis restoration.

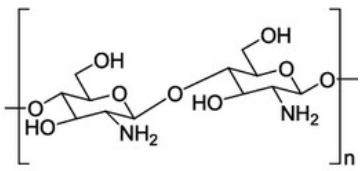
STRUCTURES OF ABUNDANT BIOPOLYMERS



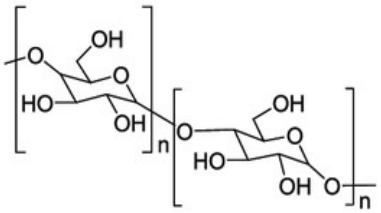
Cellulose



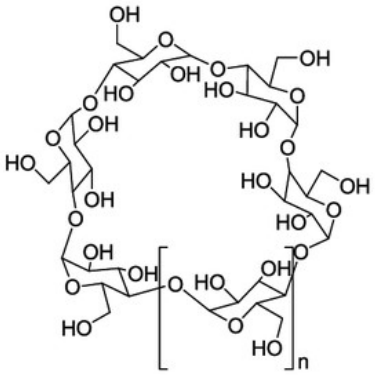
Chitin



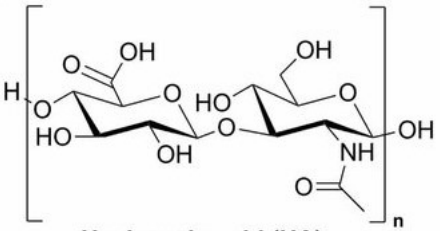
Chitosan



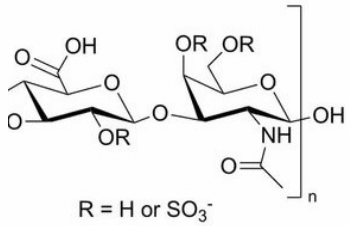
Dextran



Cyclodextrin

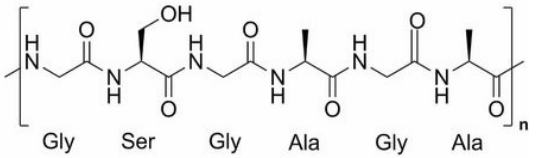


Hyaluronic acid (HA)



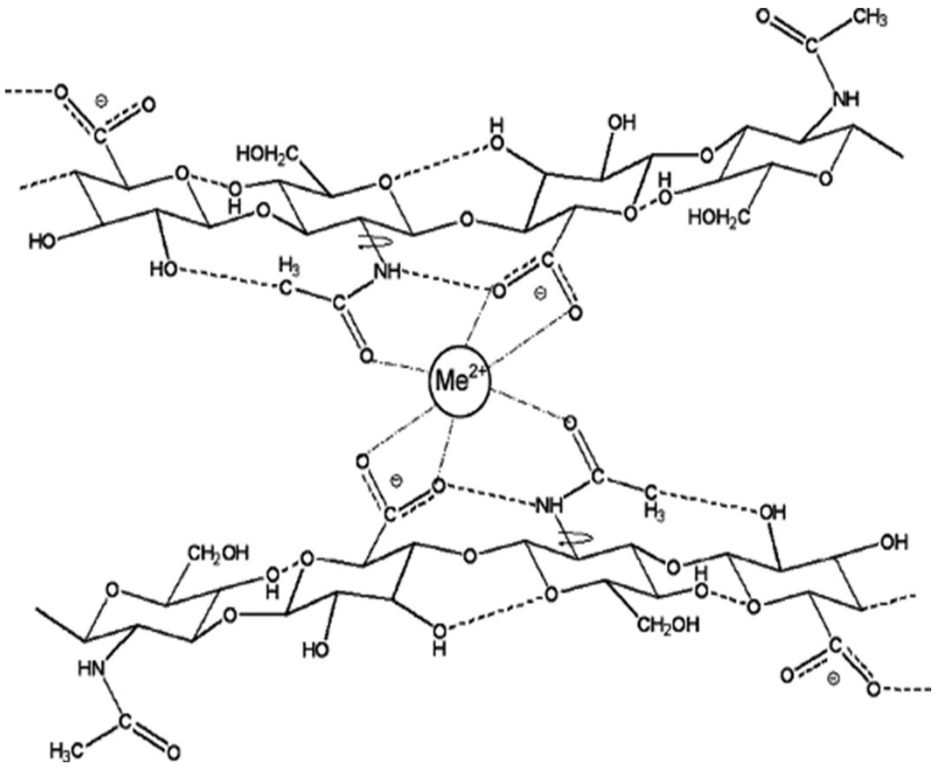
R = H or SO_3^-

Chondroitin sulfate (CS)



Silk fibroin

HYALURONIC ACID CHELATING MECHANISM



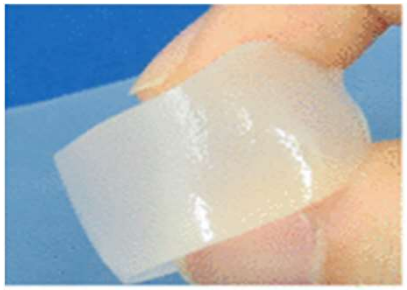
Chelate-like complex forms between a divalent cation (Me^{2+}) and two disaccharide units of hyaluronate.

The metal ion interacts with six oxygen atoms which belong to two *N*-acetyl groups and two carboxylate groups of the opposing chain sections.

