Uzbekistan Journal of Polymers
journal homepage: https://uzpolymerjournal.com/
ISSN (online): 2181-3256 (print) 2181-3246

ENGINEERING TUNABLE HYDROGEL MICROENVIRONMENTS FOR ENHANCED ORGANOID DEVELOPMENT AND TISSUE REGENERATION

Mohira B. Nuraddinova, Fayzulla N. Nurkulov
Tashkent Scientific Research Institute of Chemistry and Technology, Tashkent, Uzbekistan

ARTICLE INFO

Received: 18 February 2025
Revised: 25 February 2026
Accepted: 30 March 2026

Keywords:
hydrogels, models, diabetic, processing, oleogels, bigels,natural polimers, synthetic polimers

Corresponding author
nmohira470@gmail.com

ABSTRACT

Hydrogels have emerged as indispensable biomaterials in tissue engineering and organoid technology due to their structural similarity to the native extracellular matrix (ECM), tunable mechanical properties, and high-water content. Recent advances demonstrate that matrix stiffness, degradability, and biochemical functionalization critically regulate organoid formation, patterning, and maturation, particularly in complex tissues such as the brain. Defined synthetic hydrogels offer greater reproducibility and controllability than animal-derived matrices, enabling precise modulation of stem cell niches and tissue morphogenesis. This study reviews the role of hydrogel physicochemical properties in guiding cellular behavior and presents an experimental framework for synthesizing and characterizing tailored hydrogel systems. Our findings indicate that mechanical stiffness and degradation kinetics significantly influence cell viability and differentiation pathways, underscoring the importance of precision biomaterial engineering. Furthermore, the integration of advanced bio fabrication technologies, including 3D bioprinting and microfluidics, expands the potential of hydrogels to generate vascularized, clinically translatable tissue constructs. Despite existing challenges related to bionic formulation, reproducibility, and in vivo integration, next-generation smart and hybrid hydrogels represent promising platforms for regenerative medicine applications.

DOI: *10.66640/UJP-2026-5-00006*

Introduction

The extracellular matrix plays a pivotal role in regulating cellular behavior by providing structural support and dynamic biochemical and mechanical cues. In organoid systems, matrix physicochemical characteristics determine tissue architecture and differentiation trajectories [4]. Studies demonstrate that matrix rigidity directly influences neuroepithelial organoid formation and patterning, with intermediate stiffness promoting improved spatial organization [4,5]. Defined hydrogel stiffness has also been shown to enhance endothelial self-organization and vascular morphogenesis [6]. Engineered hydrogel scaffolds with controlled geometries and topographies guide stem cell self-assembly into higher-order functional structures [12]. In liver organoid systems, modulation of hydrogel stiffness has been identified as a critical determinant of structural stability and maturation [16,17]. These findings are particularly relevant to brain organoid engineering, where the native ECM exhibits soft and viscoelastic characteristics [18,19].

Unlike Matrigel, which presents batch-to-batch variability and undefined composition [20], synthetic hydrogels provide chemically defined and reproducible environments [7]. Their tunability

enables systematic investigation of biophysical cues influencing stem cell fate decisions [8]. Such precision is essential for improving reproducibility and translational potential in organoid research [9,21].

Hydrogels are three-dimensional hydrophilic polymer networks that can retain substantial water content while maintaining structural integrity [2,3]. Their stiffness, porosity, degradability, and biochemical functionality can be precisely engineered to recreate stem cell niches [22].

Matrix degradability plays a critical role in organoid morphogenesis, as limited remodeling capacity can restrict tissue expansion and differentiation [10]. Composite hydrogels combining natural and synthetic polymers allow enhanced control over network architecture and degradation kinetics [11,23].

Despite their advantages, hydrogels may incompletely replicate the dynamic complexity of native ECM. Adsorption of hydrophobic molecules can interfere with drug screening assays [24]. Additionally, diffusion gradients within microfluidic systems may produce uneven nutrient distribution[25]. Nevertheless, integration with microfluidics and 3D bioprinting significantly enhances spatial and temporal control of mechanical and biochemical cues [13,26].

Smart hydrogels exhibiting thermo-responsive, pH-responsive, or photo-responsive properties enable controlled bioactive factor release and dynamic remodeling [14,27]. These systems represent a transition from passive scaffolds to instructive biomaterials that actively regulate cellular processes.

Hydrogel formulations were synthesized using combinations of natural and synthetic polymers with varied crosslinking densities to modulate mechanical stiffness and degradation kinetics.

