

# Hyaluronic-Acid Methacrylate/Methacryloyl Photoresins: Source, Molecular Weight, Substitution, DLP Hybrid Networks, Hydration, Hyaluronidase Degradation and Qualification

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## Statement of Significance

Hyaluronic-acid methacrylate or methacryloyl is not one material. Biological or fermentation source, molecular-weight distribution, salt form, derivatisation, purification and storage define the macromer. Hybrid-network composition, exposure, washing, hydration and hyaluronidase history define distinct network and article states.

**Keywords:** *hyaluronic acid; HAMA; molecular weight; substitution; DLP; hybrid network; hydration; hyaluronidase; degradation; qualification*

## Abstract

Hyaluronic-acid methacrylate or methacryloyl is a family of derivatives, not a single photoresin. Biological or fermentation source, molecular-weight distribution, salt form, derivatisation reagent, substitution method, purification and storage define the macromer. HAMA is frequently used in DLP as a component of GelMA, PEG or cleavable hybrid bioinks, so printability and mechanics cannot automatically be assigned to neat HA. This review separates parent-polymer identity, substitution, formulation, exposure, washing, hydration, network contribution and hyaluronidase-sensitive degradation, and withholds universal biological or clinical claims.

## 1. Scope and boundaries

ER-124 owns material-specific identity and qualification of hyaluronic-acid methacrylate or methacryloyl photoresins and their DLP hybrid networks. It covers biological or fermentation source, molecular-weight distribution, salt form, derivatisation, purification, formulation, exposure, washing, hydration, mechanics and hyaluronidase-sensitive degradation.

ER-06 retains biological-response methodology; ER-10 geometric metrology; ER-15 degradation and mechanical evolution; ER-27 conversion; ER-33 washing and drying; ER-67 generic hybrid-network architecture; ER-86 extractables; ER-100 corpus architecture; and ER-121 to ER-123, ER-125 and ER-126 neighbouring natural-polymer derivative families. [C1,C2,C3,C4,C5,C6,C7,C8,C9,C10,C11,C12,C13].

General AM characteristics, geometric test artefacts and geometrical tolerancing should follow the declared standards [S1,S3,S4].

HA source is not molecular weight. Methacrylation feed is not measured substitution. HAMA is not one universal chemistry, and neat HAMA is not a GelMA, PEG or cleavable-linker hybrid. Green, washed, hydrated and enzyme-exposed articles must remain separate; in-vitro degradation is not a universal in-vivo lifetime.

## 2. Controlled hyaluronic-acid photoresin state chain

| State                    | Minimum identity                                                                                                       | Failure if omitted                                       |
|--------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| Incoming hyaluronic acid | HA source, fermentation or tissue route, molecular-weight distribution, salt form, purity and storage                  | The word hyaluronan replaces polymer identity            |
| Photoactive derivative   | methacrylation reagent, feed and reaction, purification, drying, measured incorporation and calculation basis          | Feed or HAMA acronym is treated as chemistry             |
| Vat or bioink            | Derivative concentration, water/buffer, initiator, absorber, cells or additives, temperature and age                   | Formulation and biological state disappear               |
| Article                  | Exposure and layer strategy, green geometry, wash, hydration, secondary structure, conversion, residuals and mechanics | Green, washed, hydrated and tested objects are conflated |

Table 1. Minimum state chain for hyaluronic-acid methacrylate/methacryloyl photocurable networks.

This material and article chain is separate from process and production-site qualification under ISO/ASTM 52920:2023 [S2].

### 3. Primary evidence and controlled interpretation

#### 3.1 Parent-polymer identity is not a HAMA concentration

Methacrylated HA retains a highly hydrated polyelectrolyte backbone, but molecular-weight distribution, source, salt form and substitution route alter viscosity, charge density and network formation. A nominal HAMA concentration is therefore insufficient without parent-polymer and derivative traceability.

#### 3.2 Concentration, hydration and mechanics are coupled

Methacrylation feed is not measured substitution. NMR or another validated method must report calculation basis, and purification must address unreacted reagent and low-molecular species. Conversion, gel fraction and residuals are separate from substitution and must be measured on the relevant printed state.