The equivalent molar relation of cations and disaccharide units of the native hyaluronate is approximately 1:5

Mayer C. et al, 2008

ADSORBENTS HYDROGELS DESIRABLE PROPERTIES

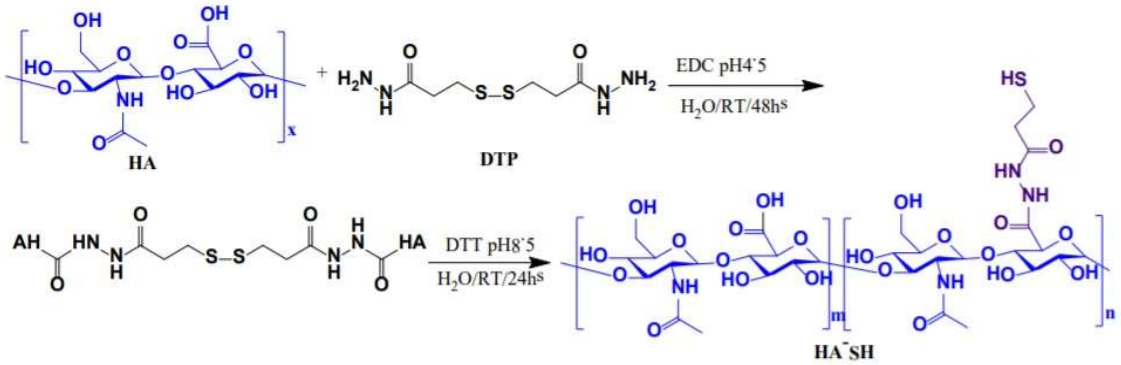


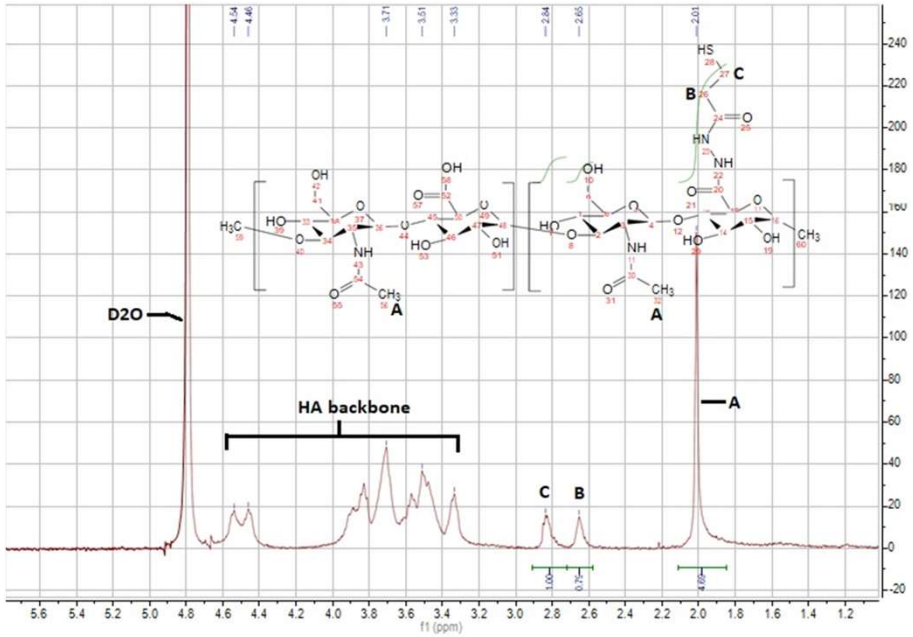
Shortcomings	Advantages
Large specific surface area	Environmentally friendly nature
Mechanical strength	Easy processing and reusability
Controllable morphology	Low cost
Thermal stability	High adsorption capacity and selectivity

THIOLATION OF HYALURONIC ACID FOR A REDOX-SENSITIVE SYSTEM

Hyaluronic acid

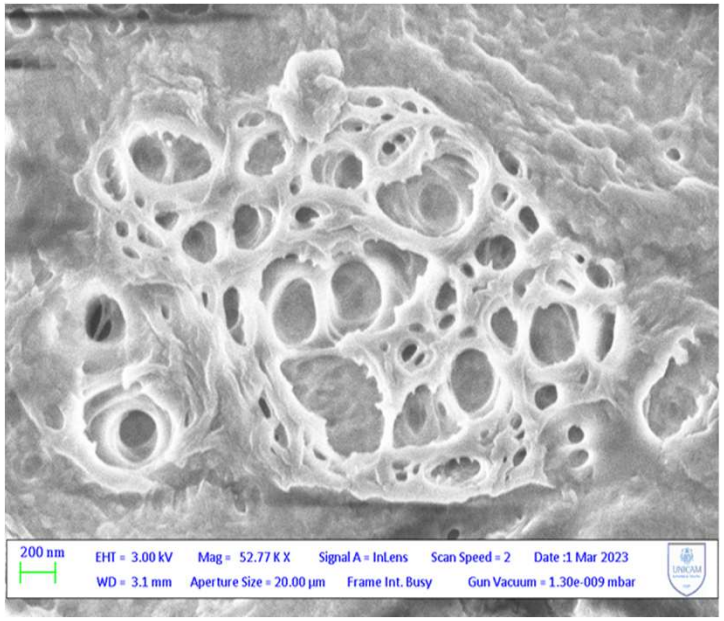
- Natural polysaccharide Mw: 38 KDa
- The main constituent of the extracellular matrix
- Thiolation of HA with different degrees of substituition (DS% 30; 50 and 70)
- Disulfide bonds are redox-sensitive HA-SH + HA-SH → HA-S-S- HA



