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# Design and Characterization of Hybrid Hydrogel Architectures Based on Agarose and Functional Copolymers

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## INTRODUCTION & AIM

Agarose, a marine-derived polysaccharide, is a widely used biomedicine due to its biocompatibility, gel-forming capacity, and inert nature [1]. However, its poor biodegradability and mechanical limitations restrict further clinical use [2]. To address this, we propose the preparation of novel biodegradable semi-IPN combining agarose (*component 1*) with synthetic copolymers (*component 2*) based on methacrylate monomers like 2-(*N*,*N*-dimethylamino)ethyl methacrylate (DMAEMA), 2-hydroxyethyl methacrylate (HEMA) or oligo(ethylene glycol) methacrylate (OEGMA). The incorporation of other methacrylate-type monomers (furfuryl [FMA] and vinyl [VMA] methacrylates) will enable labile cross-linking, thereby enhancing degradation and preventing the formation of microplastics.

## METHODS

25 copolymers were synthesized via optimized living polymerizations (RAFT and ATRP). Cross-linking was carried out via ionic or covalent (Diels–Alder or thiol–ene) interactios, either individually or within an agarose matrix (*Figures 1* and *2*). The resulting 7 hydrogels were characterized by NMR, SEC, SEM, and rheological analyses.

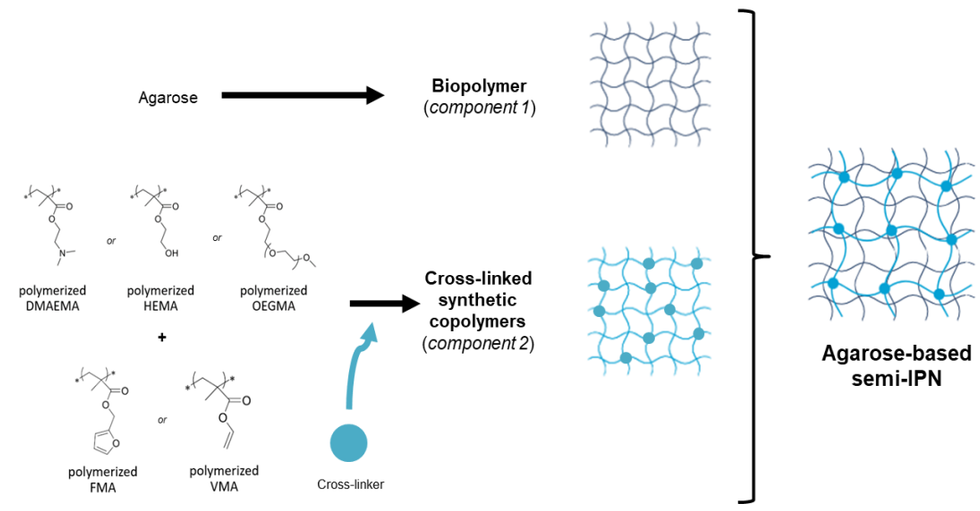



*Figure 1*. Scheme of semi-IPN formation and used monomers.

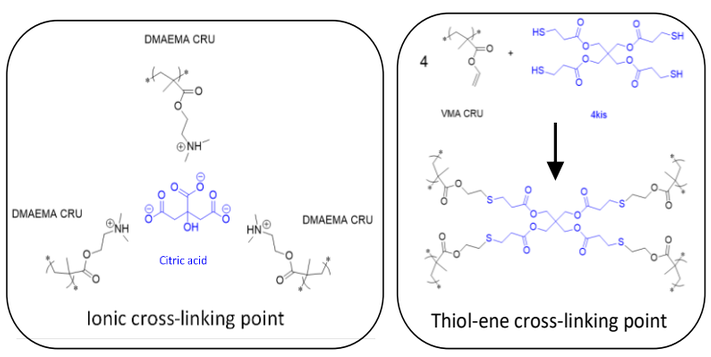
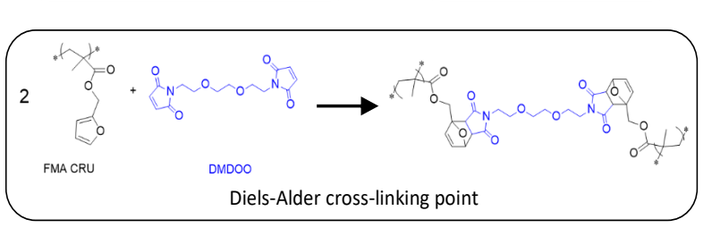



*Figure 2*. Scheme of cross-linking points




## RESULTS & DISCUSSION

Both polymerization techniques successfully yielded copolymers with the targeted monomer ratios, although RAFT provided narrower dispersity (*Table 1*). As seen in *Figure 3*, HEMA produced the strongest hidrogels under identical cross-linking conditions, while thiol–ene cross-linking became the most effective strategy, offering superior rheological properties.

