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Microgel-mediated organoid engineering: Biomaterial design, microenvironmental regulation, and biofabrication strategies

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Abstract

Organoids are organ-like structures formed by the self-organization of stem cells, progenitor cells, or patient-derived cells within a three-dimensional (3D) microenvironment. They are capable of mimicking the cellular composition, spatial structure, and functional characteristics of *in situ* tissues. Organoids have become an important platform for developmental biology, disease modeling, drug screening, and regenerative medicine. However, current organoid culture remains highly dependent on animal-derived matrices. The poorly defined composition, substantial batch-to-batch variability, and limited tunability of the mechanical and degradation properties of these matrices hinder the clinical translation of organoid models. Microgels typically refer to micrometer-scale hydrogel particles (1–1,000 μm) formed by the crosslinking of natural or synthetic polymers. Compared to traditional bulk hydrogels, microgels combine the design flexibility of individual particles with their collective ability to assemble into larger structures. By adjusting the size, stiffness, porosity, surface ligands, degradation rates, and factor release behavior of microgels, they can provide cells with a more controllable local microenvironment. This review focuses on the fundamental material properties, structural characteristics, fabrication techniques, and functional mechanisms of microgels in organoid engineering. It discusses their applications as cell-encapsulation units, scaffold templates, self-assembling building blocks, and bioactive-factor delivery platforms and evaluates their potential for standardized and scalable organoid manufacturing. Finally, we summarize the key challenges facing the field and outline the future directions for stimuli-responsive microgels, cellular microgelation, pure-cell building blocks, and smart biomanufacturing in next-generation organoid engineering.

Keywords: Microgel; Microsphere; Organoid; Biofabrication; Regenerative medicine

1. Introduction

Organoids are self-organizing three-dimensional (3D) cellular systems derived from pluripotent stem cells, tissue-resident stem or progenitor cells, or patient-derived tumor cells.[1,2] They reproduce a subset of an organ's cellular diversity, spatial organization, developmental trajectory, or physiological function.[3] Landmark intestinal, cerebral, liver-bud, kidney, airway, gastric, and skin models established that stem cell populations can generate tissue-

like structure outside the body when supplied with an appropriate combination of soluble signals and extracellular matrix (ECM) support.[4,5] Such organoid structures can reproduce selected organ functions and serve as platforms for drug evaluation. Certain organoid systems have also shown potential for transplantation-based tissue repair.[6] Organoids now enable mechanistic studies of human development, host–pathogen interactions, hereditary disease, cancer evolution, toxicology, and individualized drug response.[7] Their value is greatest where conventional monolayers erase tissue polarity and heterogeneity, or where animal models incompletely reproduce human genetics, immunology, metabolism, and therapeutic response.[8]

However, organoid experiments remain vulnerable to uncontrolled starting conditions and incomplete maturation.[9] The number and state of initiating cells, aggregate diameter, matrix droplet size, distance to a medium interface, and operator technique all influence outcome.[10] Organoids within one well can differ in lineage composition, geometry, and growth rate, making the result difficult to predict. Large structures develop hypoxic or stressed cores, while small structures may not establish the cell–cell interactions needed for patterning.[11] Moreover, many methods generate immature tissues and lack vasculature, immune cells, nerves, or stroma.[12] Therefore, the materials introduced in organoid engineering are not merely intended to optimize appearance. They must also be capable of replicating the complex tissue interactions and biological properties of the missing tissue.

The ECM is not a passive container in organoids. It controls whether cells remain isolated, aggregate, polarize, form lumens, bud, migrate, or fuse.[13] Basement membrane extracts such as Matrigel remain widely used because their laminin-rich, collagen IV-containing composition supports many epithelial organoids[13]. Nevertheless, Matrigel is derived from a mouse tumor, contains a complex and incompletely defined mixture of structural proteins and growth factors, varies across lots, has a narrow range of mechanical properties, and is difficult to spatially pattern or qualify for transplantation.[14] Bulk collagen, fibrin, alginate, gelatin, hyaluronic acid (HA), polyethylene glycol (PEG), and decellularized ECM (dECM) gels provide valuable alternatives. But a continuous polymer network still couples cell confinement, diffusion, stiffness, degradability, and processability.[15] For example, increasing polymer concentration to improve print fidelity may simultaneously restrict organoid expansion and molecular transport.[16] PEG networks presenting integrin ligands and protease-cleavable crosslinks supported intestinal stem cell expansion and subsequent organoid differentiation.[17] Synthetic matrices enabled intestinal regeneration after transplantation and long-term culture of human intestinal and endometrial epithelia.[18,19] Fibrin–laminin hydrogels, pancreatic tumor-inspired matrices, brain dECM, and endodermal tissue dECM further showed that tissue-specific biochemical cues and dynamic mechanics can improve morphogenesis and disease fidelity.[20] However, bulk hydrogels remain challenging to modularize after crosslinking, exchange without disrupting tissue, or combine into high-density constructs with independently specified microscale regions. Microgels address this architectural limitation by discretizing a hydrogel into particles. A particle can be designed as a local niche, cell carrier, morphogen depot, mechanical inclusion, sacrificial spacer, or assembly node.[21] Thousands of particles can then be cultured individually, flowed through microfluidic systems, packed into a granular matrix, annealed into a macroscopic scaffold, or printed together with cells and organoids. The result is that the chemistry and mechanics of each microgel define cell-scale instruction, while particle size, shape, mixture, and packing define tissue-scale transport and rheology.[21] Studies of granular microgels have demonstrated that restructuring a widely used bulk ECM material into packed microgels can increase permeability without altering its underlying biological composition.[22] More engineered systems exploit reversible yielding and stress relaxation to hold printed organoid patterns during deposition and then permit large morphogenetic deformation during culture.[23]

Microgels perform best when used as targetable morphogenic units, rather than as miniaturized versions of macroscopic gels. Therefore, we search relevant article according to the search strategy outlined in the supporting information and classify this field by function—encapsulation, templating, assembly, and delivery. We link particle-level variables to organoid outcomes, compare different materials and preparation methods, and focus on their applications in fields such as bone, cartilage, skin, and cancer. This review integrates material design, manufacturing processes, biological validation, and the maturity of evidence within a single framework, thereby clarifying where microgels have already addressed bottlenecks in organoid research and where promising but yet-to-be-validated applications remain (Figure 1).

2. Different microgels for organoid construction

2.1. The evolution of microgels

The evolution from bulk hydrogels to microgels follows a shift from homogeneous encapsulation toward modular control. In a conventional bulk hydrogel, cells and soluble factors are mixed with a precursor before crosslinking or placed into a preformed matrix. This arrangement provides continuous mechanical support and is experimentally simple, but all regions share the same formulation unless gradients or multiple casting steps are introduced.[24] Organs-

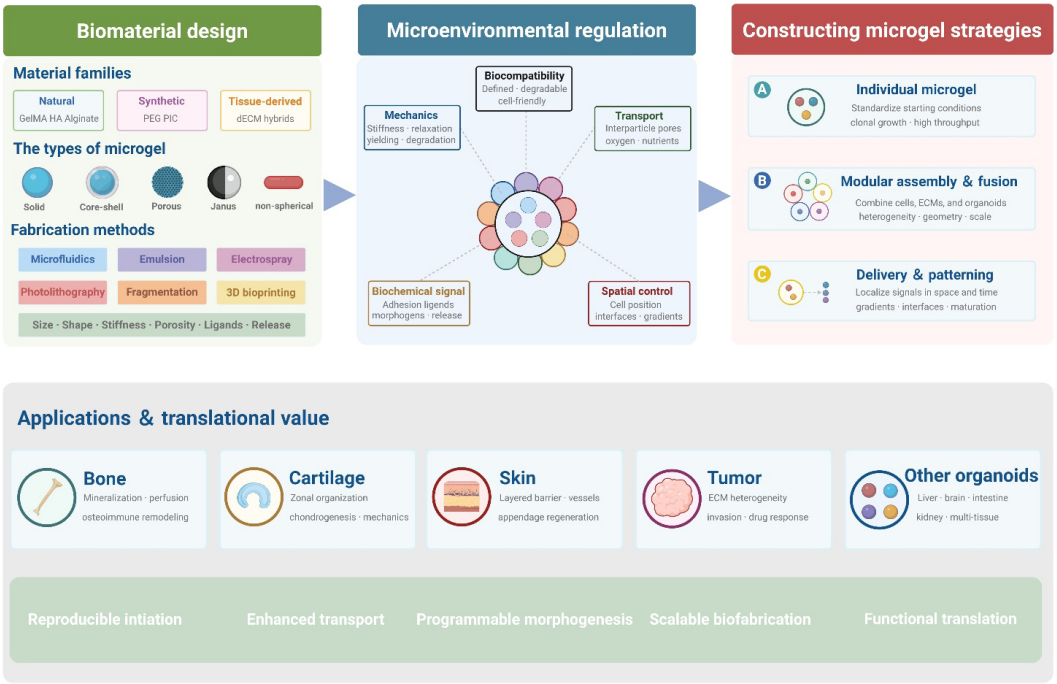


Figure 1. Microgel-mediated organoid engineering. Created in BioRender. Luo, Z. (2026) https://BioRender.com/ujbwwu5.

on-chips add perfusion, fluid shear, interfaces, and sensor integration, but most still rely on a bulk hydrogel inside the device.[25] Microgels are material modules that can be used within both. A chip governs boundary conditions and flow, the organoid supplies self-organizing biology, and the microgel controls the immediate pericellular niche.[26] Early bottom-up tissue engineering established that cell-laden, shape-controlled microgels could be assembled into multicellular constructs with prescribed microscale architecture. Subsequent work introduced jammed and annealed particles, reversible host-guest interactions, and heterogeneous particle mixtures.[27] Microporous annealed particle scaffolds demonstrated that interparticle voids permit rapid cell infiltration and accelerate wound repair, while guest-host granular microgels showed that particle chemistry can independently program degradation and molecular release.[28] Collectively, these studies laid the conceptual groundwork for particle-based approaches to organoid engineering, in which microgel particles are first fabricated, then incorporated with cells or bioactive cues, and finally assembled into a dynamic matrix.[29]

2.2. The types of microgel

A microgel is a swollen, crosslinked polymer network with a characteristic dimension of approximately 1–1,000 micrometers that is manipulated as a discrete object in cell culture or biofabrication. This operational range covers cell-sized particles, single-cell capsules, organoid-scale beads, and the particles most often used to form granular matrices.[30] Smaller crosslinked particles can be termed nanogels. Larger millimeter-scale units are better described as bulk hydrogel or hydrogel modules.[31] Size should always be reported as a distribution rather than a nominal value because dispersity influences packing, pore connectivity, encapsulation occupancy, and dose.[32] Microspheres are typically solid or porous spheres in which the loaded material is uniformly distributed throughout the matrix.[33] Microcapsules, on the other hand, have a distinct outer shell that encloses a core of liquid, soft material, or cells.[33] Core–shell microgels combine a hydrated network with a radially partitioned structure[33]. Because the granules rearrange when subjected to force, they exhibit shear-thinning and yield stress characteristics. Granular hydrogels are macroscopic agglomerated structures formed by the aggregation of numerous microgels.[34] If the granules are interconnected via covalent or physical bonds after packing, they form annealed or assembled microgel scaffolds.

Spherical microgels, often described as hydrogel microspheres, are typically micrometer-scale particles characterized by a high specific surface area, structural

simplicity, and self-assembly capability, making them attractive for 3D cell culture, drug delivery, and tissue regeneration.[35] According to their microstructure, microspheres can be broadly classified as solid, core–shell, hollow, Janus, and porous systems.[35] Solid microspheres are commonly used as biodegradable depots for long-acting drug delivery, but their clinical performance may be limited by an initial burst release, particularly for water-soluble drugs.[36] Core–shell microspheres address this limitation by introducing a protective outer layer that improves cargo retention, controls release, and enables stimulus-responsive behavior, whereas hollow microspheres provide a large internal cavity suitable for loading drugs, proteins, and nucleic acids.[37] Janus microspheres contain two chemically or functionally distinct regions, allowing otherwise incompatible properties to be integrated within a single particle. For example, asymmetric Janus microgels combining adhesive and anti-adhesive surfaces have demonstrated enhanced tissue retention and adhesion-prevention effects.[38] Porous microspheres possess interconnected pores, high permeability, and compressibility, facilitating cell attachment, nutrient transport, and tissue infiltration.[39] Injectable porous gelatin methacryloyl (GelMA) microspheres have consequently been used as cell carriers to support stem cell viability, osteogenic differentiation, and bone regeneration.[39] Overall, microsphere architecture determines cargo, loading capacity, release kinetics, cellular interactions, and regenerative performance, allowing particle design to be tailored to specific biomedical applications.