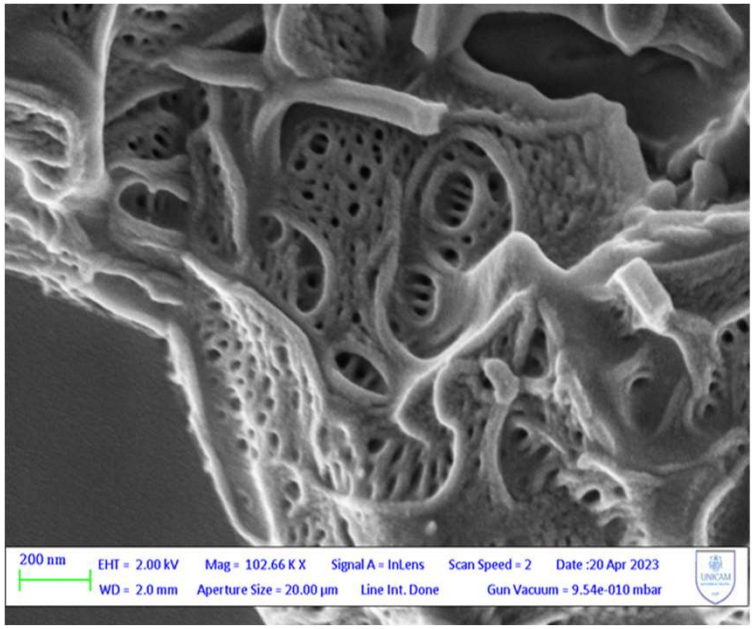


SEM analysis of hydrogels 30-50-70% DS

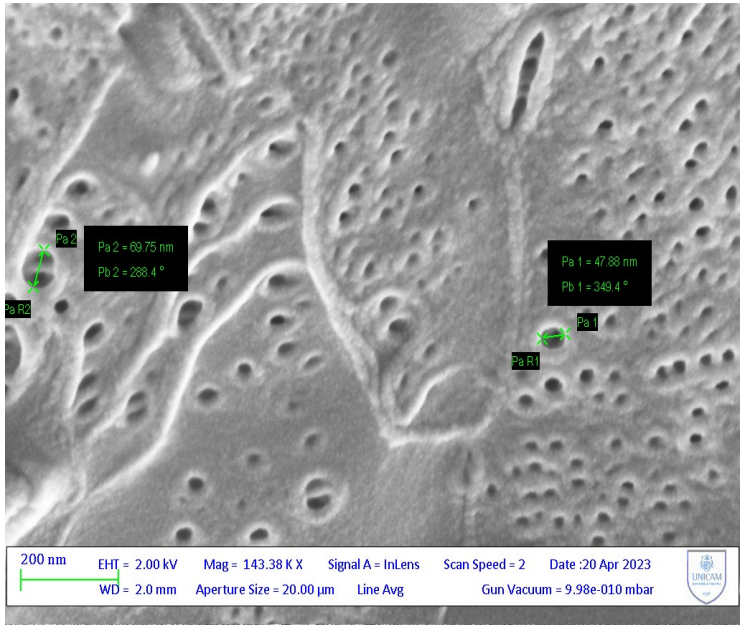
- DS 30%



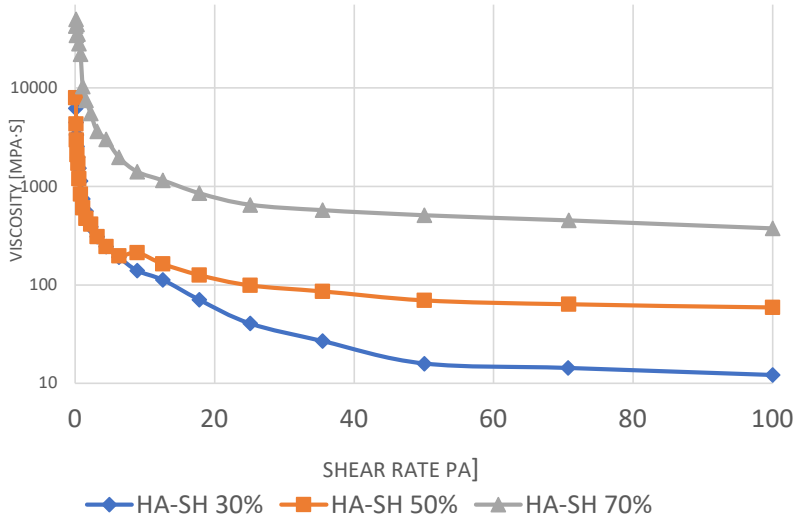
- DS 50%

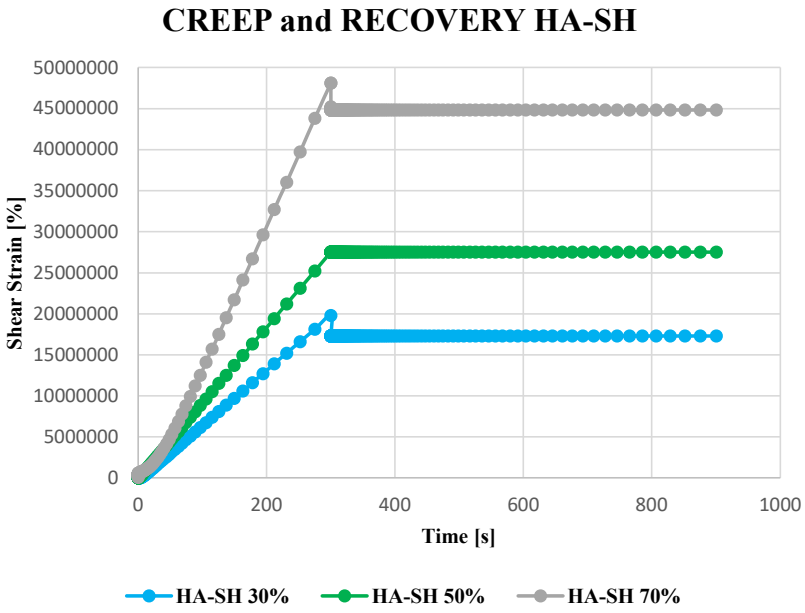


- DS 70%

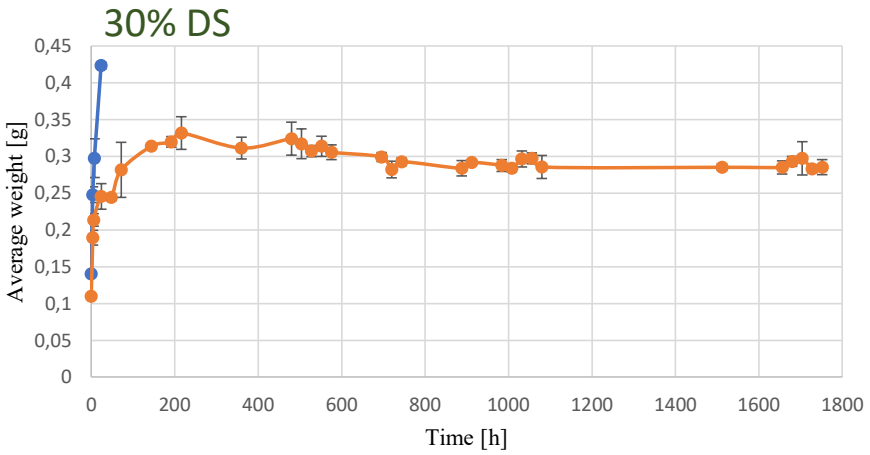


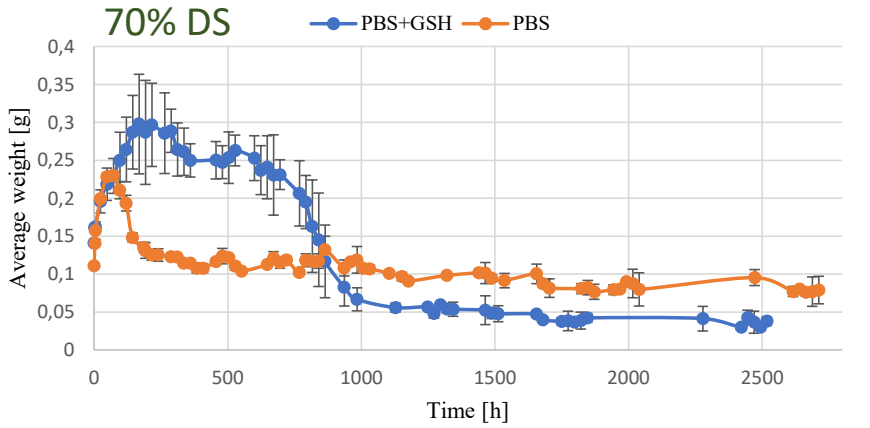
RHEOLOGICAL STUDIES

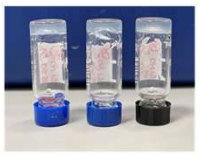




Hydrogels redox-responsiveness







After 6 hours in PBS+ GSH

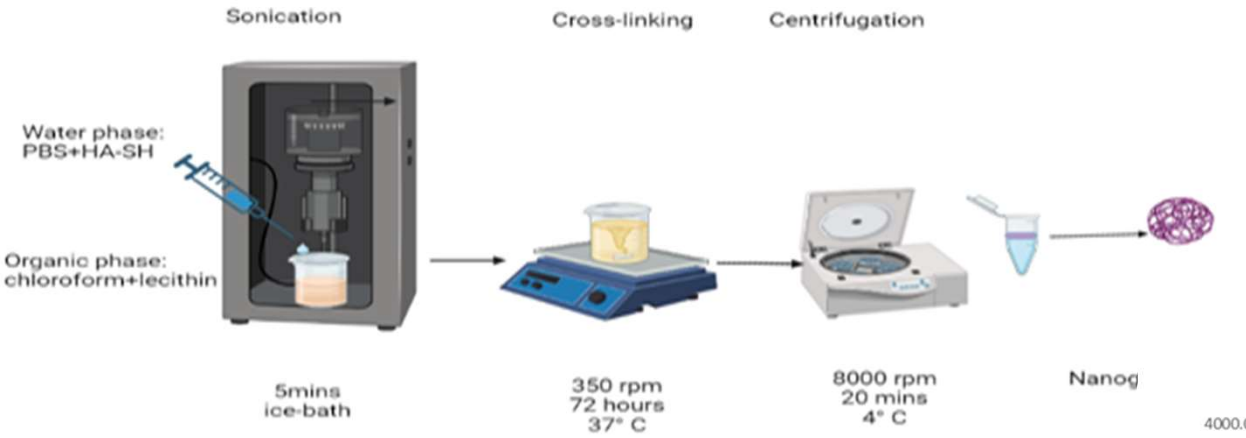