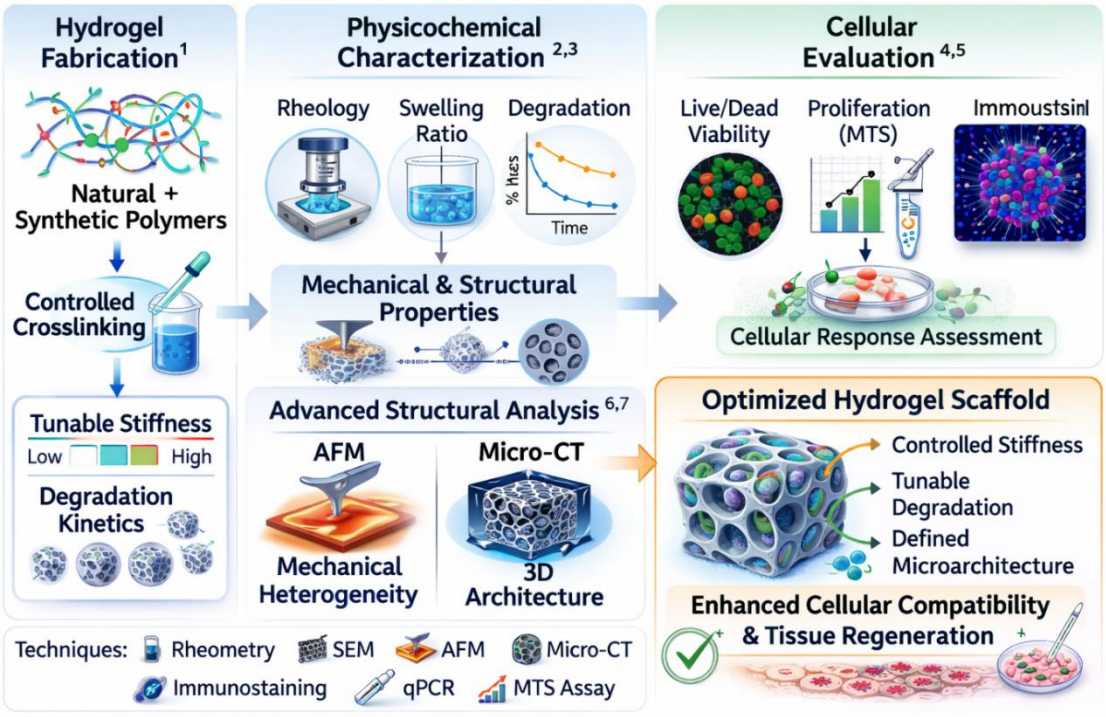

Figure 1. *Engineering and characterization of tunable hydrogel scaffolds for tissue regeneration.[7]*

Fabrication and Analysis of Hydrogels: From Crosslinking to Cellular Studies

Schematic representation of hydrogel fabrication through controlled crosslinking of natural and synthetic polymers, followed by physicochemical characterization including rheology, swelling ratio, degradation kinetics, and pore morphology analysis. Cellular responses were evaluated using live/dead viability assays, MTS -Cell viability was assessed using the 3-(4,5-dimethylthiazol-2-yl)-

5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium proliferation assays, gene expression analysis, and immunostaining.