Spherical microgels provide limited control over cell alignment and anisotropic tissue organization because their isotropic geometry and dense packing restrict directional interparticle interactions.[40] Their production may also be difficult to scale owing to reliance on oil phases, chemical additives, or low-viscosity polymer solutions.[30] In recent years, various non-spherical microgel shapes have been created, including granular microgels,[41] ribbon-like microgels,[42] strip-like microgels,[43] and fiber-like microgels.[44] Non-spherical microgels, including rods, ribbons, strips, fibers, and irregular granules, have therefore been developed using microfluidics, photolithography, wet spinning, and mechanical fragmentation. Their anisotropic geometry creates mechanically interlocked assemblies with shear-thinning and self-supporting behavior, enabling extrusion through needles followed by rapid structural recovery after printing.[45] Unlike conventional bulk hydrogels, these granular assemblies also contain interconnected interparticle pores that facilitate cell proliferation, migration, differentiation, and nutrient transport, while their modularity permits the combination of particles with different material or biological properties.[46] These characteristics are particularly valuable for regenerating structurally anisotropic tissues. Ribbon-like gelatin microgels, for example, provide microporous, mimetic cartilage scaffolds that promote chondrogenesis and improve mechanical performance.[42] Similarly, fibrinogen-coated poly(lactide-co-glycolide) strip-like microgels can assemble into injectable 3D scaffolds that enhance osteogenic differentiation, collagen deposition, and mineralization of mesenchymal stem cells.[47] Overall, particle anisotropy expands the mechanical, architectural, and manufacturing capabilities of microgel systems, although further studies are required to establish scalable production methods, standardized design principles, and long-term regenerative efficacy (Figure 2).

2.3. Roles of microgels in organoid construction

The first role of microgels in organoid construction is compartmentalization. Droplet-generated microgels isolate one cell, a controlled number of cells, an embryoid body, a tissue fragment, or an established organoid. Isolation standardizes the initial condition and prevents faster-growing clones from merging with or outcompeting neighbors.[48] Agarose microgels, for example, enabled controlled formation and spatial identity mapping of primate epiblast and amnion spheroids.[49] All aqueous droplets have produced thousands of defined pancreatic cancer organoids from single cells, while pump-free gas shearing devices generated alginate microgels that supported pancreatic cancer organoid features.[50] Encapsulation can also improve handling during sorting, imaging, freezing, or drug exposure. Its main risks are excessive confinement, insufficient adhesive signaling, delayed cell–cell contact, and polymerization damage.

Microgels can provide either persistent or temporary boundaries for organoid tissue formation. Particle stiffness, deformability, surface chemistry, and degradation determine whether cells spread on a microgel, compress it, displace it, or bridge between particles. Packed microgels create a discontinuous matrix that can support growth while yielding locally to budding and fusion. Graham *et al.*[23] developed a Matrigel–alginate granular–interstitial composite (MAGIC) matrix that exhibits yield-stress behavior at low temperatures, facilitating precise embedded printing. Upon heating, it forms a soft, stress-relaxing environment suitable for the morphogenesis of intestinal and other organoids. Conversely, intentionally designed high-resistance particles can impose constraints. Using polyacrylamide microgels mixed with Matrigel, Rosas *et al.*[51] observed distinct swelling, polarization, rotation, and pulsation behaviors in normal and tumor-derived pancreatic duct organoids. The same platform principle can thus either release or apply mechanical constraints.

Microgels can serve as building blocks for constructing larger structures. Microgels containing different cells,

ECM components, mechanical properties, or signaling molecules can be mixed stochastically or positioned deliberately. Interparticle pores improve transport, while secondary crosslinking stabilizes the assembled geometry. Heterogeneous microgel assembly bioinks use reversible surface interactions to combine otherwise incompatible modules and preserve printability.[52] Organoids can also be handled as building blocks alongside microgels. Spatially patterned organoid transfer (SPOT) uses a nanoparticle, self-healing support material, and magnetic placement to arrange neural and glioma organoids into assembloids.[53] Aspiration-assisted bioprinting similarly places spheroids or organoids with low mechanical damage.[54] In these systems, microgels provide spacing, adhesion, support, and positional memory while living units fuse or communicate.

Microgels can serve as delivery vehicles for growth factors, drugs, and ligands. Because microgels have high surface area and short diffusion paths, they can release growth factors, drugs, extracellular vesicles, oxygen-generating compounds, or adhesive ligands with specific particle kinetics. Sulfated glycosaminoglycan microgels, termed microgel units to instruct development (microGUIDEs), tune electrostatic affinity for morphogens and generate vascular endothelial growth factor (VEGF) distributions in vascular and kidney organoid cultures.[55] Other particles display PEG-lipid moieties that immobilize them on islet-organoid surfaces, creating a modular coating without exposing the organoid to an organic phase.[56] Delivery microgels are therefore not simply slow-release carriers. When positioned around or within an organoid field, they behave as artificial signaling centers that can bias symmetry breaking and tissue interfaces. The four roles of microgels are not mutually exclusive. A microsphere containing cells can simultaneously protect the cells, release factors, form a printable granular ink, and subsequently degrade to allow fusion. The design challenge lies in clearly defining the primary function of each stage and avoiding compromising morphogenesis due to process improvements.

3. Properties of microgels and organoids

3.1. Stiffness and viscoelasticity

Organoid morphogenesis is a mechanical communication between growing tissue and its matrix. Matrix stiffness changes integrin clustering, cytoskeletal tension, and nuclear deformation, influencing survival, stemness, differentiation, and branching. However, the elastic modulus measured at small strain is only one descriptor. Organoids apply large, time-dependent deformations. A material with a favorable initial modulus can still arrest budding if it cannot relax, yield, or degrade.[57] Microgels offer several independently tunable mechanical parameters: individual particle modulus, interparticle contact forces, packed-bed yield stress, interstitial-phase elasticity, and interparticle annealing strength.[58] Therefore, reporting only the storage modulus of the final suspension can obscure the boundary conditions experienced by the cells. Particle-scale heterogeneity can be constructive. Soft particles adjacent to an organoid permit expansion, while stiffer particles maintain overall shape or transmit forces. Mixing particles with different moduli generates a mechanically heterogeneous niche without requiring a continuous gradient. Conversely, rigid or nondegradable microgels can model fibrotic confinement.[59] In a microgel–Matrigel composite, tumor-derived pancreatic ductal organoids overcame yield stress through rapid lumen expansion and collective pulsing, whereas normal organoids expanded more slowly and frequently altered polarity.[51] The results show that a granular matrix is both a culture material and a force-reporting environment. Particle displacement, organoid pressure, polarity, and matrix rheology should be measured together.

Native ECM dissipates stress through molecular unbinding, fiber rearrangement, fluid flow, and proteolysis. Stress-relaxing bulk hydrogels enhance spreading, proliferation, and osteogenic differentiation even when their initial elastic modulus is unchanged.[51] More broadly, matrix viscoelasticity influences cell volume, migration, differentiation, and tissue organization.[60] Granular materials introduce an additional relaxation mode: particles translate, rotate, deform, and exchange. This mechanism can accommodate large organoid strains without requiring polymer network cleavage. The rate and magnitude of relaxation should be matched to the biological process. Rapid small-strain recovery is useful for printing, because the support bath must close after nozzle passage. Long-time relaxation at large strain is necessary for crypt budding, lumen expansion, neurite extension, or organoid fusion. The MAGIC system proposed by Graham *et al.*[23] separates these requirements thermally. It behaves as a reversible yield stress support during cold printing and as a permissive, stress-relaxing niche during warm culture. Optimized formulations produced more uniform and complex organoids than poorly relaxing granular conditions. Yield stress must nevertheless remain below the force that a developing tissue can generate. Otherwise, geometric fidelity is achieved at the expense of morphogenesis.

3.2. Interparticle pores and material transport

Dense bulk hydrogels have nanoscale polymer meshes that permit diffusion of small solutes but can slow macromolecules and exclude cells. Packing microgels creates interstitial voids on the micrometer scale. Void size is controlled by particle diameter, shape, stiffness, surface friction, size dispersity, and compaction. Larger or less deformable microgels generally create larger connected

pores, whereas soft polydisperse particles fill voids and reduce permeability. In microporous annealed particle scaffolds, particle size modulated pores over a cell-relevant range and enabled rapid infiltration.[28] Restructuring Matrigel into microgels similarly increased transport of colloids and dendritic cells.[22]

For organoids, improved transport can reduce oxygen and nutrient gradients, facilitate waste removal, accelerate exposure to differentiation factors, and enable immune or endothelial cells to reach the tissue surface. It does not eliminate diffusion limits inside a large organoid, where consumption and avascular distance still govern hypoxia. Pore connectivity may also decline as cells proliferate and deposit ECM. Useful characterization therefore includes permeability, effective diffusivity across multiple molecular sizes, oxygen tension, consumption rates, and time-dependent pore closure. Core–shell and hollow microgels provide another solution. A liquid or weakly crosslinked core allows a spheroid to form while the shell sets size and protects the tissue during handling. The shell must be sufficiently permeable and degradable to avoid converting protection into chronic mass transfer resistance.[61]

3.3. Biochemical signal transduction

Microgels can present adhesive peptides, full-length ECM proteins, glycans, protease-sensitive linkers, and tissue-derived signals at defined densities. Covalent immobilization sustains local signaling but may reduce ligand mobility. Affinity-based binding preserves reversible exchange and can protect growth factors from rapid degradation. The microGUIDE platform demonstrates how sulfation pattern and glycosaminoglycan concentration program morphogen affinity, allowing localized VEGF presentation in vascular constructs and kidney organoids.[55] Natural material particles provide multivalent biological cues but are compositionally complex, whereas PEG-based particles offer precise control and require deliberate addition of adhesion and degradation sites.

Temporal presentation is as important as dose. A microgel may release agonists during stem cell expansion, then degrade or be removed so that differentiation can proceed.[62] Distinct particle populations can deliver antagonistic signals with different kinetics, creating moving or sequential boundaries without changing the whole medium. Release depends on diffusion, affinity, network degradation, particle radius, and sink conditions.[63] Consequently, release measured in buffer should not be assumed to predict release in protein-rich organoid medium. Spatial mapping of ligand concentration and downstream pathway activity is needed to show that a designed gradient actually reaches the cells.

3.4. Spatial organization and multicellular interaction

Organoids often lack stromal, immune, vascular, and neural compartments because the relevant lineages develop at different times and respond to incompatible media. Microgels enable staged integration. One particle population can carry endothelial or stromal cells, another an epithelial organoid, and a third a morphogen. The units can be combined only when each component is competent. Interparticle pores permit processes to extend and anastomose, while particle surfaces regulate the distance and duration of contact. Fredrikson *et al.*[64] first matured granular neural tissues and subsequently combined them with prostate spheroids or renal cell carcinoma organoids to establish innervation in a manipulable chip chamber.

Spatial control must exceed simple co-encapsulation. Random mixing can reproduce distributed stroma, whereas directed assembly is required for epithelial–mesenchymal boundaries, zonal cartilage, aligned vasculature, or brain region interfaces. Magnetic transfer and bioprinting can position organoids without forcing them through a narrow nozzle.[53] Particle identity can also be encoded by fluorophores, barcodes, or degradability, enabling post hoc reconstruction of which niche generated a phenotype. This creates an experimental advantage over bulk gels, where many local microenvironments can coexist in one culture while remaining traceable.[54]

3.5. Biocompatibility

Microgels used for organoids need to have good biocompatibility. Cells encounter precursor purity, osmolarity, pH, oil and surfactant residues, crosslinkers, photoinitiators, ultraviolet or visible light, shear, electric fields, and demulsification steps before they encounter the final gel.[50] A benign alginate network can still yield poor organoids if ionic crosslinking causes local hypertonicity or if oil removal extracts membrane lipids. All aqueous emulsions and pump-free gas shearing reduce some of these risks, while one-step droplet solidification and purification shorten exposure to oil.[56]

Minimum validation should include immediate and longitudinal viability, apoptosis, proliferation, lineage composition, karyotypic or genomic stability when relevant, and tissue-specific function. For implanted systems, residual reagents, degradation products, endotoxin, inflammation, fibrosis, and biodistribution must also be assessed. The most convincing microgel is therefore not the one with the highest live/dead percentage after 24 h, but the one that maintains reproducible organoid identity and function throughout manufacturing, culture, retrieval, and intended use[65] (Figure 2).

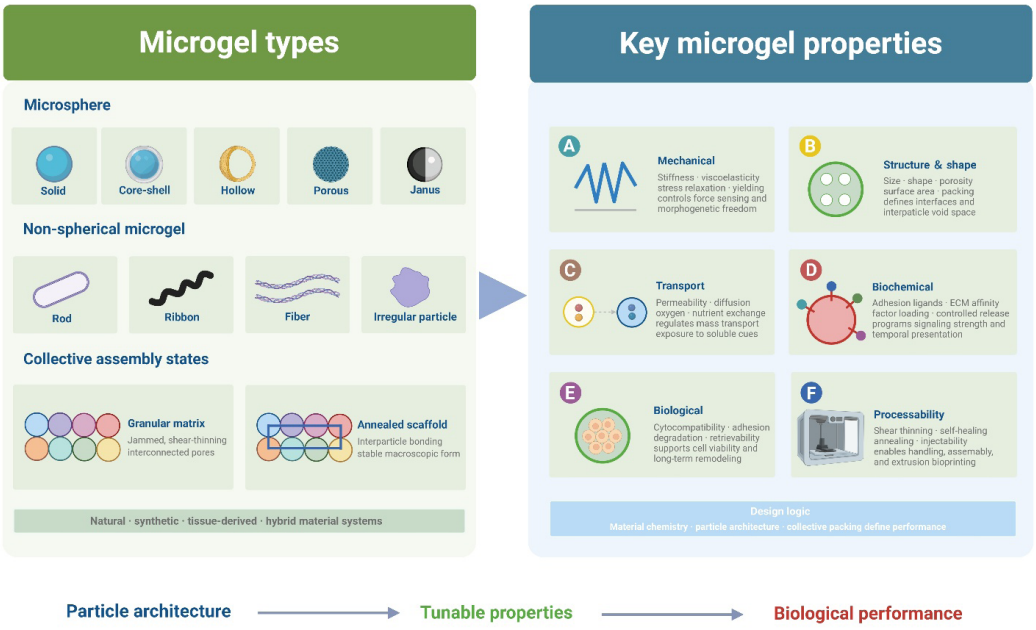


Figure 2. Microgel types and key properties. Created in BioRender. Luo, Z. (2026) https://BioRender.com/dnpmoak.