After 72 hours in PBS

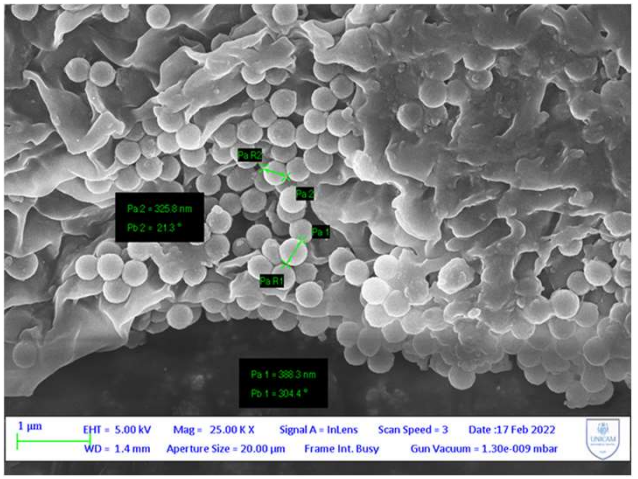
After 193 hours in PBS

- Complete degradation of the hydrogel in the redox environment after 24 hours
- Swelling and stable state of the hydrogels in PBS after 75 days- still going on

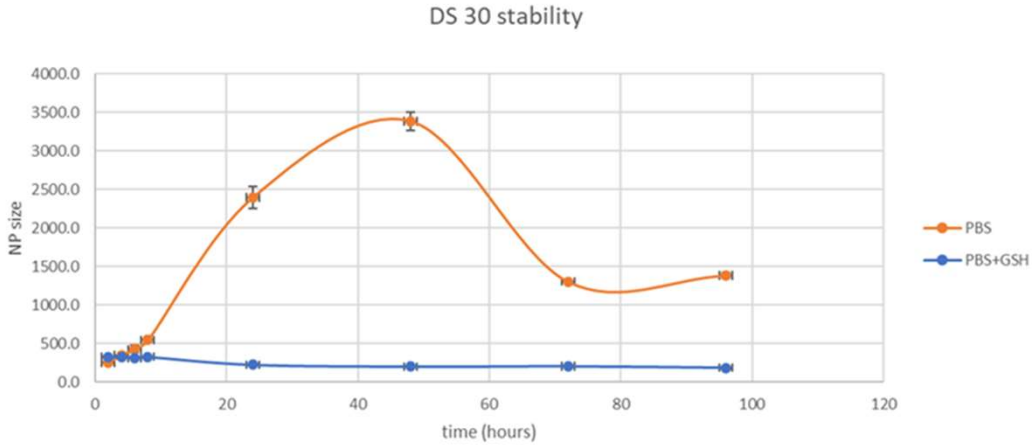
- High and continuous swelling in the redox environment until 36 days
- Less swelling in PBS and a steady state after almost one week continuing for almost 105 days- still going on