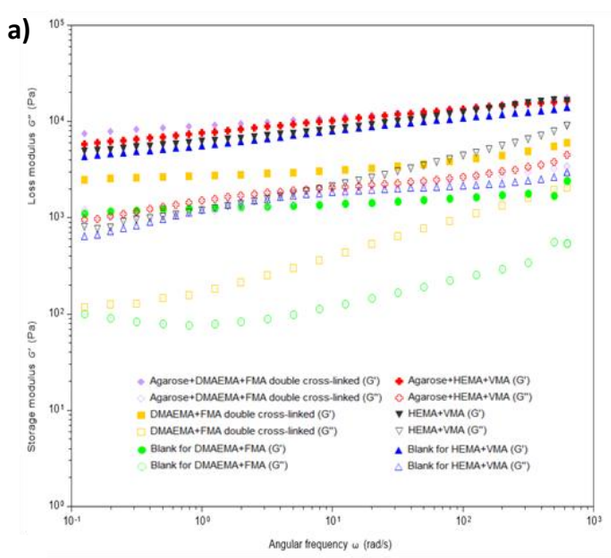
*Table 1*. Selected copolymers: theoretical data vs. experimental data (NMR and SEC).

| Copolymer | *Theoretical data* | | | *Experimental data (NMR)* [a] | | *Experimental data (SEC)* | | |
|---|---|---|---|---|---|---|---|---|
| | Monomers ratio (mol %) | Degree of polymerization | $M_n$ | Monomers ratio (mol %) | Degree of polymerization | $M_w$ [b] | $M_n$ [b] | $M_w/M_n$ [b] |
| **OEGMA+FMA** | 80:20 (OEGMA:FMA) | 120 | 33,000 | 82.7:17.3 (OEGMA:FMA) | 107 | 20,500 | 17,900 | 1.14 |
| **HEMA+VMA** | 70:30 (HEMA:VMA) | 60 | 7,700 | 72:28 (HEMA:VMA) | 99 | 43,000 | 20,300 | 2.12 |
| **HEMA+FMA** | 80:20 (HEMA:FMA) | 60 | 8,400 | 69:31 (HEMA:FMA) | 118 | 146,400 | 87,200 | 1.68 |
| **DMAEMA+FMA** | 70:30 (DMAEMA:FMA) | 60 | 9,800 | 65:35 (DMAEMA:FMA) | 67 | 56,100 | 29,900 | 1.88 |

[a]Mol % for each monomer calculated using integrals for the peaks at δ 3.38 ppm (from OEGMA moiety: 3 H), δ 3.58 ppm (from HEMA moiety: 2 H), δ 2.57 ppm (from DMAEMA moiety: 2 H), δ 7.44-7.67 ppm (from FMA moiety: 1 H) and δ 7.11 ppm (from VMA moiety: 1 H), divided by the corresponding number of H. [b]Determined by SEC against poly(methyl methacrylate) standards.

DMAEMA: 2-(*N*,*N*-Dimethylamino)ethyl methacrylate; FMA: furfuryl methacrylate; HEMA: 2-hydroxyethyl methacrylate; NMR: nuclear magnetic resonance; OEGMA: oligo(ethylene glycol) methacrylate; SEC: size exclusion chromatography; VMA: vinyl methacrylate.

Diels–Alder cross-linked networks did not exhibit retro-Diels–Alder behavior upon heating unless equilibrium was deliberately shifted. Incorporation of agarose to form semi-IPN enhanced the rheological performance of all systems compared to blanks (*Figure 3a*). SEM analysis revealed well-defined microporous architectures, supporting the potential of these semi-IPN for biomedical applications (*Figure 3b*).



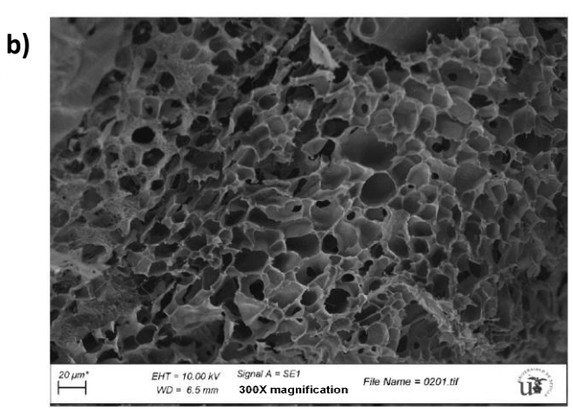




*Figure 3*. **a)** Frequency sweep ($\pi$/25 to 200$\pi$ rad/s) of selected systems and blanks. Filled symbols = $G'$; open symbols = $G''$. **b)** Microstructure of semi-IPN with agarose and cross-linked HEMA-VMA copolymer (70%:30%).

## CONCLUSIONS

- Novel agarose-based biomaterials with enhanced mechanical strength and porous microstructures were developed for biomedical applications.
- Both RAFT and ATRP effectively yielded copolymers from HEMA, OEGMA, DMAEMA, FMA, and VMA with targeted monomer ratios.
- Gelation was accomplished through both covalent and ionic cross-linking, with Diels–Alder yielding the most robust semi-IPN.

## FUTURE WORK / REFERENCES

- Future work will focus on validating the responsive behaviors of the hydrogels, assessing thermosensitivity and pH responsiveness, and evaluating the effects of freeze-drying.
- Additional studies will also explore their potential in tissue engineering and drug delivery.

[1] *Molecules*. 2023, doi: 10.3390/molecules21111577
[2] *Pharmaceutics*. 2023, doi: 10.3390/pharmaceutics15102514

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