4. Materials and preparation of microgels for organoids

4.1. Materials used for microgels in organoids

The type of polymer used in synthesizing microgels has a significant impact on the properties of the microgels.[66] Microgel components used in organoids can be categorized into biopolymers derived from natural sources and synthetic polymers.[67] Alginate is attractive for microgel production because divalent ions rapidly crosslink its guluronate-rich blocks under mild aqueous conditions. It is inexpensive, optically clear, and compatible with droplet microfluidics, electrospray, and extrusion. Mammalian cells lack receptors for native alginate. Therefore, arginine–glycine–aspartic acid (RGD) or ECM components are usually added when adhesion is required. Ion exchange can soften or dissolve the network over time, and uncontrolled calcium gradients can produce radial differences in crosslink density.[68] These properties are useful for transient capsules but complicate long-term mechanical interpretation. GelMA combines cell-binding and protease-sensitive motifs inherited from gelatin with photocrosslinkable methacryloyl groups. Light dose and degree of substitution tune stiffness and degradation, making GelMA common in microfluidic microspheres, patterned particles, and printable microgels.[69] Its biological origin and batch variation are disadvantages relative to PEG, and radical polymerization can damage cells if photoinitiator concentration, wavelength, oxygen, and exposure are not optimized. Native gelatin is thermoreversible and useful as a sacrificial or injectable phase, but lacks stability at culture temperature unless secondarily crosslinked. HA is abundant in developing and adult connective tissues and can be modified with methacrylate, norbornene, hydrazone, host, or guest groups. HA microgels are particularly useful for cartilage, neural, and tumor systems because receptor interactions and viscoelastic chemistry can be tuned.[70] Collagen and fibrin support adhesion, remodeling, and vascular sprouting. But their fibrillar polymerization is sensitive to temperature, pH, concentration, and shear. dECM retains specific tissue proteins and glycosaminoglycans. Endodermal dECM hydrogels and brain ECM-enhanced devices have improved organoid phenotypes.[71] Converting dECM into microgels improves modularity, yet donor variability, decellularization residues, sterilization, and incomplete compositional definition remain major controls. Silk fibroin provides robust mechanics, slow degradation, and processability. RGD-functionalized silk fibroin with DNA microspheres has supported cartilage organoid precursors, while silk microgels containing oxygen-generating mineral phases have been used as conformal bone organoid units.[72,73] DNA, fibrin, collagen, and other supramolecular components add dynamic bonding or bioactivity, but each added constituent increases analytical and regulatory burden. Natural systems should therefore be chosen for a demonstrated biological function rather than for presumed biomimicry alone.[73]

Synthetic polymers can also serve as materials for microgels. PEG is the most established defined platform. Its molecular weight, architecture, crosslink density, ligand density, and degradable linkers can be specified independently, and orthogonal click reactions permit rapid microgel formation. Bioinert PEG reduces uncontrolled protein adsorption but requires engineered adhesion and remodeling.[17] Polyisocyanopeptides provide thermoresponsive, strain-stiffening matrices, while polyacrylamide offers mechanically stable, nondegradable particles useful for confinement studies but is unsuitable for many implantation settings. Synthetic matrices are strongest when they convert a biological hypothesis into controlled variables, as shown by defined organoid matrices that separate integrin engagement, degradation, and mechanics.[19]

Hybrid microgels combine the instructiveness of natural materials with the reproducibility or mechanics of synthetic networks. Examples include alginate–Matrigel interpenetrating particles, gelatin–HA microgels, laminin-enriched dECM microspheres, and hybrid natural–synthetic granular inks. Nanoparticles can add mineralization, conductivity, magnetism, oxygen release, or controlled drug delivery. Dynamic covalent bonds such as hydrazones and boronated esters, and supramolecular host–guest or hydrogen-bonding interactions, enable self-healing and stress relaxation. Surface coatings can make otherwise incompatible microgels assemble into a single ink.[29] The design opportunity is large, but formulation complexity should be constrained. Every component should have a defined critical function, measurable range, and acceptable residual level. Crosslinking chemistry is a central selection variable. Ionic gelation is rapid and cell-friendly but sensitive to competing ions. Radical photopolymerization offers spatial control but introduces light and initiator dose. Enzymatic reactions are mild yet depend on enzyme activity and substrate diffusion. Click reactions can be fast and orthogonal but require modified precursors, and dynamic physical bonds enable recovery at the cost of lower long-term strength.[52] Dual networks often separate handling from remodeling, for example by using a reversible bond for injection and a covalent bond for stability (Figure 3).

4.2. Fabrication techniques for microgels used in organoid construction

With the widespread application of microgels in relevant research fields, various microgel fabrication techniques have been developed. Depending on the intended application, the fabrication method may involve a combination of physicochemical reactions, intercellular interactions, external driving forces, or droplet formation.[74] Microgel fabrication techniques vary according to their mechanisms of particle formation and the characteristics of the materials used. This section discusses six principal microgel-fabrication methods, followed by 3D bioprinting as a strategy for assembling microgels into larger constructs and several additional fabrication approaches.

Extrusion-based droplet generation is a widely used strategy for microgel fabrication, in which a polymer precursor is forced through a needle and subsequently crosslinked to form discrete particles.[74] Microgel size, porosity, and aggregation are primarily governed by nozzle diameter, precursor viscosity, and extrusion flow rate.[75] The resulting particles can exhibit shear-thinning, self-healing, and self-assembly properties, enabling their use as injectable materials and printable building blocks for complex 3D scaffolds.[76,77] Gas-shear extrusion provides an oil-, surfactant-, and photoinitiator-free alternative with broad material compatibility and improved biocompatibility.[78,79] Particle dimensions, ranging from tens of micrometers to millimeters, can be adjusted through gas and liquid flow rates, nozzle geometry, collection conditions, and precursor concentration. Moreover, specialized nozzle and airflow configurations enable the fabrication of multicompartment microgels containing two to eight spatially defined regions, allowing different cells or biomolecular signals to be organized within a single particle.[32] Thus, extrusion strategies offer a scalable and versatile platform for producing microgels with controllable structural, mechanical, and biological properties.

Droplet microfluidics generates droplets through interfacial shear between immiscible or partially immiscible fluids, providing precise control over particle size, morphology, and monodispersity through flow-rate ratios and channel geometry.[80] This method has been used to fabricate tunable HA microgels, including injectable particles smaller than 100 μm for wound healing and tissue regeneration.[81,82] However, its dependence on oils and surfactants may complicate purification and impair cell viability.[83]

Electrohydrodynamic spraying generates microgels by applying an electric field that overcomes the surface tension of a polymer precursor at the needle tip, producing charged droplets that are subsequently crosslinked.[84] Although initially used mainly to fabricate small drug-delivery particles with limited size uniformity,[85] advances in process control have substantially improved its precision and reproducibility.[86] Microgel size and morphology can be regulated by the applied voltage, precursor viscosity and concentration, flow rate, nozzle dimensions, and nozzle-to-collector distance.[87] Because the process is mild and does not require oil or surfactants, it is particularly suitable for cell encapsulation and delivery, with reported cell viabilities of approximately 80%–95% owing to reduced mechanical stress.[88] Monodispersity nevertheless remains

more difficult to achieve than with microfluidic methods. Recent optimization strategies have enabled the production of relatively uniform microgels for bone regeneration, organoid culture, and biomimetic enzyme systems.[89–91] Electrohydrodynamic spraying also offers higher throughput than conventional microfluidic fabrication, although with somewhat lower dimensional precision. The successful encapsulation of viable chondrocytes in alginate microgels further demonstrates its potential for cartilage and bone tissue engineering.[88] Overall, this technique provides a scalable, cell-compatible platform for microgel production, but improved control over particle uniformity remains an important research priority.

Photolithography enables the precise fabrication of microgels from photosensitive polymers by using patterned light exposure instead of conventional solid molds.[81] Unlike droplet-based methods, which generally favor spherical geometries, photolithographic masks can define particle size and produce a wide range of spherical and non-spherical shapes.[92–94] Integration with microfluidics further enables continuous production; for example, flow lithography combined with droplet microfluidics has been used to fabricate polyethylene glycol diacrylate microgels with tunable dimensions and properties.[95] Imprint lithography similarly generates structured particles by curing hydrogel precursors within pre-patterned molds. These approaches provide excellent control over microgel geometry and are particularly valuable for investigating shape-dependent cell behavior and particle assembly. However, reliance on masks or molds limits the complexity of internal structures, while multistep processing, low throughput, phototoxicity, and restricted material compatibility may hinder cell encapsulation and large-scale biomedical applications.[96] Therefore, future developments should focus on increasing production efficiency and expanding the range of cytocompatible, photocrosslinkable materials.

Emulsification is a simple and scalable method for microgel fabrication in which an aqueous polymer precursor is dispersed in an immiscible oil phase and stabilized with surfactants. Particle size and emulsion stability are primarily controlled by surfactant concentration, polymer concentration, mixing rate, and the water-to-oil ratio.[97] Single-emulsion systems generate conventional droplets, whereas double- and multiple-emulsion strategies enable core–shell, Janus, and multicompartment microgels. Interfacial tension can also be adjusted using different surfactants to transform encapsulated droplets into Janus-like structures.[98] Despite its low cost, operational simplicity, and high production efficiency, emulsification often produces particles with broad size distributions. This heterogeneity reduces batch reproducibility and causes variations in encapsulated cell numbers or drug doses. Furthermore, residual oils and surfactants may compromise cytocompatibility, particularly in cell-laden formulations.[99] Improving particle-size control and developing biocompatible, easily removable emulsion components are therefore essential for broader biomedical translation.

Centrifugal microgel fabrication is an oil- and surfactant-free method in which centrifugal force ejects a polymer precursor through a capillary nozzle into a crosslinking bath. For example, sodium alginate droplets can be rapidly gelled in calcium chloride solution. Particle size and morphology are governed by centrifugal force, precursor viscosity, surface tension, and nozzle dimensions, while increasing the rotational speed can improve production efficiency.[100] The mild and biocompatible process is suitable for cell encapsulation, drug delivery, and regenerative medicine. Centrifugal forces can also regulate particle deformation and packing. Compacted GelMA granular hydrogel scaffolds have demonstrated tunable mechanical and rheological properties capable of modulating cellular and tissue responses.[101] However, continuous production changes the liquid level and nozzle-to-bath distance, potentially deforming droplets and reducing size uniformity. Moreover, particle-size adjustment generally requires capillary replacement, limiting operational flexibility and scalable production.[21] Thus, centrifugal fabrication provides a simple and cytocompatible platform, but improved collection systems and nozzle designs are needed to achieve consistent, high-throughput manufacturing.

Unlike methods that primarily generate individual microgels, 3D bioprinting enables the spatially controlled assembly of microgels into complex, cell-laden constructs. Major modalities include extrusion, inkjet, laser-assisted, digital light processing, and volumetric bioprinting, with the printing method and hydrogel composition selected according to the required cell type and tissue microenvironment.[102] Microgels are particularly attractive as bioinks because their interparticle porosity, shear-thinning behavior, yield stress, and rapid recovery support printing while facilitating cell growth, retrieval, and tissue maturation.[103] Tyramine-modified HA granular hydrogels, for example, have been processed into size-controlled particles and stabilized through secondary crosslinking. When printed with auricular chondrocytes, these constructs supported cartilage maturation for 63 days, demonstrating the importance of particle size and porosity in scaffold stability and tissue development.[104] Combining volumetric printing with embedded extrusion can further increase fabrication speed and structural complexity.[105] Bioprinting can also be integrated with microfluidic and gas-shear techniques to generate and organize multicompartment microgels.[106,107] Although challenges remain in resolution, cell viability, material selection, throughput, and process standardization, microgel-based bioprinting offers

substantial potential for organoid engineering and soft-tissue fabrication (Figure 3).