PREPARATION OF NANOPARTICLES

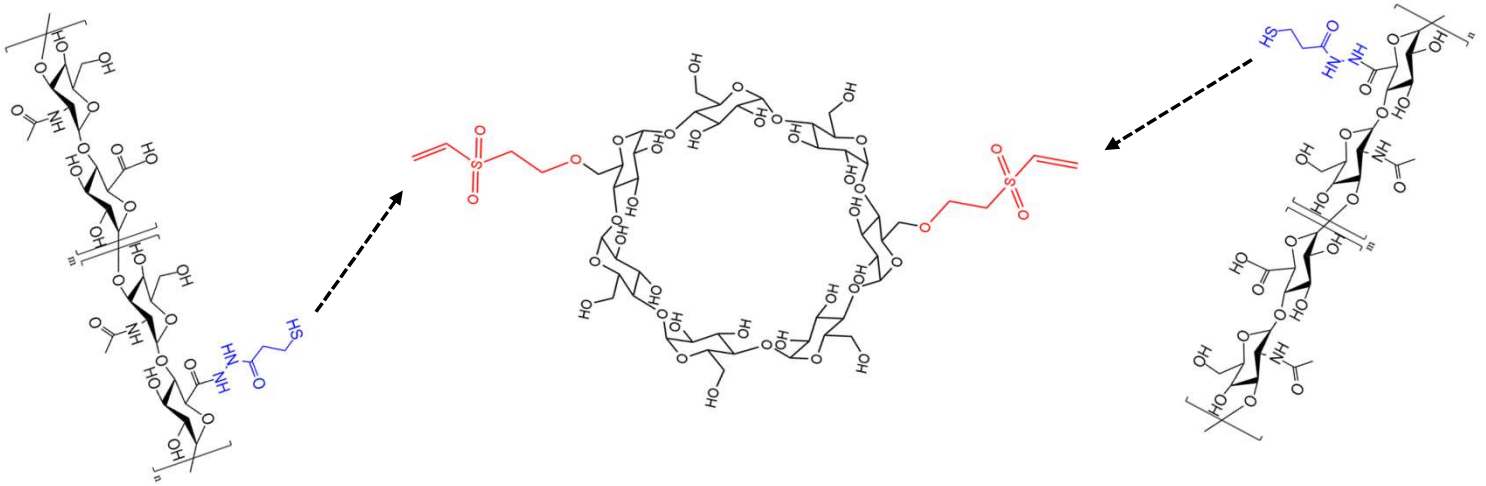




HA-SH 30% DS	Size	PDI
Without filter	300±10 nm	0.47±0.08
Filtered (0.45 µ)	170±5 nm	0.22±0.06



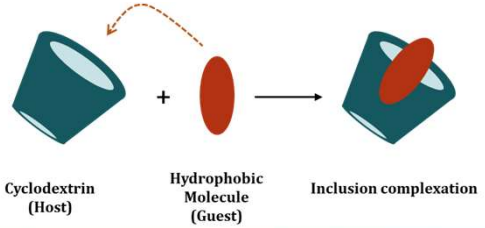
Hydrogel formulation by crosslinking via Michael addition reaction



Thiolated Hyaluronic acid
(HA-SH)

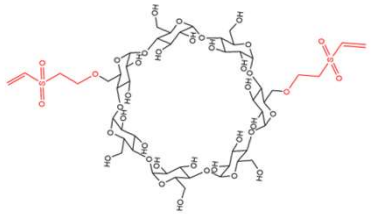
Vinyl sulfonated βcyclodextrin
(βCD-VS)

Thiolated Hyaluronic acid
(HA-SH)

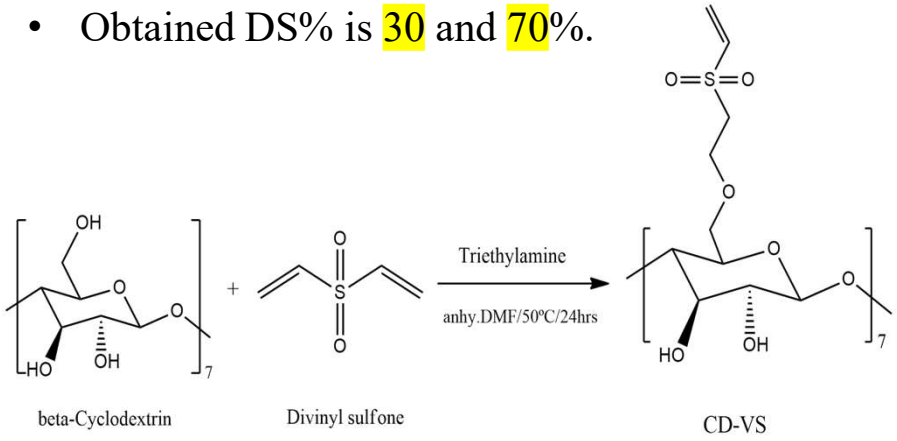


Simultaneous removal of heavy metals and toxic hydrophobic substances or encapsulation of hydrophobic drugs