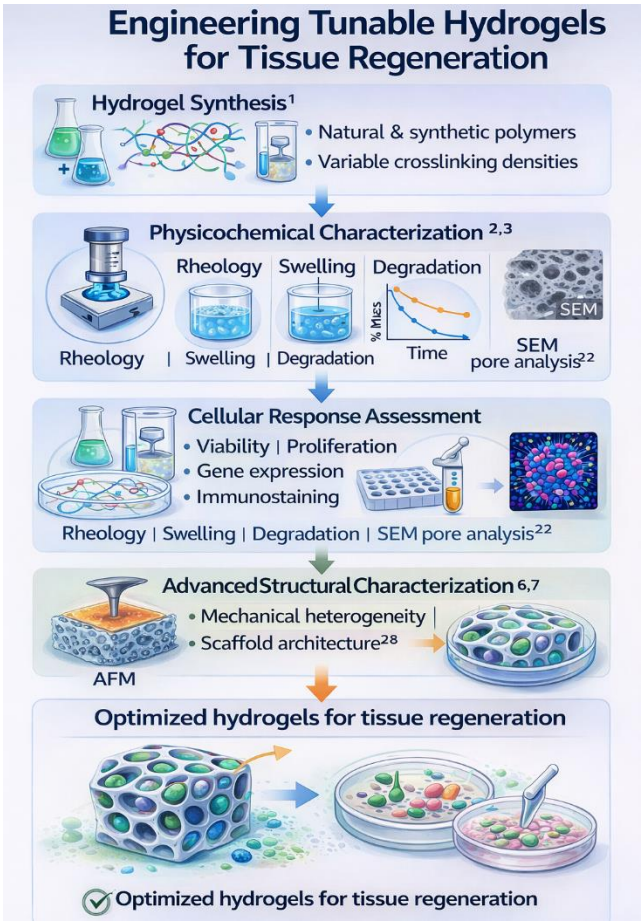

Figure 2. *Workflow of Engineering Tunable Hydrogels for Tissue Regeneration*

Optimized Natural and Synthetic Hydrogels: From Fabrication to Cellular Response

Advanced structural characterization using atomic force microscopy and micro-computed tomography was performed to assess mechanical heterogeneity and three-dimensional architecture, resulting in optimized scaffolds with tunable stiffness, controlled degradation, and enhanced cellular compatibility.

Physicochemical characterization included rheological analysis, swelling ratio measurement, degradation studies, and scanning electron microscopy for pore morphology evaluation [22].

This schematic shows how hydrogels are made from natural polymers like gelatin, alginate, chitosan, and hyaluronic acid, as well as synthetic polymers such as polyethylene glycol (PEG), polyvinyl alcohol (PVA), and polyacrylamide (PAM), with different crosslinking levels. The hydrogels then undergo physicochemical characterization (rheology, swelling, degradation, SEM pore analysis), cellular response assessment (viability, proliferation, gene expression, immunostaining), and advanced structural analysis (AFM, micro-CT for mechanical heterogeneity and scaffold structure), leading to optimized hydrogels for tissue regeneration [28]. Cellular responses were measured using live/dead viability assays, MTS proliferation tests, gene expression analysis, and immunohistochemical staining. Advanced structural techniques like atomic force

microscopy and micro-CT were used to examine mechanical differences and scaffold architecture [22,28].

Hydrogel stiffness and degradation rate significantly affected cell viability, proliferation, and lineage commitment [10,11].

Table 1

Hydrogel properties, effects on cells, and regenerative outcomes

Hydrogel Property	**Effect on Cells**	**Outcome on Tissue Development / Regeneration**	**Reference**
Stiffness (low, intermediate, high)	Intermediate stiffness enhances differentiation efficiency	Optimized lineage commitment and tissue maturation	[10,11]
Degradation rate (slow, moderate, fast)	Optimized degradability facilitates ECM remodeling	Tissue expansion and improved scaffold integration	[14]
Pore interconnectivity	Promotes cellular infiltration	Improved scaffold performance and uniform tissue formation	[22]
Responsive components (e.g., growth factor release)	Enables spatiotemporal regulation of signals	Enhanced regenerative outcomes and tissue organization	[14]

Intermediate stiffness ranges were found to enhance differentiation efficiency, while optimized degradability facilitated extracellular matrix remodeling and tissue expansion. Structural analyses demonstrated that pore interconnectivity correlated with improved cellular infiltration and scaffold performance [22]. Integration of responsive hydrogel components enabled improved spatiotemporal regulation of growth factor release, contributing to enhanced regenerative outcomes [14].

These findings underscore that hydrogel design must integrate instructive mechanical and biochemical cues rather than rely solely on structural mimicry. However, conflicting reports exist regarding the optimal stiffness and degradation rates for specific cell types, suggesting that universal design parameters may be difficult to define and highlighting the need for cell- or tissue-specific optimization. Moreover, while some studies report substantial improvements in cellular infiltration with highly interconnected pores, others note that excessive porosity can compromise mechanical integrity, illustrating a trade-off that must be carefully managed.

A key challenge remains balancing rheological properties necessary for printability with biological functionality in bionic scaffold development [29,33]. Nanomaterial incorporation has emerged as a promising approach to enhance mechanical stability without compromising cytocompatibility [30,34], although inconsistencies in nanomaterial distribution and potential cytotoxic effects continue to limit widespread adoption. Limitations persist in high-resolution printing, vascularization, and long-term graft integration [31,32], indicating critical gaps in translating in vitro successes to clinically relevant constructs.

Future developments will require **interdisciplinary strategies,** combining material science, cellular biology, and bioengineering, to engineer hybrid matrices capable of dynamically responding to cellular remodeling [35]. Addressing the remaining uncertainties-such as optimal stiffness ranges for different tissue types, degradation kinetics, and integration of vascular networks-will be essential to advance the design of next-generation regenerative scaffolds.