Additional microgel-fabrication strategies include mesh fragmentation, thermal gelation, and chemical or supramolecular crosslinking. Mesh fragmentation converts preformed bulk hydrogels into injectable particles by forcing them through porous grids of defined dimensions. Micrometer-scale steel meshes have produced polycarboxylic acid betaine microgels with controllable sizes while maintaining greater than 90% viability of encapsulated mesenchymal stromal cells and fibroblasts.[108,109] Compared with needle extrusion, mesh processing can reduce cellular shear stress and offers higher throughput than conventional microfluidic systems, making it suitable for scalable regenerative applications.[110] Thermal gelation is primarily used for protein-based materials, in which heating above the denaturation temperature induces protein unfolding, aggregation, and microgel formation. This approach has been applied to whey- and soy-protein microgels through controlled heating, cooling, and homogenization.[111,112] Chemical crosslinking provides additional control over microgel stability and responsiveness through covalent, ionic, or hydrophobic interactions. Chemically crosslinked starch microgels, for example, exhibit pH-responsive behavior and high protein-loading capacity.[113] Combining covalent networks with hydrophobic association or hydrogen bonding can further enhance mechanical strength while introducing shear-thinning and self-healing properties.[114] Collectively, these methods broaden the range of materials and functional characteristics available for biomedical microgel design (Table 1).

4.3. Selection of microgel fabrication methods for organoid engineering

The choice of microgel fabrication method should be guided by the biological task assigned to the particles. Microgels may act as individual niches that initiate organoid growth, building blocks of a porous granular matrix, or carriers that position cells and signaling molecules within a larger construct. These roles require different degrees of control over particle size, cell occupancy, geometry, mechanical properties, and production scale. Therefore, before selecting a method, researchers should define the target organoid type, the number of cells or aggregates intended for each particle, the space needed for tissue expansion, the required matrix composition, and the endpoints by which successful organoid formation will be judged.

When reproducible organoid initiation is the main priority, droplet microfluidics is often the most suitable starting point. Flow rate and channel geometry can be adjusted to control droplet volume, allowing researchers to narrow the distribution of microgel sizes and regulate the number of initiating cells or aggregates per niche. This is particularly useful for studies that compare organoid growth, differentiation, or drug responses across many nominally equivalent units. Microfluidic hydrogel droplets have, for example, been used to generate intestinal organoids with a narrower size distribution than organoids grown in comparator dome cultures.[115] The method is also appropriate when core–shell or multicompartment particles are needed to separate cell populations or spatially organize matrix components. Its advantages should be weighed against precursor viscosity limits, channel clogging, the rate at which usable particles are recovered, and the removal of oil or surfactant when an emulsion-based device is used. Occupancy, formation efficiency, and tissue-specific function must also be measured.

If the experiment requires large numbers of cell-containing particles while avoiding an oil phase, gas shear extrusion is a practical alternative. Gas flow disrupts a hydrogel precursor stream into droplets, and changes in airflow, nozzle dimensions, and liquid flow rate can alter particle size and production rate. Air-assisted coaxial jetting has produced cell-containing microgels from alginate, GelMA, and their combinations at high reported droplet generation rates.[116] This makes the method attractive for parallel organoid cultures or for producing particles that will later be assembled into larger constructs. However, a high droplet generation rate is not equivalent to a high yield of suitable organoid niches. Researchers should determine the fraction of particles within the target size range, the distribution of encapsulated cell numbers, cell survival after collection and gelation, and whether these properties remain stable throughout a production run.

Electrohydrodynamic spraying is another option when oil-free cell encapsulation and adjustable particle size are important. The electric field promotes droplet formation, while applied voltage, precursor flow rate, needle diameter, polymer concentration, and viscosity influence the final particles. This flexibility is useful when a formulation must be tuned to a particular encapsulated cell population. In a study of alginate microcapsules containing chondrocytes, changes in voltage and needle size altered particle size, whereas higher precursor viscosity could affect both particle shape and cell viability.[88] Consequently, operating conditions should be selected using both physical and biological readouts. For organoid applications, the relevant readouts extend beyond immediate viability to include aggregate formation, continued growth, and maintenance of the expected cell lineages.

Where fabrication simplicity and batch quantity are more important than strict particle uniformity, conventional emulsification may be appropriate. Mixing an aqueous precursor with an immiscible phase provides a comparatively accessible route to large particle batches and can be adapted to more complex droplet architectures.

Its suitability depends on how much variation in particle size and cellular contents the experiment can tolerate. A broad particle distribution may lead to unequal nutrient transport, different initial cell numbers, and variable timing of organoid growth. Emulsification should therefore be selected for standardized organoid production only if the target size fraction can be isolated reliably and residual oil or surfactant can be removed and assessed. In a direct comparison using related HA formulations, microfluidic fabrication, batch emulsification, and mechanical fragmentation produced particles with different morphologies and different properties after assembly into granular hydrogels.[77] This illustrates why the downstream matrix, as well as the individual particles, must be evaluated.

The need for a defined tissue architecture may favor methods that provide greater control over particle shape. Photolithography and flow lithography use patterned light to produce prescribed geometries, including non-spherical building blocks. They are appropriate when particle geometry is an experimental variable, for example when investigating whether anisotropic units influence cell orientation or the organization of an assembled tissue. Cell-containing particles with controlled size and shape have been produced by stop-flow lithography.[117] The method requires a photocrosslinkable formulation and careful assessment of light exposure and initiator conditions. For a target organoid, the added geometric control is useful if the selected chemistry also supports cell survival, matrix remodeling, and the intended differentiation program.

Centrifugal droplet generation can be considered when an oil-free process and relatively simple equipment are priorities. Centrifugal force drives a precursor through a capillary into a crosslinking bath; nozzle geometry, solution viscosity, applied force, and collection conditions determine particle formation. Engineered alginate microspheres with different sizes and structures have been generated using modular micronozzle systems.[118] For organoid production, researchers should check whether particle size and shape remain consistent as the collection bath fills and whether changing the nozzle is necessary to reach the desired size range. The method is most appropriate when its achievable particle distribution and material choices satisfy the requirements of the target culture.

Mechanical fragmentation should be considered when the microgels are intended primarily as building blocks of a granular matrix. In this method, a preformed bulk hydrogel is forced through a mesh or otherwise broken into smaller particles. It is generally well suited to producing irregular particles that pack together while leaving interconnected spaces for cell migration, tissue expansion, and transport. The key selection criteria are therefore the properties of the assembled matrix: particle size and shape distributions, interparticle pore connectivity, stiffness, stability, and the ability of growing organoids to remodel the material. If cells are present during fragmentation, the effects of processing on viability must also be established. Mechanical fragmentation is less suitable when an experiment requires nearly identical spherical niches or tightly specified occupancy of each particle.[77]

Fabrication and assembly should be planned together. If the goal is a spatially organized multicellular construct, bioprinting can place preformed microgels or shape a granular microgel formulation after particle production. Method selection should then account for both the properties of the individual particles and the behavior of the assembled material during printing, including flow through the nozzle, recovery of shape, interparticle cohesion, and survival of the embedded cells. Across all methods, the most informative comparison uses the same cell source, initial cell number, culture medium, and evaluation period. Researchers should report particle size distribution, the yield of usable particles, cell occupancy, post-fabrication viability, organoid formation efficiency, and tissue-specific maturation or function. These measurements connect a fabrication choice to the biological performance that ultimately matters for the intended organoid model (Table S1).

4.4. Process optimization, quality control, and scalable production of microgel-based organoid systems

The production rate of microgels alone is an incomplete measure of manufacturing performance. For organoid applications, the more relevant outputs are the numbers of particles that meet predefined specifications and organoids that retain the intended identity and function. Quality assessment should therefore follow the entire workflow, from precursor preparation and droplet generation to particle recovery, cell culture, and organoid analysis. Recent studies show that controlling particle formation, cell distribution, and downstream handling can each affect the consistency of the final organoid population.[49,115]

Batch control begins with defined inputs and measurements at the particle level. Records should include polymer identity and lot, concentration, functionalization, crosslinking conditions, cell source and passage, and the timing of each processing step. After gelation and washing, hydrated microgels should be assessed for size distribution, shape, aggregation, and the fraction within the target range. Where mechanical cues are part of the design, single-particle properties should be distinguished from the stiffness, yielding, and stress relaxation of the assembled matrix. This distinction is relevant to granular culture systems. A recent study tuned alginate microgels within an interstitial matrix and showed that the resulting material properties and spatial placement influenced organoid self-

organization.[23] Sampling particles at the beginning, middle, and end of each run can reveal drift associated with cell settling, flow changes, nozzle obstruction, or changes in the collection bath.

Purification should be evaluated alongside fabrication. Oil-based droplet methods require an oil-removal step, while surfactants, photoinitiators, or unreacted crosslinking reagents may require method-specific assessment after washing. In an intestinal organoid platform, an integrated cell distribution module reduced variation in droplet occupancy, and an oil-removal module transferred the hydrogel particles into an aqueous culture workflow.[115] Such integration may reduce handling variation, but residual substances, particle recovery, and cell survival still require measurement. All-aqueous microfluidics has also been used to produce microgels without oil or surfactant, providing a potential way to simplify this part of the process; its performance for a specific organoid model must be established separately.[119]

The uniformity of the particles does not guarantee uniform organoid initiation. Cell sedimentation or aggregation may result in empty particles as well as particles containing varying numbers of initiator cells. Therefore, for each batch, particular attention should be paid to the proportions of empty particles, particles occupied by a single cell, and particles occupied by multiple cells; the recovery rate of viable cells after preparation; and the survival rate during the early culture period. Organoid formation efficiency should be calculated using a clearly defined denominator, such as the number of viable cells seeded or the number of occupied microdroplets. In a fully aqueous droplet system used for pancreatic cancer organoids, approximately 80%–90% of individual starting cells formed organoids per batch, highlighting the importance of defining the starting unit. This formation rate should be distinguished from subsequent maturity assessment metrics.[49]

A batch should be evaluated against biological as well as physical criteria. Alongside organoid size and formation rate, investigators should measure tissue-specific morphology, lineage markers, and at least one relevant functional outcome at a prespecified culture time. For example, marker expression and drug response were examined in microgel-grown pancreatic cancer organoids, while intestinal organoids were assessed for lineage differentiation and growth relative to dome cultures.[49,115] Scale-up studies should then compare independent runs using the same definitions: specification-compliant particles per input volume, losses during recovery and sorting, organoid formation efficiency, variation between batches, and functional organoids per unit of production time. Acceptance ranges should be established for the intended tissue model and application rather than imposed as universal thresholds (Table S2).

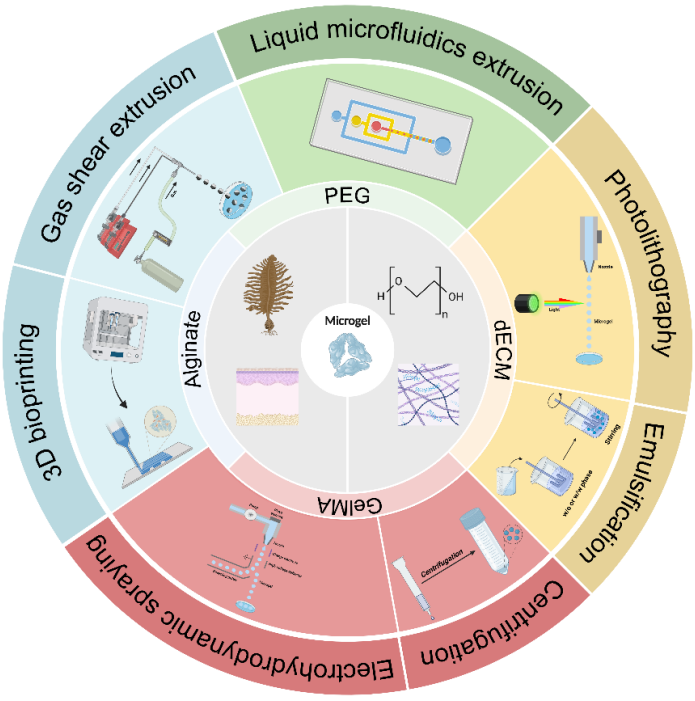


Figure 3. Materials and preparation of microgels for organoids. Created in BioRender. Luo, Z. (2026) https://BioRender.com/k86l4ei.
Abbreviations: dECM: Decellularized extracellular matrix; GelMA: Gelatin methacryloyl; PEG: Polyethylene glycol.