Foundational evidence for HA-derived hydrogels and methacrylated HA networks is represented by references [2] and [3]; their exact chemistry and article state must remain explicit.

#### 3.3 Hybrid networks are not neat HAMA

DLP studies commonly combine HAMA with GelMA or PEG derivatives, and some use selective post-print enzymatic cleavage of one network component. Such formulations are hybrid networks whose optical response, stiffness, swelling and degradation arise from all components. A successful hybrid print does not establish the manufacturability or mechanics of neat HAMA.

#### 3.4 Cleavable-bioink evidence is not a generic HAMA claim

Molecularly cleavable bioinks have enabled DLP fabrication of volumetric soft tissues [1]. The GelMA/HAMA ratio, HA molecular weight, the hyaluronidase digestion step, photoabsorber, cells, exposure and culture are part of that exact material state; the results cannot be reduced to a generic HAMA claim.

#### 3.5 Hyaluronidase testing has its own coordinates

Hyaluronidase testing requires enzyme source and activity, buffer, pH, temperature, replenishment, specimen geometry and time. Polymer dissolution, network cleavage, mass loss, dimensional change and mechanical decline must remain separate endpoints, and an in-vitro enzyme curve is not a universal in-vivo lifetime.

### 4. Photochemistry, polymer structure and process state

HA molecular-weight distribution, salt form, concentration, pH, ionic strength, temperature and ageing control viscosity and chain conformation. Derivatisation supplies photoreactivity; initiator, wavelength, irradiance, exposure, oxygen, layer thickness and optical attenuation control polymerisation. High water uptake makes conditioning and dimensional state central to every comparison.

GelMA, PEG and cleavable-linker hybrids require component-specific and neat-component controls. Conversion, gel fraction, hydration, network cleavage and hyaluronidase response are distinct coordinates that must be measured on matched green, washed and equilibrated states.

### 5. Hydration, degradation and biological boundaries

| Evidence block                             | What it can show                                                                                | What it cannot establish alone                           |
|--------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| Hydration/equilibration                    | Medium- and time-specific mass, dimensions, swelling and mechanics                              | Conversion, in-use lifetime or degradation mechanism     |
| Chain association / physical network state | Method- and state-specific chain association and hybrid-network or other conformational content | Covalent conversion or a verified second network         |
| Enzymatic incubation                       | Enzyme-, activity-, medium-, temperature-, geometry- and time-specific mass/property evolution  | Universal in-vivo resorption                             |
| Biological model                           | Response of the exact construct in the stated cell, tissue or animal model                      | General safety, clinical efficacy or regulatory approval |

Table 2. Evidence blocks that must remain separate for hyaluronic acid photo-networks.

ISO 10993-12:2021/Amd 1:2025 and ISO 10993-18:2020/Amd 1:2022 anchor sample preparation and chemical characterisation [S5,S6]. ISO 10993-1:2025 frames biological-safety evaluation within risk management [S7], while ISO 22442-1:2020 is relevant when animal-derived starting materials enter a medical-device claim [S8]. None of these standards converts a favourable cell or animal observation into general clinical suitability.

### 6. Release matrix

| Gate              | Minimum evidence                                                                                  | Claim withheld                                  |
|-------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------|
| HA identity       | Species/source, source lot, purification, dissolution, molecular distribution, purity and storage | Generic hyaluronic acid equivalence             |
| Functionalisation | Reaction conditions, purification, measured incorporation method/result and storage               | methacrylation feed or HAMA acronym as identity |

| Gate                | Minimum evidence                                                                                    | Claim withheld                                     |
|---------------------|-----------------------------------------------------------------------------------------------------|----------------------------------------------------|
| Vat process         | Concentration, initiator, wavelength, irradiance, exposure, layer thickness, temperature and ageing | Transferable print settings                        |
| Network attribution | Conversion plus independent secondary-structure and physical-state evidence with controls           | Unverified dual network                            |
| Article state       | Green, washed and hydrated x/y/z, mass, residuals and conditioning history                          | Unqualified dimensions or mechanics                |
| Biological boundary | Exact formulation, construct, dose, wash, model, endpoint and statistics                            | Universal biocompatibility or clinical suitability |

Table 3. Minimum release architecture for hyaluronic-acid methacrylate/methacryloyl photocurable constructs.