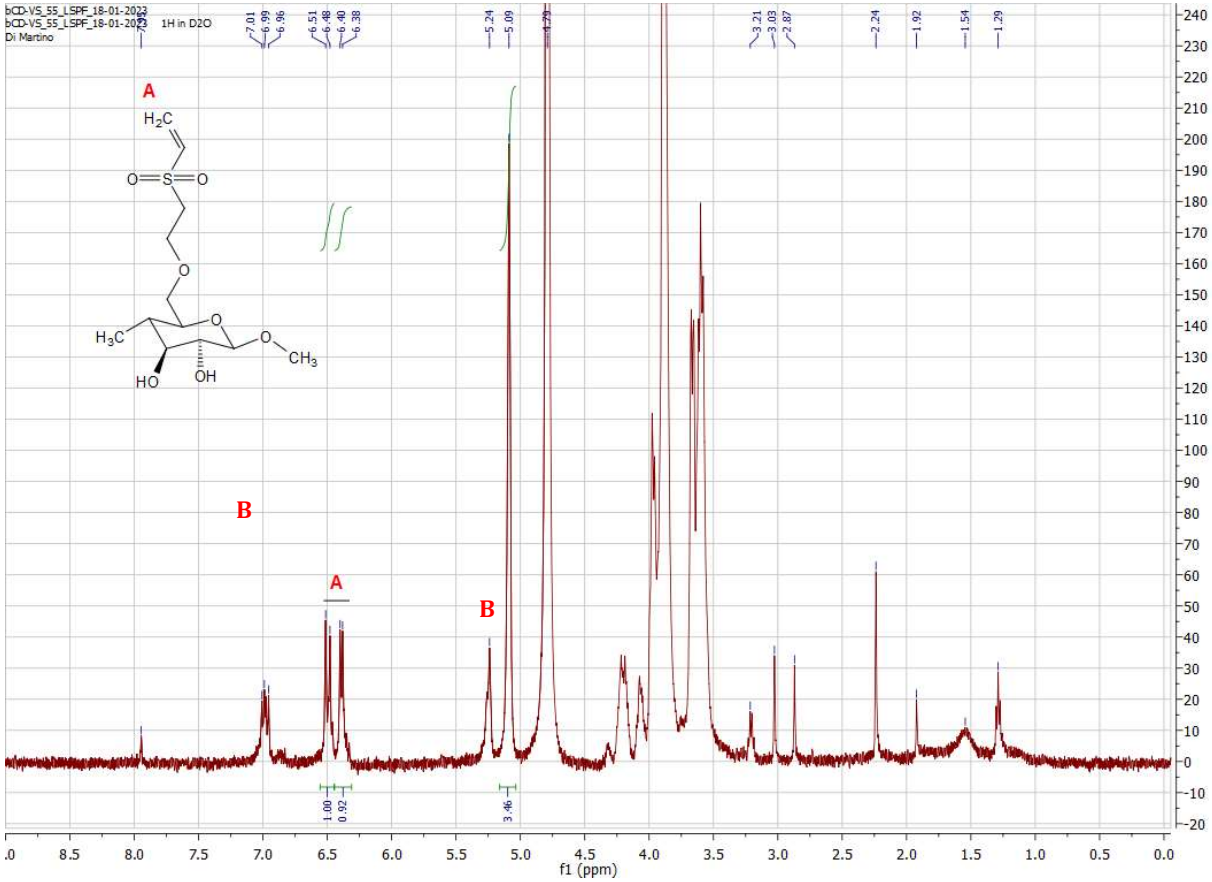
Vinyl sulfonated βcyclodextrin
(βCD-VS)



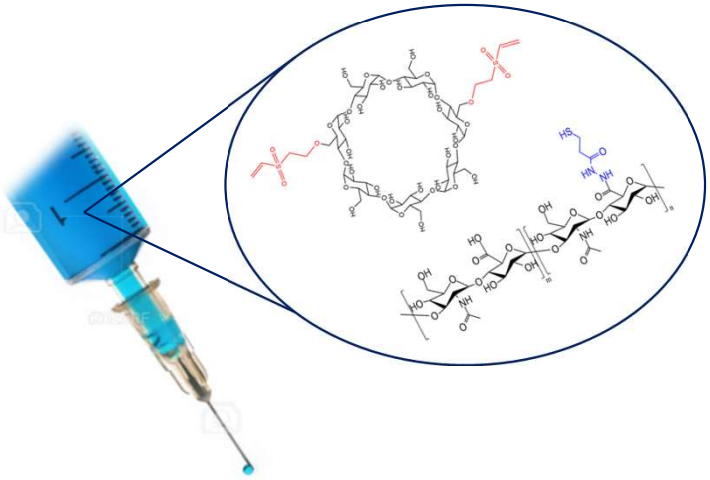
- NMR confirmed the structure.
- Obtained DS% is 30 and 70%.

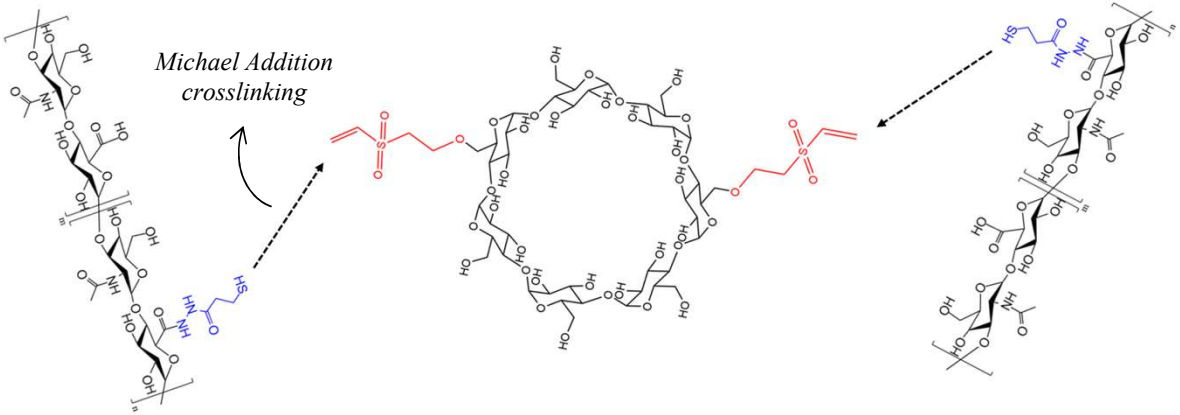


beta-Cyclodextrin Divinyl sulfone CD-VS



Cyclodextrin/hyaluronic acid-based HYDROGEL





Thiolated Hyaluronic acid
(HA-SH)

Vinyl sulfonated βcyclodextrin
(βCD-VS)