Table 1. The fabrication methods of microgels

Method	Principle	Main advantage	Main limitation	Main application
Liquid microfluidics	Interfacial shear forms droplets in microchannels[120]	Precise size control and high monodispersity[121]	Low throughput and use of oils or surfactants[121]	Uniform cell or organoid encapsulation[122]
Extrusion-based droplet generation	Extrusion, such as gas flow, breaks a liquid jet into droplets[79]	Oil-free, cytocompatible, and scalable[78]	Lower particle uniformity[78]	Cell-laden and multicompartment microgels[32]
Electrohydrodynamic spraying	An electric field generates charged droplets[123]	Mild processing and high cell viability[124]	Difficult monodispersity control[125]	Cell delivery and tissue regeneration[126]
Photolithography	Patterned light crosslinks photosensitive polymers[127]	Precise control of complex particle shapes[127]	Limited materials and potential phototoxicity[128]	Anisotropic and shape-defined microgels[127]
Emulsification	Aqueous precursors are dispersed in an oil phase[123]	Simple, inexpensive, and high-throughput[129]	Polydispersity and surfactant-related cytotoxicity[130]	Drug delivery and large-scale production[131]
Centrifugatiol droplet generation	Centrifugal force ejects droplets into a crosslinking bath[100]	Simple, oil-free, and cell-compatible[21]	Limited size control and scalability[21]	Cell encapsulation and granular scaffolds[101]
3D bioprinting	Microgels are deposited into spatially defined structures[103]	Fabricates complex multicellular constructs[104]	Resolution–throughput trade-off[105]	Organoid assembly and tissue fabrication[132]

5. Main strategies for constructing organoids using microgels

5.1. Individual microgel as a microenvironment for organoid formation

In traditional 3D culture, because stem cells/progenitor cells are embedded in a solid hydrogel as a single-cell suspension, initial adhesion between the cells and the matrix is often uneven, leading to inconsistencies in differentiation fate across batches. In contrast, encapsulating individual cells within microgels provides each cell with an independent, standardized "starting niche," allowing cells to undergo proliferation, differentiation, and self-organization independently within a confined yet uniform microenvironment.[48] This approach not only enhances the reproducibility of organoid formation but also facilitates traceability analysis of single-cell fates. For example, using microfluidic droplet technology to encapsulate individual small intestinal stem cells within collagen I/basement membrane extract particles enables high-throughput organoid production.[115]

In tissue engineering, researchers encapsulate multicellular spherical aggregates—known as embryoid bodies or spheroids—entirely within microgels. This approach not only protects existing intercellular connections from damage caused by dissociation but also accelerates the differentiation and maturation of organoid lineages within the biochemical microenvironment provided by the microgels.[49] PEG-based microgels can encapsulate human pluripotent stem cell-derived spheroids within core–shell microcapsules, promoting rapid aggregation of cells into spherical structures inside the capsules, while the encapsulation process has a minimal impact on cell viability. In applications involving liver organoids, incorporating nanoporous gelatin microspheres into human induced pluripotent stem cell (hiPSC) embryoid bodies to construct a 3D culture system allows the porous structure of microspheres to act as efficient transport channels for oxygen, nutrients, and signaling molecules.[55] This significantly reduces hypoxia and cell death in the core region of the spheroids while maintaining the expression levels of pluripotency markers. Following hepatogenic differentiation, these organoids demonstrated significant improvements in indicators such as hepatocyte/cholangiocyte marker expression, albumin secretion, urea synthesis, and cytochrome P450 family 3 subfamily A member 4 (CYP3A4) activity.[60]

Significant progress has been made in the organ-specific engineering of microgels across various organ types. In the field of intestinal organoids, researchers found that regulating the mechanical properties of GelMA alone cannot fully replicate the polarity signals mediated by the basement membrane matrix; instead, it leads to an "apical-out" polarity reversal phenotype in the organoids. However, when laminin-111 was added, the organoids partially regained their "basal-out" polarity characteristics. The researchers believe that this controlled polarity reversal may provide a unique window for accessing the apical membrane in engineered intestinal organoids.[115] For liver organoids, the researchers proposed that they could be

efficiently prepared from PEG microporous arrays, or that hiPSC-derived hepatoblast organoids could be cultured to maturity in polystyrene microplate wells.[133] For brain organoids, the researchers proposed using endothelial cells for the culture of induced pluripotent stem cell-derived cortical organoids. Compared to traditional Matrigel systems, cortical organoids in this system exhibit a higher degree of transcriptomic similarity to human fetal forebrain tissue, and the neurons display a richer array of spontaneous excitatory postsynaptic currents.[134] In the field of kidney organoids, researchers proposed using VEGF-loaded glycosaminoglycan-based microgels to guide vascular morphogenesis. The localized VEGF gradient enhances the directed homing of $CD31^+$ endothelial cells toward nascent nephrons, thereby optimizing the vascularization process of kidney organoids. Additionally, PEG microporous arrays and agarose and polydimethylsiloxane microfluidic systems have been employed for high-throughput studies on the differentiation and maturation of brain organoids.[133]

5.2. Microgel-based organoid assembly and fusion

The modular nature of microgels gives them a natural advantage in constructing multicellular microtissues. Different cell populations can be encapsulated separately in individual microgels, which can then be assembled into heterogeneous cell communities with a specific spatial logic through physical arrangement or chemical stimulation. This modular, building-block-style assembly approach overcomes the limitations of uncontrollable cell distribution in traditional monolithic hydrogels, providing the technical foundation for reconstructing tissue hierarchies at the millimeter or even micrometer scale.

The directed fusion of multiple pre-differentiated organoids into assemblies is a core method researchers use to simulate complex biological processes such as neural projections between different brain regions and immune-epithelial interactions. Traditional methods typically involve manually transferring and culturing organoids in centrifuge tubes using pipettes to achieve fusion. This method has extremely low spatial precision and is particularly deficient in controlling the relative positions and numerical ratios of different types of organoids. The SPOT platform developed by Roth *et al.*[53] fundamentally addresses this challenge. Researchers encapsulate organoids in a hydrogel loaded with iron oxide nanoparticles, which are then precisely picked up, transported, and deposited with the assistance of a magnetic 3D printing head. Cellulose nanofibers serve as a shear-thinning, self-healing scaffold to anchor the spatial position of the organoids. Using the SPOT platform, researchers have successfully constructed neural assemblies formed by the fusion of forebrain organoids and dorsal forebrain organoids derived from human pluripotent stem cells, as well as disease models involving the co-culture of neural organoids with patient-derived glioma organoids. This spatially controlled assembly strategy has also been extended to bioprinting platforms, enabling the large-scale, reproducible preparation of human-derived assemblies.

In the construction of assemblies, microgels can serve not only as cell carriers but also as tools for spatial coding. By designing the shape, size, and surface chemistry of the microgels, researchers can impart a certain degree of directionality to the arrangement of cells within the assembly during the stacking and alignment process. For example, when cells are encapsulated in hollow collagen microgel beads, they adhere to and spread across the inner walls of the collagen, ultimately forming hollow, tissue-like structures. This provides a model for constructing tubules or vascular organoids with internal lumens.[135] Combined with techniques such as bioprinting and magnetic manipulation, this strategy holds promise for achieving a paradigm shift from random fusion to programmed construction.

5.3. Microgels as delivery and patterning platforms

Using microgels as delivery and spatial-patterning platforms provides another strategy for regulating organoid development. Microgels can release growth factors, small molecules, nucleic acids, extracellular vesicles, oxygen, or ions. They can also sequester endogenous factors. A spatial pattern of particles can approximate a developmental organizer more faithfully than a uniform medium. MicroGUIDEs exploit tunable glycosaminoglycan affinity to control VEGF distribution and thereby vascular morphogenesis in kidney organoid contexts.[55] In bone organoid units, calcium peroxide phases sustain oxygen supply while immune cells modulate inflammation.[73] Endothelial, perivascular, immune, neural, or mesenchymal cells can be matured separately in particles and introduced when the organoid is competent to interact. Sequential assembly resolves incompatible differentiation schedules and reduces the risk that one lineage dominates early culture. Granular neural networks have been established before the addition of cancer spheroids and patient-derived renal tumor organoids, producing an innervated organoid-on-chip model.[64] Similarly, skin fabrication can combine adipose-derived stem cell (ADSC) microspheres, fibroblasts, endothelial channels, and a surrounding hydrogel in one printed construct.[132]

Patterning can be random, gradient-based, or deterministic. Random mixtures are scalable and suitable for distributed paracrine signals. Gradients require control of particle density, payload, diffusion, and binding. Deterministic placement through printing, magnetic manipulation, acoustic fields, or aspiration offers the most precise geometry but introduces additional handling. The choice of method should be determined by the biological length scale, which varies depending on the tissue type.

Crypt-scale signaling may require tens of micrometers, vascular corridors hundreds of micrometers, and organ-organ interfaces millimeters. More spatial precision is not inherently better if the tissue remodels faster than the pattern can be maintained.[132]

Individual encapsulation controls starting cell number and local niche. Modular assembly controls tissue composition and geometry. Delivery microgels control signal location and timing. Individual microgels are strongest for high-throughput screens, clonal analysis, and uniform initiation, but they can impose confinement and complicate organoid retrieval. Assembly supports heterogeneity, fusion, and scale, but introduces variable interparticle contacts and more demanding image analysis.[136] Delivery platforms provide localized instruction with minimal interference in organoid self-organization, but require quantitative pharmacokinetics and spatial validation. Hybrid workflows are likely to dominate. An organoid can be initiated in a degradable capsule, released into a stress-relaxing granular matrix, combined with endothelial microgels, and printed adjacent to a perfusable channel. Each transition should have a release criterion, such as minimum organoid diameter, polarity, lineage composition, or mechanical integrity (Table 2).

Table 2. Comparison of principal microgel-based organoid construction strategies

Strategy	Primary design control	Principal advantage	Critical risk and validation need	Reference
Individual encapsulation niche	Cell number, aggregate size, capsule geometry, and matrix	Standardized initiation and parallel culture	Confinement may limit cell interactions; validate lineage development and release.	48
Modular assembly and fusion	Particle geometry, packing, adhesion, and unit ratio	Construction of larger heterogeneous tissues	Interfaces may impair fusion; validate mechanics, perfusion, and spatial fidelity.	132
Delivery and spatial patterning	Payload affinity, release rate, particle position, and clearance	Localized and patterned signaling	Tissue dose may be uncertain; distinguish carrier and payload effects.	137

6. Applications of microgel-enabled organoids

6.1. Bone organoids

Bone is a highly mineralized, dynamic connective tissue whose macroscopic structure consists of dense cortical bone and porous cancellous bone. At the microscopic level, it is characterized by a scaffold of mineralized type I collagen fibers, embedded with osteoblasts, osteocytes, and osteoclasts that form dynamic remodeling units. Healthy bone tissue possesses a dense network of blood vessels that not only delivers oxygen and nutrients but also plays a central role in the signaling regulation of bone remodeling. At the same time, immune cells in the bone microenvironment, especially macrophages, precisely regulate the timing of inflammation resolution and bone regeneration through M1/M2 polarization switching.[73]

Traditional bone organoid construction generally relies on animal-derived matrices such as Matrigel or involves encapsulating bone marrow mesenchymal stem cells (BMSCs) in a solid, static hydrogel. Although these approaches can induce a certain degree of mineralization locally, they suffer from three major drawbacks. The dense network of the solid hydrogel severely restricts the diffusion of oxygen inward, causing the core region of the organoid to remain in a state of chronic hypoxia, which leads to high rates of cell necrosis. Conventional systems often exhibit an "immune vacuum," completely overlooking the regulatory role of immune components such as macrophages in osteogenesis-resorption coupling. When repairing large or irregular bone defects, prefabricated block-like structures lack conformability and cannot closely conform to the contours of the defect, resulting in poor interface integration.[73]

Deng *et al.*[73] developed a strategy for constructing multifunctional bone-like organoids based on silk fibroin methacryloyl hydrogel microspheres. They used microfluidic technology to pre-fabricate porous microspheres. Calcium peroxide-hydroxyapatite (CaO_2-HAp) oxygen-releasing particles, BMSCs, and RAW264.7 macrophages were simultaneously encapsulated within a single microsphere unit, achieving a highly integrated "one microsphere, three functions" system. The CaO_2-HAp particles continuously release oxygen for up to 30 days, and their hydrolysis products—Ca^{2+} and PO_4^{3-}—further synergistically promote the deposition of the mineralized matrix (Figure 4A and 4B). A 28-day *in vitro* culture of fibroin microsphere-based organoid-like units demonstrated three major synergistic effects. Continuous oxygen supply maintained high BMSC survival rates and significantly enhanced alkaline phosphatase activity and mineralization. Macrophages were effectively directed

toward the M2 anti-inflammatory phenotype, with downregulated expression of pro-inflammatory factors and upregulated expression of anti-inflammatory factors and angiogenesis markers. The microsphere units can serve as a particulate filler material, suitable for conformal filling of bone defects of various shapes. In a mouse model of critical-size cranial defects, new bone formation and tissue integration at 8 weeks were significantly superior to those achieved with conventional methods[73] (Figure 4C and 4D). Another strategy employs a dynamic DNA/GelMA dual-network hydrogel (CGDE) to support woven bone organoid formation. By leveraging hydrogen bonding between DNA and GelMA combined with GelMA network crosslinking, researchers created a dual-network hydrogel with appropriate mechanical strength and enhanced viscoelastic properties that more closely mimic the dynamic mechanical environment of the natural bone ECM. During 21 days of 3D culture, the CGDE hydrogel effectively promoted cell migration and self-organization, facilitating the formation of a woven bone organoid through intramembrane ossification.[137] The woven bone organoid derived from the CGDE system demonstrated unique adaptive properties. *In vivo* studies showed rapid osseointegration as early as four weeks post-implantation, providing a robust and scalable platform for the development of bone organoids.[137] By comparison, this strategy is clearly less effective than using microgels directly to construct bone organoids.

Microgels are particularly useful for bone organoid construction because discrete particles can bring osteogenic cells, mineral components, oxygen sources, and immune-regulating cues into close proximity while conforming to irregular defects. This addresses two practical problems in bone-like constructs: insufficient oxygen supply during culture and poor adaptation of a preformed scaffold to the defect shape.[73] Their modularity, however, should not be equated with the formation of integrated bone tissue. Interfaces between particles may persist, and improved mineralization or defect filling does not by itself demonstrate a functional vascular network, osteocyte organization, or sustained bone remodeling. Future comparisons should therefore assess tissue continuity and host integration alongside conventional osteogenic markers.