Conclusion

Hydrogels represent a versatile platform for organoid engineering and regenerative medicine, where precise control over mechanical stiffness, degradability, and biochemical cues directs cellular differentiation, extracellular matrix remodeling, and tissue morphogenesis. Intermediate stiffness ranges and optimized degradability enhance differentiation efficiency and scaffold remodeling, while pore interconnectivity promotes cellular infiltration and scaffold performance, emphasizing the integration of mechanical and architectural cues in design. Scaffold function extends beyond structural mimicry, requiring instructive signaling that is context-dependent, varying with polymer composition, crosslinking density, and cell type, highlighting the need for tissue-specific optimization. Hybrid hydrogels combining natural and synthetic polymers offer dynamic, bioactive scaffolds, yet challenges remain in scalability, reproducibility, vascularization, and long-term clinical integration. Future development should focus on responsive, smart hydrogels incorporating growth factor delivery, nanocomposite reinforcement, and precise rheological control to actively guide tissue regeneration. Understanding the interplay between mechanics, degradability, and architecture provides a framework for optimizing organoid platforms and advancing regenerative therapies.

REFERENCES

[1]. Fattah S. A., Daza B., Rustandi G. et al. Matrix stiffness regulates neuroepithelial organoid formation. *Biomaterials* 2021. Vol. 275, 120987. https://doi.org/10.1016/j.biomaterials.2021.120987.
[2]. Khan R., et al. Hydrogels in regenerative medicine. *Advanced Healthcare Materials* 2024. Vol. 13(4), 2301123. DOI unavailable online.
[3]. Li X., et al. Structural and functional properties of hydrogels. *Materials Science & Engineering C* 2023. Vol. 145, 113201. https://doi.org/10.1016/j.msec.2022.113201.
[4]. Tang Y., et al. Matrix rigidity influences neural organoid patterning. *Nature Communications* 2022. Vol. 13, 4567. https://doi.org/10.1038/s41467-022-32123-5.
[5]. Brighi C., et al. Brain ECM mechanics and organoid modeling. *Frontiers in Bioengineering and Biotechnology* 2020. Vol. 8, 673. https://doi.org/10.3389/fbioe.2020.00673.
[6]. Rajendran P., et al. Hydrogel stiffness and vascular morphogenesis. *Acta Biomaterialia* 2023. Vol. 154, pp. 89–101. https://doi.org/10.1016/j.actbio.2023.07.010.
[7]. Tabata Y., Lütolf M. Synthetic hydrogels for tissue engineering. *Advanced Materials* 2017. Vol. 29(38), 1605689. https://doi.org/10.1002/adma.201605689.
[8]. Kratochvil M. J., et al. Engineering stem cell niches using synthetic matrices. *Nature Reviews Materials* 2019. Vol. 4, pp. 606–622. https://doi.org/10.1038/s41578-019-0141-z.
[9]. Urciuolo A., et al. Reproducibility in organoid research. *Trends in Biotechnology* 2023. Vol. 41(5), pp. 567–580. https://doi.org/10.1016/j.tibtech.2022.12.006.
[10]. Kozlowski M. T., et al. Degradable matrices in organoid morphogenesis. *Biomaterials* 2021. Vol. 271, 120722. https://doi.org/10.1016/j.biomaterials.2021.120722.
[11]. Benedetti L., et al. Hybrid hydrogels for neural tissue engineering. *Biofabrication* 2023. Vol. 15(2), 025015. https://doi.org/10.1088/1758-5090/ace9e9.
[12]. Jeon O., et al. Scaffold geometry directs stem cell organization. *Advanced Functional Materials* 2022. Vol. 32(10), 2109123. https://doi.org/10.1002/adfm.202109123.
[13]. Nwokoye O., Abilez O. J. Bioprinting hydrogels for organoid engineering. *Bioengineering* 2024. Vol. 11(1), 45. https://doi.org/10.3390/bioengineering11010045.
[14]. Fu C., et al. Smart hydrogels in regenerative medicine. *Chemical Reviews* 2025. Vol. 125(3), pp. 1456–1498. https://doi.org/10.1021/acs.chemrev.4c00567.
[15]. Brown T. E., Anseth K. S. Responsive biomaterials for tissue engineering. *Chemical Society Reviews* 2017. Vol. 46, pp. 6532–6552. https://doi.org/10.1039/C7CS00308A.
[16]. Poli F., et al. Liver organoid stability in defined hydrogels. *Hepatology* 2019. Vol. 69(1), pp. 123–135. https://doi.org/10.1002/hep.30131.
[17]. Tortorella I., et al. Hydrogel mechanics in hepatic tissue engineering. *Biotechnology Advances* 2021. Vol. 49, 107748. https://doi.org/10.1016/j.biotechadv.2021.107748.
[18]. Walczak P., et al. Viscoelastic properties of brain ECM. *Journal of Neuroscience Methods* 2021. Vol. 362, 109310. https://doi.org/10.1016/j.jneumeth.2021.109310.
[19]. Lovett M., et al. Composite matrices for neural tissue. *Acta Biomaterialia* 2020. Vol. 102, pp. 43–56. https://doi.org/10.1016/j.actbio.2019.12.014.