## 7. Failure-mode interpretation

- A nominally identical HAMA becomes much less viscous: verify source, molecular-weight distribution, salt form and dissolution, chain degradation, concentration, temperature, storage and freeze-thaw history before changing exposure.
- A higher methacrylation feed does not increase modulus: measure incorporated functionality and conversion; feed, measured degree of substitution and network density are different quantities.
- The green object is accurate but expands after washing: report x/y/z, mass and medium history after a defined wash and equilibration; do not publish green dimensions as in-use dimensions.
- Mechanical strength rises during incubation: measure water content and secondary structure before assigning further covalent cure or degradation.
- A GelMA or PEG hybrid prints better than neat HAMA: retain hybrid identity, filler state and optical absorption; do not transfer the result to neat HA resin.
- Cells remain viable after printing: retain the exact HA source route, formulation, light, wash, construct and model; do not infer approval or universal biocompatibility.

## 8. Minimum workflow and research priorities

- Freeze HA source route, molecular-weight distribution, salt form, purity, bioburden and storage.
- Report methacrylation feed, pH, temperature, time, mixing, purification, dialysis cutoff and duration, drying, measured incorporation and calculation basis.
- Map viscosity, absorbance and working curves over temperature, ageing and the complete build-duration window.
- Measure conversion, gel fraction, residuals and retained HA on matched green, washed and hydrated states.
- Quantify secondary structure independently from covalent conversion and distinguish physical reinforcement from a verified second network.
- Track mass and x/y/z dimensions through washing, equilibration, drying, rehydration and degradation.
- Report enzyme or medium identity, activity, pH, temperature, replenishment, geometry and time rather than one generic degradation rate.
- Separate model-specific viability, differentiation, adhesion or healing observations from safety, efficacy and regulatory conclusions.

## 9. Conclusions

Hyaluronic-acid photoresins are controlled parent-polymer, derivative, formulation, network and article states. Source, molecular-weight distribution and salt form define HA; derivatisation and measured substitution define the macromer; formulation and exposure define the green network; washing and hydration define the tested article.

Primary evidence supports photopolymerisable HA derivatives and DLP hybrid bioinks, including molecularly cleavable systems. Hybrid performance cannot be assigned automatically to neat HAMA.

Release requires traceability through source, molecular weight, salt form, derivatisation, formulation, exposure, wash, hydrated geometry, conversion, residuals, mechanics, hyaluronidase testing and biological model. HAMA alone is not a specification.

## Limitations

This paper is a qualitative engineering review, not a systematic meta-analysis. The cited studies use related but non-identical HA sources and derivatisation routes, formulations, printers, exposures, specimens and biological models. Numerical values are retained as study-specific evidence and must not be treated as universal design values.

## Author contributions

Juan Seguro: conceptualisation, evidence synthesis, boundary definition, engineering interpretation, manuscript preparation and final author verification.

## Competing interests

The author is founder and CEO of 3Dresyns by Resyner Technologies S.L. No comparative product recommendation is made.

## Data availability

No new experimental dataset was generated. Scientific statements derive from the cited primary literature and official standards. The review package includes QA and source-boundary controls.

## Company information

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- [S3] ISO/ASTM 52902:2023. Additive manufacturing - Test artefacts - Geometric capability assessment of additive manufacturing systems. Edition 2. <https://www.iso.org/standard/79683.html>
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- [S7] ISO 10993-1:2025. Biological evaluation of medical devices - Part 1: Requirements and general principles for the evaluation of biological safety within a risk management process. Edition 6. <https://www.iso.org/standard/10993-1>
- [S8] ISO 22442-1:2020. Medical devices utilizing animal tissues and their derivatives - Part 1: Application of risk management. Edition 3. <https://www.iso.org/standard/74280.html>

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