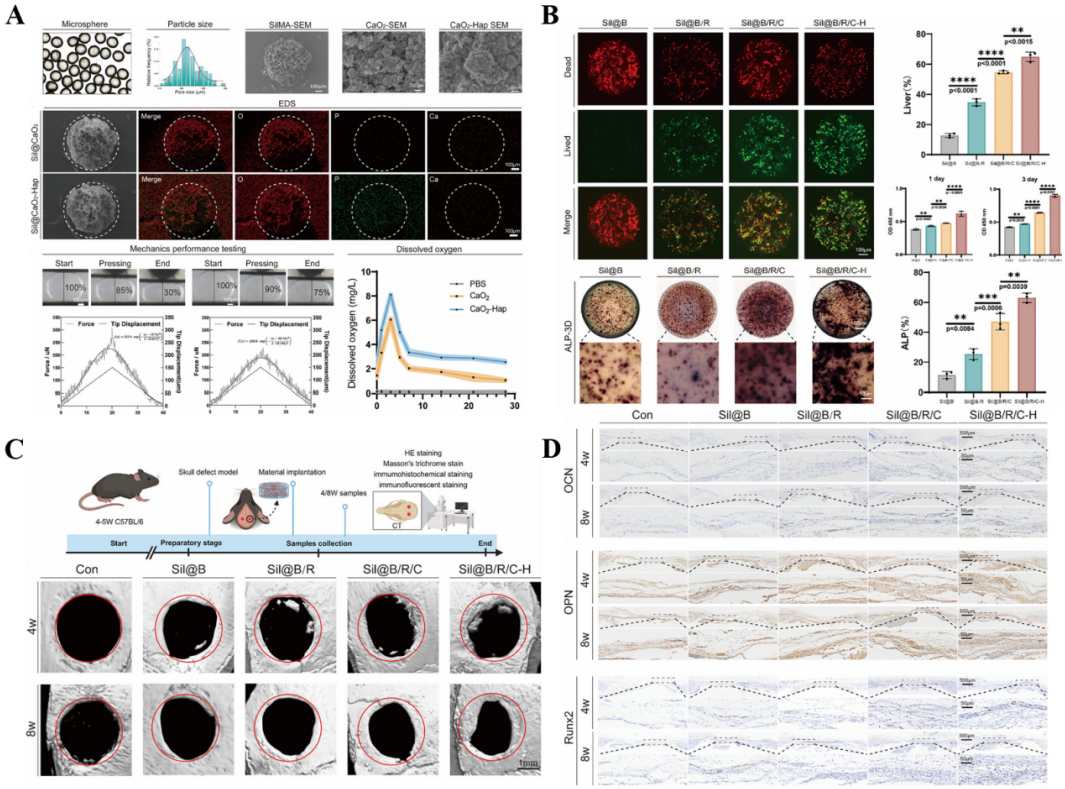


Figure 4. Applications of microgels in bone organoids. (A) Characterization of hydrogel microspheres and oxygen-releasing materials. (B) Effects of oxygen-releasing SilMA microspheres on cell viability, proliferation, osteogenesis, and immunomodulation. (C) Schematic illustration of the experimental design for bone regeneration evaluation, including the skull defect model, material implantation, and analysis at 4 and 8 weeks. (D) Immunohistochemical analysis of osteogenic markers in defect areas treated with oxygen-releasing SilMA microspheres. Reprinted from Deng *et al.*[73]
Abbreviations: ALP: Alkaline phosphatase; Con: Control; CT: Computed tomography; EDS: Energy-dispersive X-ray spectroscopy; HAp: Hydroxyapatite; HE: Hematoxylin and eosin; OCN: Osteocalcin; OPN: Osteopontin; PBS: Phosphate-buffered saline; Runx2: Runt-related transcription factor 2; SEM: Scanning electron microscopy; SilMA: Silk fibroin methacryloyl.

6.2. Cartilage organoids

Cartilage is a specialized type of connective tissue that is avascular, aneural, and has a low cell density. Its cellular composition consists solely of a single lineage of chondrocytes, embedded in a highly hydrated ECM composed of type II collagen and aggregated proteoglycans. This structure endows cartilage with exceptional compressive elasticity and a low-friction surface. However, precisely because of its lack of blood supply and nerve innervation, cartilage has virtually no ability to repair itself following injury, and defects often evolve into fibrotic scar tissue or progress to osteoarthritis.[138,139]

Microfracture, which is currently widely used in clinical practice, can only induce fibrocartilage repair, whose mechanical properties are far inferior to those of natural hyaline cartilage. Autologous chondrocyte transplantation, on the other hand, carries risks of donor site damage and dedifferentiation. Allogeneic transplantation is limited by immune rejection and a shortage of donor sources.[138] At the basic research level, the construction of traditional cartilage organoids largely relies on prolonged *in vitro* pre-differentiation followed by implantation. Not only are the culture cycles lengthy and the costs high, but it is also difficult to maintain stable cell phenotypes during *in vitro* differentiation, and the integration efficiency with host tissue after implantation is suboptimal. Most critically, existing strategies generally overlook the core biological event of cartilage development: the aggregation process of mesenchymal stem cells.[139,140]

Lin *et al.*[140] developed a biodegradable heterogeneous microgel assembly. This system consists of two functionally complementary microgel components: slow-degrading microgels (S-microgels) and fast-degrading microgels (F-microgels). S-microgels are responsible for grafting hepatitis A virus (HAV) peptides to promote cell adhesion and aggregation, while F-microgels carry stromal cell-derived factor-1 (SDF-1) to actively recruit endogenous BMSCs. After implantation, the F-microgels degrade first and release SDF-1, forming cavities with a "micro-nest cluster" structure within the *in situ* tissue. This, in synergy with the HAV peptides on the surface of the S-microgels, drives the aggregation and chondral differentiation of BMSCs. *In vitro* experiments confirmed that this method significantly promotes the secretion of cell aggregation-related markers and chondral matrix. Shen *et al.*[72] developed a novel RGD–silk fibroin–DNA hydrogel microsphere (RSD-MS) via a microfluidic system by integrating photopolymerization with self-assembly techniques and then modified it with Pep-RGDfKA. The RSD-MSs exhibited uniform size, porous surface, and optimal swelling and degradation properties. *In vitro* studies demonstrated that RSD-MSs enhanced BMSC proliferation, adhesion, and chondrogenic differentiation (Figure 5C). Transcriptomic analysis showed RSD-MSs induced chondrogenesis mainly through integrin-mediated adhesion pathways and glycosaminoglycan biosynthesis. Moreover, *in vivo* studies showed that seeding BMSCs onto RSD-MSs to create cartilage organoid precursors significantly enhanced cartilage regeneration. In conclusion, RSD-MS was an ideal candidate for the construction and long-term cultivation of cartilage organoids, offering an innovative strategy and material choice for cartilage regeneration and tissue engineering (Figure 5D). Gao *et al.*[141] incorporated sulfobetaine methacrylate (SBMA) into a hyaluronic acid methacrylate (HAMA) matrix to develop a novel microgel, HAMA–SBMA, that combines adhesion properties, chondrocyte differentiation-promoting activity, and anti-inflammatory activity. Concurrently, allogeneic BMSCs were loaded onto porcine articular cartilage dECM particles to construct cartilage organoids with characteristics of articular cartilage (Figure 5A). In rat and sheep cartilage defect models, the combined treatment with HAMA–SBMA and these cartilage organoids demonstrated excellent cartilage repair effects by activating Frizzled-related proteins to suppress inflammatory factors and enhance integrin expression (Figure 5B). Together, these particle-based and hydrogel-assisted approaches address several limitations of conventional cartilage tissue engineering, including insufficient cell condensation, limited local signaling control, and poor integration at cartilage defect sites. By mimicking the core step of mesenchymal stem cell aggregation during natural cartilage development, the core–shell microgel system bypasses the lengthy *in vitro* pre-differentiation process—core–shell microgels can even be implanted directly without any *in vitro* culture and form cartilage tissue *in vivo* within three weeks.[132]

The main advantage of microgels for cartilage is their ability to regulate cell condensation locally—a necessary early step in chondrogenesis—while presenting adhesive signals or releasing recruitment factors from separate particle populations.[140] Cell-bearing microspheres can also serve as manipulable cartilage-like precursors and have shown regenerative effects after implantation.[72] The principal limitation is that successful chondrogenesis does not necessarily produce durable articular cartilage: particle boundaries, nonuniform matrix deposition, and incomplete zonal organization may compromise load bearing and long-term function. Accordingly, cartilage microgel systems should be judged by integrated matrix architecture and mechanical performance, not only by chondrogenic marker expression or short-term defect repair.

6.3. Skin organoids

The skin is the largest organ in the human body, consisting of the epidermis and dermis, along with various appendages such as hair follicles, sebaceous glands, and

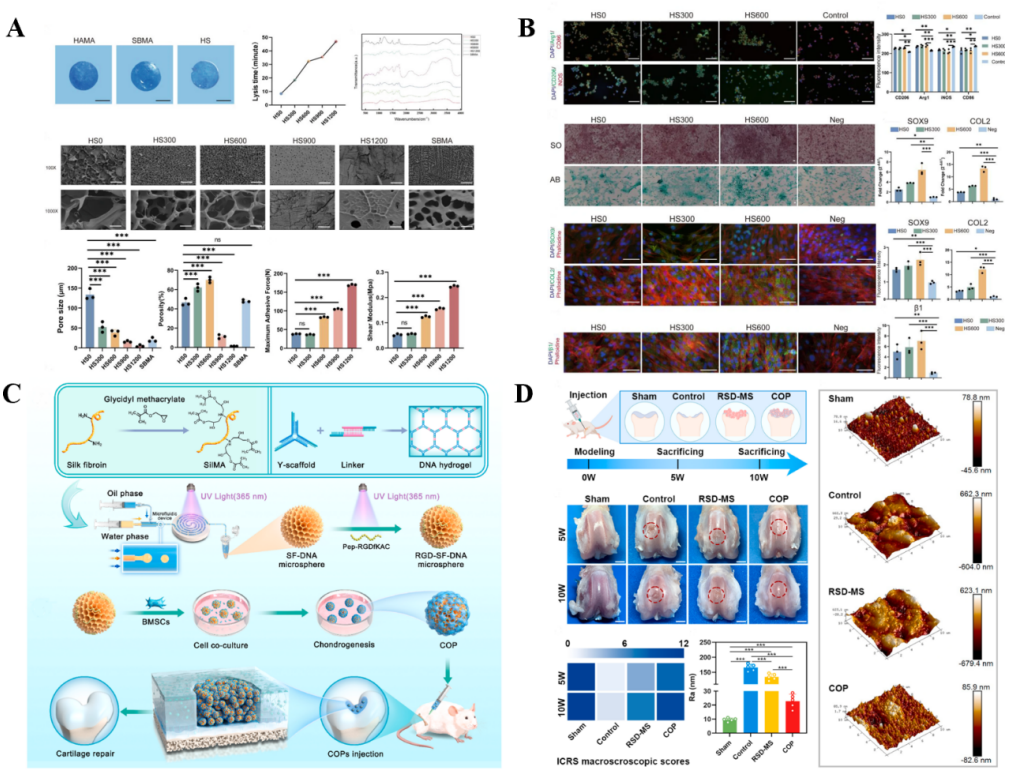


Figure 5. Applications of microgels in cartilage organoids. (A) Preparation and characterization of HAMA–SBMA hydrogel. (B) HAMA–SBMA microgel suppresses inflammation and promotes chondrogenesis in cartilage organoid composites while enhancing integrin β1 expression. (A, B) Reprinted with permission from Gao *et al.*[141] Copyright © 2025 Springer Nature. (C) Schematic diagram of the synthesis of RGD–silk fibroin–DNA microspheres and their application in the preparation of cartilage organoid precursors and cartilage regeneration. (D) Scheme of cartilage defect modeling and treatment protocol. (C, D) Reprinted with permission from Shen *et al.*[72] Copyright © 2024 Elsevier.