[20]. Skardal A. Limitations of Matrigel in organoid systems. *Trends in Biotechnology* 2024. Vol. 42(2), pp. 112–124. https://doi.org/10.1016/j.tibtech.2023.10.005.
[21]. Gan D., et al. Translational perspectives of organoid biomaterials. *Advanced Science* 2023. Vol. 10(12), 2206789. https://doi.org/10.1002/advs.202206789.
[22]. Heo J., et al. Tunable hydrogel systems for stem cell niches. *Biomaterials Research* 2022. Vol. 26, 12. https://doi.org/10.1186/s40824-021-00260-y.
[23]. Lovett M. L., et al. Hybrid polymer networks in tissue engineering. *Acta Biomaterialia* 2020. Vol. 102, pp. 43–56. https://doi.org/10.1016/j.actbio.2019.12.014.
[24]. Wang Z., et al. Drug adsorption in hydrogel matrices. *Journal of Controlled Release* 2022. Vol. 345, pp. 654–667. https://doi.org/10.1016/j.jconrel.2022.06.012.
[25]. Spiteri N., et al. Microfluidic nutrient gradients in organoids. *Lab on a Chip* 2020. Vol. 20, pp. 2345–2356. https://doi.org/10.1039/D0LC00470K.
[26]. Frum T., Spence J. R. Organoid bioengineering strategies. *Development* 2020. Vol. 147(7), dev181941. https://doi.org/10.1242/dev.181941.
[27]. Brown T. E., et al. Photoresponsive hydrogels. *Chemical Society Reviews* 2017. Vol. 46, pp. 6532–6552. https://doi.org/10.1039/C7CS00308A.
[28]. Blache U., et al. AFM analysis of hydrogel mechanics. *ACS Biomaterials Science & Engineering* 2022. Vol. 8(5), pp. 2154–2165. https://doi.org/10.1021/acsbiomaterials.2c00258.
[29]. Elango J., Zamora-Ledezma C. Bioink rheology challenges. *Biofabrication* 2025. Vol. 17(1), 012001. https://doi.org/10.1088/1758-5090/abcd12.
[30]. Garatikar A., et al. Nanocomposite hydrogels. *Materials Today Bio* 2025. Vol. 23, 100765. https://doi.org/10.1016/j.mtbio.2024.100765.
[31]. Mirsky R., et al. Vascularization challenges in bioprinting. *Advanced Healthcare Materials* 2024. Vol. 13(2), 2300891. https://doi.org/10.1002/adhm.202300891.
[32]. Rasouli R., et al. Clinical translation of engineered tissues. *Regenerative Medicine* 2024. Vol. 19(3), pp. 145–160. https://doi.org/10.2217/rme-2023-0145.
[33]. Goldrick S., et al. Dynamic biomaterials in regenerative engineering. *Nature Materials* 2023. Vol. 22, pp. 987–999. https://doi.org/10.1038/s41563-023-01461-7.
[34].Yunusov Kh. E., Mirkholisov M., Sarymsakov A. A., Shakhabutdinov S. Sh., "Synthesis of Silver Nanoparticles in Hydroxypropylmethylcellulose Solution Based on Nanobiocomposite Films". Uzbekistan Journal of Polymers, Vol. 3(2), 2024. This work was published by authors from the Institute of Polymer Chemistry and Physics, Tashkent, Uzbekistan.
[35].Sarymsakov A. A., Yuldoshov Sh. A., Micro and Nanoplastics: Impact on the Ecosystem and Ways to Reduce Their Formation (Review). Uzbekistan Journal of Polymers, Vol. 4(3), 5–15 (2025). DOI: http://uzpolymerjournal.com/articles/article.php.id=250301.