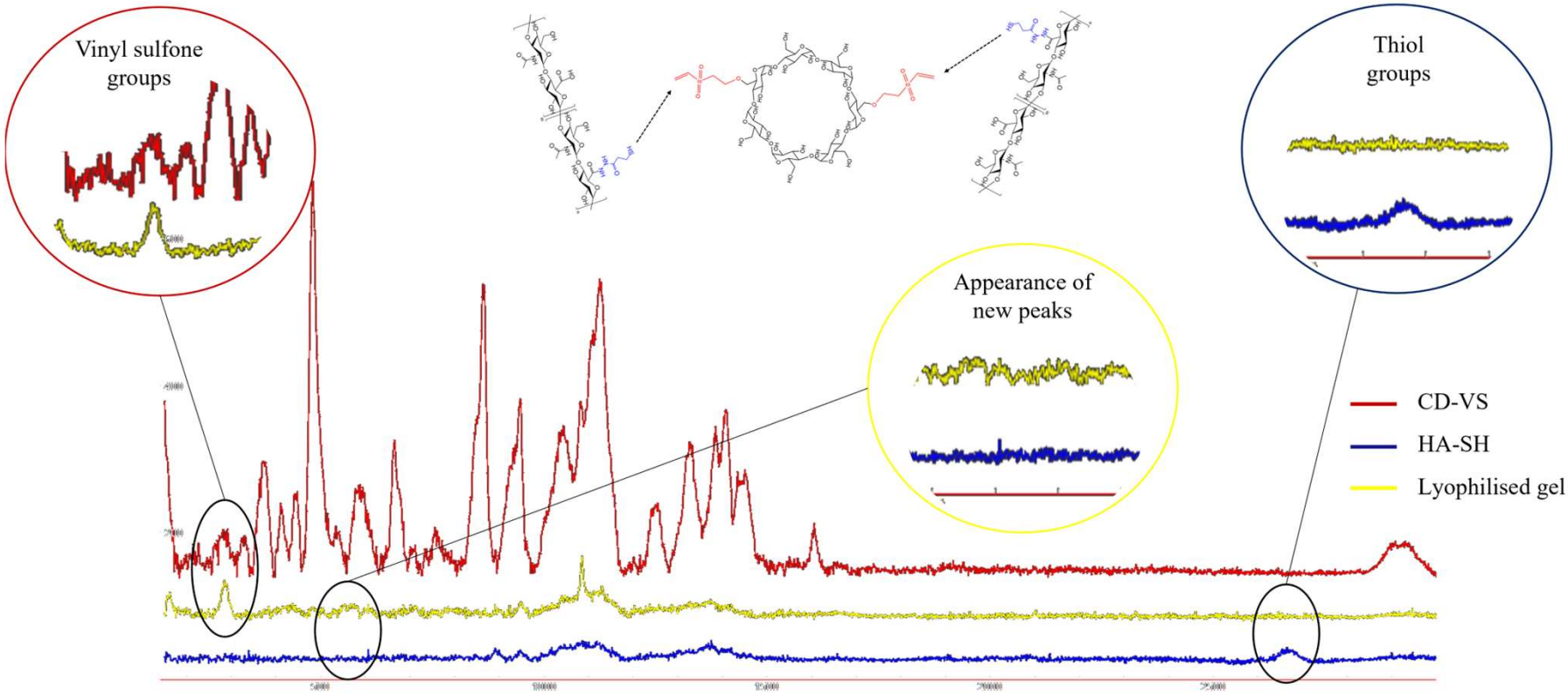
Thiolated Hyaluronic acid
(HA-SH)

37°C

pH 7.4 (PBS)