Abbreviations: β1: Integrin β1; AB: Alcian blue; Arg-1: Arginase 1; BMSCs: Bone marrow-derived mesenchymal stem cells; COL2: Collagen type II; COP: Cartilage organoid precursor; DAPI: 4′,6-Diamidino-2-phenylindole; F-actin: Filamentous actin; HAMA: Hyaluronic acid methacrylate; HS: HAMA–SBMA hydrogel; ICRS: International Cartilage Repair Society; iNOS: Inducible nitric oxide synthase; Neg: Negative control; ns: Not significant; RGD: Arginine–glycine–aspartic acid; RSD-MS: RGD–silk fibroin–DNA hydrogel microsphere; SBMA: Sulfobetaine methacrylate; SEM: Scanning electron microscopy; SF: Silk fibroin; SF-DNA: Silk fibroin–DNA; SilMA: Silk fibroin methacryloyl; SO: Safranin O; SOX9: SRY-box transcription factor 9; UV: Ultraviolet.

sweat glands. The skin's barrier function depends on the stratified keratinization process of the epidermis, while its regenerative capacity relies on stem cells in the hair follicle bulge and complex signaling interactions between the epidermis and dermis. When skin defects result in the loss of these accessory structures, even if the epidermis is restored, full physiological functions, such as sweating, sebum secretion, and hair regrowth, cannot be fully restored.[142,143]

Traditional skin-based sheet-like organoids have been widely used in drug and cosmetic testing, but they suffer from limitations such as low testing efficiency, high costs, and difficulty in adapting to high-throughput screening platforms. Although microspheric skin organoids, which have emerged in recent years, offer hope for high-throughput screening, their preparation largely relies on random cell self-aggregation. This results in inadequate simulation of skin's hierarchical structure and poor uniformity in sphere size. Most notably, the epidermal and dermal layers in most micro-spherical models are inverted (epidermis on the inside, dermis on the outside).[143] A deeper bottleneck is that traditional skin organoids lack an integrated vascular network, limiting their long-term culture capacity as well as their survival rate and integration efficiency following large-area implantation. Furthermore, the regeneration of functional appendages is a core indicator of skin regeneration; the vast majority of existing systems are unable to achieve *in situ* regeneration of hair follicles, sebaceous glands, and sweat glands during the healing process.[132,142]

Xie *et al.*[143] introduced a methodological innovation. They first used collagen gel to form uniformly sized dermal-like core microgels with human dermal fibroblasts. Subsequently, they co-cultured human keratinocytes with the dermal-like core microgels in a stirred bioreactor, allowing the keratinocytes to adhere to the outer surface

of the microgels and form a multilayered epidermal-like structure, which was further induced to develop into a complete epidermal barrier (Figure 6A). The innovation of this method lies in correcting the inverted structure of traditional microsphere models—where the epidermis is on the inside and the dermis on the outside—to the correct spatial arrangement consistent with natural skin, with the epidermis on the outside and the dermis on the inside. Furthermore, high-throughput production is achieved through batch culture in the bioreactor (Figure 6B). In terms of vascularization, Wang *et al.*[132] proposed a pre-vascularized skin organoid model (PV-SOM). The PV-SOM employs a one-step coaxial 3D printing strategy: the inner phase utilizes a temperature-responsive sacrificial material and endothelial cells to form hollow vascular channels, while the outer phase employs microspheres loaded with ADSCs and a biomimetic hydrogel matrix containing skin fibroblasts (Figure 6C). By activating the PI3K–AKT–mTOR pathway, ADSC microspheres can regulate the migration, tubulogenesis, and maturation of vascular endothelial cells in multiple stages, thereby enabling rapid vascular closure and maturation *in vitro*. Furthermore, the implanted constructs supported the formation of extensive neovascular networks in large-area skin defects, accelerating wound closure and improving collagen remodeling (Figure 6D). Xiong *et al.*[142] further demonstrated that the ultimate target of wound healing is the regeneration of appendages. This target can be achieved through materials engineering rather than relying solely on cell transplantation. Regeneration-directing artificial skin can activate the wound's endogenous repair capacity without exogenous cells, promoting the *in situ* regeneration of hair follicles, sebaceous glands, and sweat glands.

For skin construction, microscale cell carriers offer a way to position dermal, stromal, and vascular-supporting populations within a larger construct. This is valuable because epidermal organization and vascular support impose different spatial requirements. A printed system incorporating ADSC microspheres improved vascular development and wound repair, but its outcome reflects the combined microsphere–continuous-hydrogel construct, not an isolated microgel effect.[132] Moreover, vascularization and wound closure are insufficient evidence of a fully functional skin organoid: epidermal barrier integrity, stable epidermal–dermal coupling, and appendage formation require separate assessment. The collagen-based spherical skin model illustrates epidermis-out organization but is better treated as an architectural comparator than as conventional microgel evidence.[143]

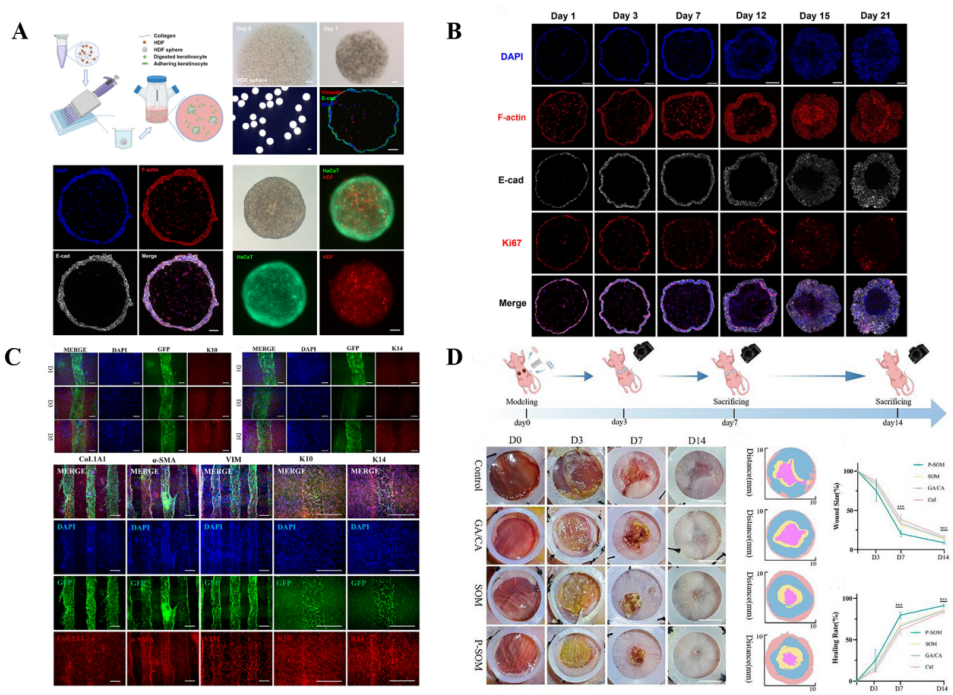


Figure 6. Applications of microgels in skin organoids. (A) Fabrication of microspheric skin organoids. (B) Characteristics of microspheric skin organoids. (A, B) Reprinted from Xie *et al.*[143] (C) Multilineage characterization of pre-vascularized skin organoid model. (D) *In vivo* evaluation of wound healing with pre-vascularized skin organoids. (C, D) Reprinted from Wang *et al.*[132]

Abbreviations: α-SMA: Alpha-smooth muscle actin; COL1A1: Collagen type I alpha 1 chain; Ctrl: Control; DAPI: 4′,6-Diamidino-2-phenylindole; E-cad: E-cadherin; F-actin: Filamentous actin; GFP: Green fluorescent protein; HaCaT: Immortalized human keratinocyte cell line; HDF: Human dermal fibroblast; K10: Keratin 10; K14: Keratin 14; K18: Keratin 18; Ki67: Proliferation marker Ki-67; VIM: Vimentin.

6.4. Tumor organoids

A tumor is a complex ecosystem comprising cancer cells, cancer-associated fibroblasts, immune infiltrating cells, endothelial cells, and a heterogeneous ECM. The stiffness, composition, and topology of the ECM play an active regulatory role in tumor invasion, drug resistance, and immune evasion. Therefore, an ideal tumor organoid must simultaneously replicate both the intrinsic genetic characteristics of cancer cells and the extrinsic physicochemical cues of the tumor microenvironment. Conventional two-dimensional monolayer culture methods can no longer meet the research needs for studying the 3D spatial heterogeneity of tumors and the mechanisms of drug resistance. Although tumor spheroids address some of these limitations with their 3D structure, traditional methods often rely on the high proliferative activity and self-aggregation behavior of tumor cells, frequently overlooking the mediating role of the ECM. As a result, the matrix density, stiffness gradients, and biochemical signaling within the spheroids differ vastly from those in real tumors. More critically, most traditional tumor spheroids lack the ability to controllably adjust matrix composition, making it difficult to systematically study the effects of different ECM components on tumor invasion and drug resistance on a single platform.[144]

Kim *et al.*[144] used a flow-focusing microfluidic device to prepare bioactive microgels composed of gelatin and HA, encapsulating hepatocellular carcinoma (HCC) cells within them to induce the formation of liver tumor spheroids (Figure 7A). By precisely modulating the crosslinking density and polymer composition ratio of the microgels, the researchers were able to independently program the mechanical stiffness and HA content of the microgels. The two HCC cell lines exhibited differences in spheroid morphology, differentiation states, and chemoresistance under the investigated microgel conditions, strongly demonstrating that regulatory factors in the microenvironment, rather than simple intrinsic cellular properties, play a dominant role in determining tumor physiology (Figure 7B). The gelatin–HA microgel system enables independent regulation of key components of the tumor ECM and mechanical stiffness on a single platform, allowing researchers to systematically decouple the independent contributions of various ECM parameters to tumor invasion and drug resistance. Song *et al.*[145] molecularly assembled a human uterine cervix-specific ECM microenvironment with cervical squamous cell carcinoma (CSCC) organoids, thereby reflecting the tumor's pathological characteristics while preserving the uterine cervix extracellular matrix (UCEM) microenvironment (Figure 7C). This pathological model

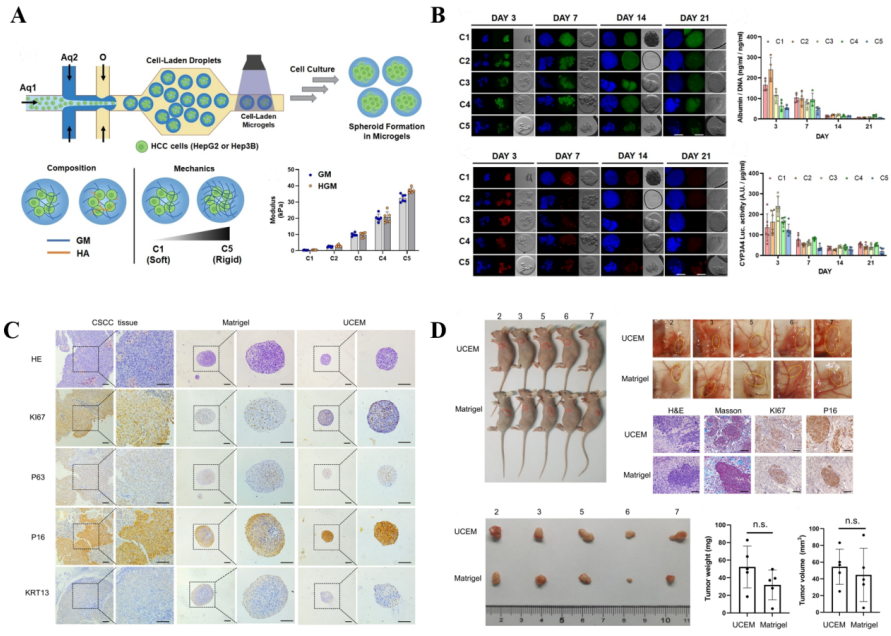


Figure 7. Applications of microgels in tumor organoids. (A) Schematic illustration of a flow-focusing microfluidic fabrication of microgels encapsulated with HCC cells. (B) Immunofluorescent imaging of albumin and nuclei of HepG2 spheroids in microgels with varying stiffness C1 to C5 monitored for 21 days. (A, B) Reprinted with permission from Kim *et al.*[144] Copyright © 2024 Wiley-VCH GmbH. (C) Structural and phenotypic characteristics of native tumor tissue and CSCC organoids. (D) Detection of tumorigenic ability of CSCC organoids *in vivo*. (C) Reprinted from Song *et al.*[145]
Abbreviations: Aq1: First aqueous phase; Aq2: Second aqueous phase; C1–C5: Microgel formulations with increasing stiffness; CSCC: Cervical squamous cell carcinoma; CYP3A4: Cytochrome P450 family 3 subfamily A member 4; GM: Gelatin methacrylate; HA: Hyaluronic acid; HCC: Hepatocellular carcinoma; HE/H&E: Hematoxylin and eosin; HGM: Hyaluronic acid-containing gelatin methacrylate; Ki67: Proliferation marker Ki-67; KRT13: Keratin 13; n.s.: Not significant; O: Oil phase; P16: p16 protein; P63: p63 protein; UCEM: Uterine cervix extracellular matrix.

of cervical cancer organoids more closely approximates the actual pathophysiological state in patients, facilitating the reflection of tumor heterogeneity and offering greater research and application value as an *in vitro* pathological model. RNA sequencing revealed that UCEM organoids exhibit greater similarity to primary CSCC and reflect tumor heterogeneity by demonstrating CSCC-associated signaling pathways. Additionally, UCEM organoids developed resistance to chemotherapy (Figure 7D).

Microgels can improve tumor-organoid experiments by standardizing the number of initiating cells and independently varying selected matrix properties, making differences in growth or drug response easier to interpret.[49,51] That control is also their limitation: a uniform particle niche may exclude the spatially heterogeneous matrix, stromal cells, immune interactions, and vascular influences present in a patient tumor. Furthermore, results obtained with microgel-supported cancer cell-line spheroids should not be generalized to patient-derived organoids; the two models offer different levels of biological validation.[144] The value of a tumor microgel platform therefore depends on the question being asked—mechanistic isolation or faithful disease modeling—and should be tested against an appropriate patient-derived or conventional-matrix comparator.