Cyclodextrin/hyaluronic acid-based HYDROGEL

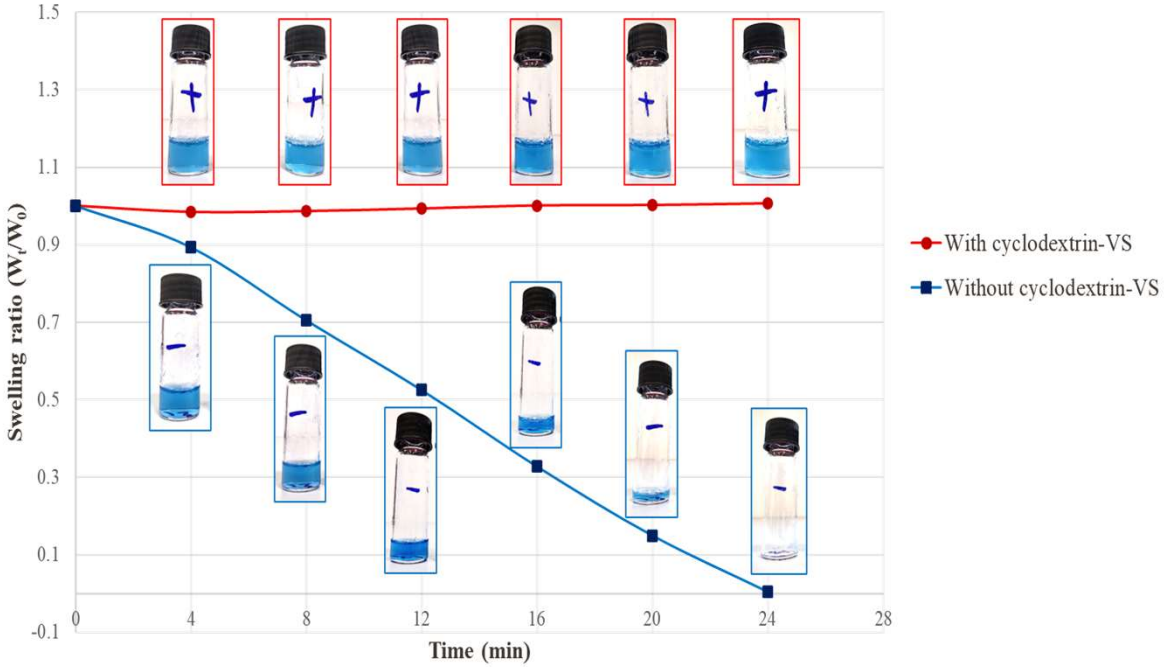
RAMAN Spectroscopy



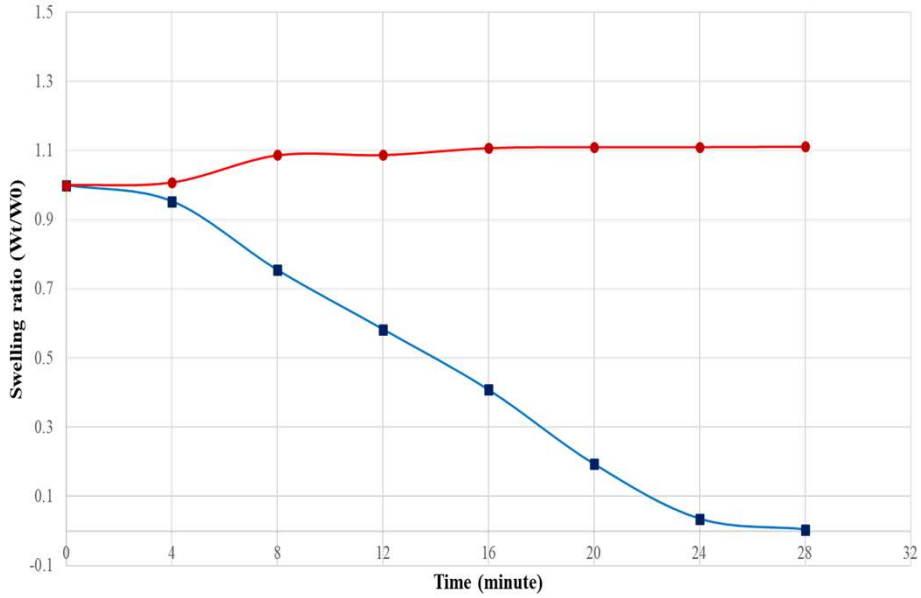
Cyclodextrin/hyaluronic acid-based HYDROGEL

Stability Test Under Reductive Environment

Low MW HA (23 kDa)

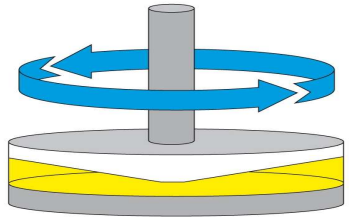


High MW HA (99 kDa)

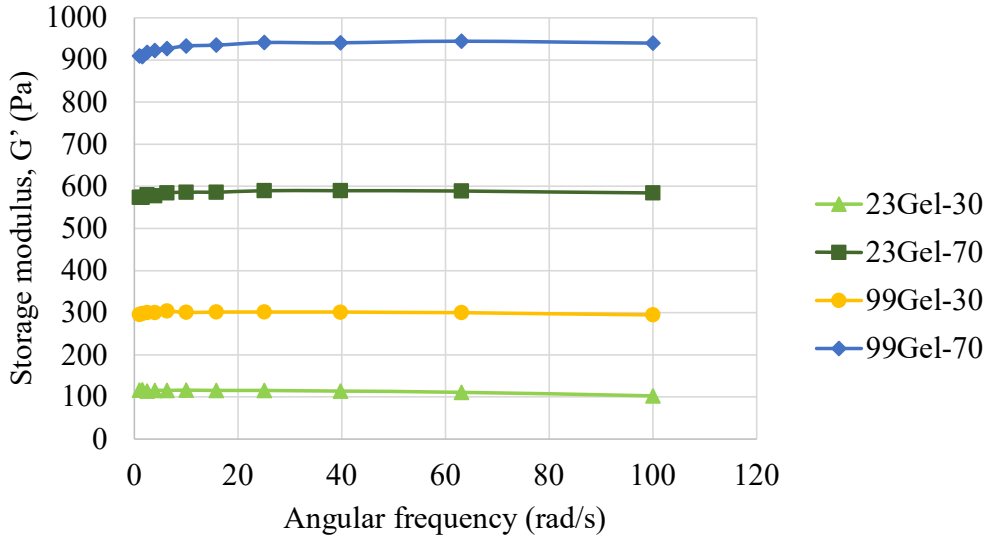


Cyclodextrin/hyaluronic acid-based HYDROGEL

Rheological Studies



Frequency Test



- ✓ Increased G' exhibits the proportionality of the elastic response to the crosslink density and the network structure.

CONCLUSIONS

Hyaluronic acid is a versatile biopolymer, suitable for the chemical modification and chemical crosslinking.

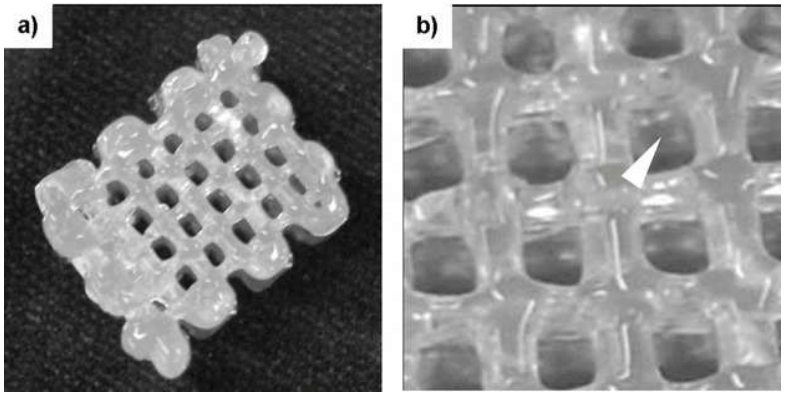
- Disulfide crosslinking
- Michael addition crosslinking via cyclodextrins

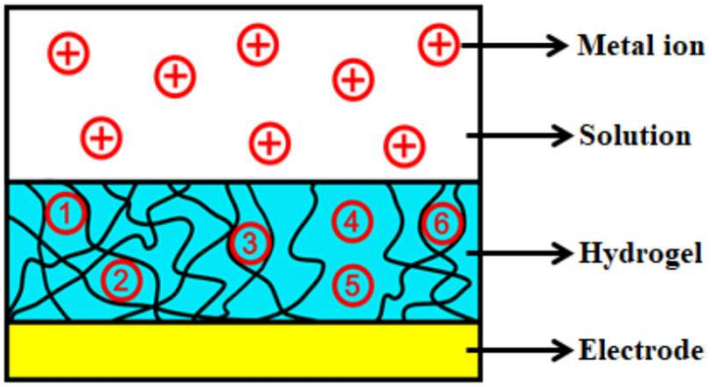
Improvement of intrinsic drawbacks of native polysaccharides:

- Higher and tunable mechanical strength
- Controllable morphology, from macro- to nano-hydrogels
- Proof of concept studies on 3D printing, to enhance surface area and filtration efficiency, and fabrication of electrodevices to improve heavy metals concentration gradient towards hydrogels

Wide range of applications:

- Water remediation from heavy metals and hydrophobic contaminants
- Drug delivery and homeostasis rebalance





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