6.5. Other organoids

The construction of liver organoids presents a unique challenge: how to precisely control the ratio and spatial distribution of the two major cell lineages—hepatocytes and cholangiocytes—within a single organoid. Wang *et*

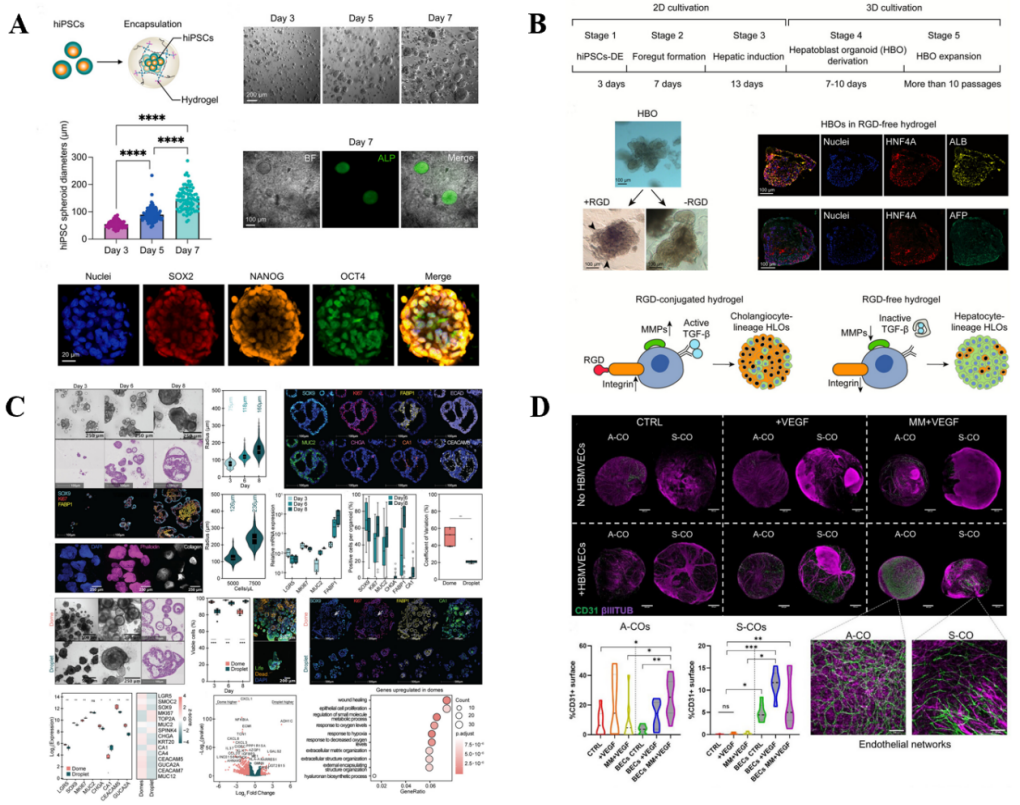


Figure 8. Applications of microgels in other organoids. (A) RGD-free hydrogel supports 3D cultivation and maintenance of pluripotency in hiPSCs. (B) Impact of hydrogel adhesiveness on hepatoblast organoid lineage behavior. (A, B) Reprinted from Wang *et al.*[146] (C) Development of colon organoids in droplets and comparison to traditional dome cultures. (C) Reprinted from Lavickova *et al.*[115] (D) Abundant multicellular endothelial networks are formed on the surface of brain organoids. (D) Reprinted from Fumadó *et al.*[134]

Abbreviations: βIIITUB: Beta-III tubulin; A-COs: Cerebral organoids derived from the A-iPSC line; AFP: Alpha-fetoprotein; ALB: Albumin; ALP: Alkaline phosphatase; BECs: Brain endothelial cells; BF: Bright-field; CA1: Carbonic anhydrase 1; CEACAM5: Carcinoembryonic antigen-related cell adhesion molecule 5; CHGA: Chromogranin A; COs: Cerebral organoids; CTRL: Control; ECAD: E-cadherin; FABP1: Fatty acid-binding protein 1; HBO: Hepatoblast organoid; HBMVECs: Human brain microvascular endothelial cells; H&E: Hematoxylin and eosin; hiPSCs: Human induced pluripotent stem cells; HLOs: Human liver organoids; HNF4A: Hepatocyte nuclear factor 4 alpha; Ki67: Ki-67 proliferation-associated protein; LGR5: Leucine-rich repeat-containing G-protein-coupled receptor 5; mIF: Multiplex immunofluorescence; MKI67: Marker of proliferation Ki-67; MM: Mixed medium; MMPs: Matrix metalloproteinases; MUC2: Mucin 2; NANOG: NANOG homeobox; ns: Not significant; OCT4: Octamer-binding transcription factor 4; RGD: Arginine–glycine–aspartic acid; S-COs: Cerebral organoids derived from the S-iPSC line; SOX2: SRY-box transcription factor 2; SOX9: SRY-box transcription factor 9; TGF-β: Transforming growth factor beta; VEGF: Vascular endothelial growth factor.

al.[146] developed a system based on dendritic polyglycerol-bicyclononyne and poly(N-isopropylacrylamide)-co-polyethylene glycol azide, successfully induced human liver organoids derived from hiPSCs under completely xeno-free conditions, and achieved effective regulation of organoid growth and development by adjusting the hydrogel's elastic modulus and viscoelasticity (Figure 8A). The study revealed a key mechanism of differentiation switching. The presence or absence of RGD adhesion peptides in synthetic hydrogel influenced the lineage specification of liver organoids. In RGD-free microgels, organoids tend toward a hepatocyte fate, highly expressing functional proteins such as albumin and CYP3A4 (Figure 8B). In RGD-containing microgels, organoids primarily differentiate into bile duct cells. This switch-like effect on lineage selection is mediated by the integrin-TGF-β signaling pathway, suggesting that the biochemical design of the microgels directly determines the extent and direction of signaling pathway activation[146] (Table 3).

The most critical bottleneck in the long-term culture of brain organoids is central necrosis. As organoids grow in size, passive diffusion of oxygen and nutrients can no longer reach the central regions, leading to massive cell death. This not only limits the maturation time and final size of the organoids but also significantly compromises the physiological relevance of the model. Fumadó *et al.*,[134] by introducing endothelial cells into a soft hydrogel to form a vascular network, successfully created a "mini-brain" capable of simulating a neurovascular unit. These organoids can grow to larger sizes, exhibit significantly reduced cell mortality in the central region, and display structural features of a protective blood-brain barrier, providing *in vitro* models that more closely mimic physiological conditions for mechanistic studies and drug screening of neurodegenerative diseases such as stroke, Alzheimer's disease, and Parkinson's disease (Figure 8D).

The technical challenges in developing intestinal organoids lie in the precise maintenance of spatial polarity

Table 3. Comparison of microgel-enabled organoid construction

Organoid type	Key design requirement	Microgel-specific feature	Main advantage	Main limitation
Bone	Mineralization, vascularization, immune regulation, and mechanical support[73]	Mineral- or oxygen-releasing microgels combined with osteogenic and immune cells[73]	Enhances osteogenesis, angiogenesis, and adaptation to irregular defects[137]	Long-term perfusion, mechanical maturation, and remodeling remain difficult[137]
Cartilage	Cell condensation, zonal organization, and stable chondrogenic phenotype[138]	Injectable core–shell or heterogeneous microgels with chondrogenic and anti-inflammatory signals[138]	Promotes chondrogenesis, nutrient transport, and defect filling[141]	Risk of hypertrophy, ossification, and incomplete tissue integration[141]
Skin	Epidermal–dermal organization, vascularization, barrier formation, and appendages[132]	Dermal core microgels coated with keratinocytes or combined with vascular modules[132]	Improves layer orientation, uniformity, vascularization, and wound repair[143]	Appendage, nerve, immune, and long-term barrier reconstruction remain limited[143]
Tumor	Tumor heterogeneity, ECM mechanics, stromal interactions, and drug response[144]	Tissue-specific microgels with tunable stiffness, composition, and cell populations[144]	Enables reproducible modeling of invasion, heterogeneity, and drug resistance[145]	Incomplete immune and vascular microenvironments may reduce clinical relevance[145]
Liver	Hepatocyte–cholangiocyte balance, metabolism, and bile-duct organization[146]	Adhesive-ligand and viscoelastic microgels regulate lineage specification[146]	Supports controlled differentiation and xenogeneic-free culture[146]	Perfusion, bile drainage, and long-term metabolic maturation remain challenging[146]
Brain	Neural maturation, vascularization, connectivity, and prevention of central necrosis[134]	Soft ECM-rich microgels combined with endothelial or neural modules[134]	Improves nutrient transport, neuronal organization, and neurovascular integration[134]	Functional vascular perfusion and mature electrophysiological connectivity are difficult to achieve[134]
Intestine	Crypt–villus polarity, luminal access, uniformity, and scalable production[115]	Microfluidically generated dECM- or GelMA-based microgels[115]	Enables uniform, high-throughput culture and reduces dependence on Matrigel[115]	Long-term barrier function and microbial or immune integration remain limited[115]

(*Cont'd...*)

Table 3. (***Continued***)

Organoid type	Key design requirement	Microgel-specific feature	Main advantage	Main limitation
Kidney	Nephron organization, vascularization, and filtration interfaces[147]	VEGF-binding microgels create localized angiogenic gradients[147]	Promotes endothelial recruitment and spatial vascular patterning[147]	Mature filtration and stable vascular–nephron integration remain unresolved[147]

Abbreviations: dECM: decellularized extracellular matrix; ECM: Extracellular matrix; GelMA: Gelatin methacryloyl; VEGF: Vascular endothelial growth factor.

along the crypt–villus axis and the ability to produce them at scale with high uniformity. Traditional manual methods struggle to meet the demands of clinical translation in terms of both reproducibility and throughput. To address this challenge, a highly integrated microfluidic platform enables the high-throughput encapsulation of intestinal stem cells within hydrogel microparticles. Both healthy and tumor-derived intestinal organoids can be successfully cultured and differentiated within these microparticles, with inter-batch uniformity and reproducibility far superior to those achieved by traditional manual methods. Lavickova *et al.*[115] proposed an integrated microfluidic platform that enables the high-throughput generation of uniform microgels embedded with primary human adult intestinal stem cells. A photo-crosslinked microgel composed of decellularized porcine small intestinal submucosa and a fish collagen–GelMA composite offers a cost-effective alternative to Matrigel. This approach not only supports the normal growth of small intestinal organoids but also represents a significant step toward clinical-grade cultivation by avoiding the immunogenicity and batch-to-batch variability associated with Matrigel (Figure 8C; Table 3).

7. Conclusion

The translation of microgel-enabled organoid systems is constrained by inconsistent organoid terminology, insufficient functional validation, and the complex coupling of particle size, mechanics, degradation, porosity, ligand presentation, and release kinetics. Although microgels improve interstitial transport, they cannot fully overcome diffusion limitations within large avascular organoids or independently ensure vascular, neural, immune, and stromal maturation. Manufacturing introduces further challenges, including the trade-off between throughput and particle uniformity, batch variability, cell sedimentation, residual reagents, and the absence of standardized quality-control criteria. Persistent microgels may also interfere with imaging, tissue dissociation, omics analysis, and drug quantification. For clinical translation, implantable systems must address degradation, biodistribution, inflammation, sterility, and regulatory classification, whereas tumor-screening platforms require analytical reproducibility and clinical concordance. Microgel complexity is therefore justified only when it provides measurable biological or translational advantages over simpler culture systems.[148]

Future microgel platforms are expected to employ chemically defined and dynamically programmable particles that independently regulate stiffness, interparticle adhesion, degradation, and molecular presentation throughout organoid development. Cell-responsive, enzymatically triggered, or optically controlled transitions could allow microgels to support cell handling, morphogenesis, differentiation, and subsequent tissue recovery at different stages. Closed-loop manufacturing systems integrating particle generation, imaging, sorting, culture, and release testing could improve reproducibility through real-time monitoring and automated process adjustment. High-content imaging, single-cell and spatial analyses, mechanical measurements, and artificial intelligence may further establish quantitative relationships between material properties and organoid phenotypes. Transient or removable microgels could reduce persistent foreign material after tissue assembly, while integration with organ-on-chip platforms could introduce perfusion, mechanical stimulation, sensing, and inter-organ communication. These developments will support increasingly adaptive, modular, and physiologically relevant organoid systems.[149]

Microgels transform organoid matrices from continuous and difficult-to-modify materials into discrete, programmable, and addressable building blocks. Their principal advantages include standardized initial conditions, improved interparticle transport, tunable mechanics, localized factor delivery, modular cellular organization, and compatibility with injection, assembly, and bioprinting. These properties can enhance organoid scalability, spatial patterning, vascularization, neural integration, and regenerative function across multiple tissue models. However, progress toward practical application requires the field to move beyond proof-of-concept formulations and establish quantitative design rules, rigorous definitions of organoid identity, long-term functional validation, and quality-controlled manufacturing. Ultimately, the value of microgel technology will depend on whether it produces organoids that are more reproducible, mechanistically interpretable, and biologically predictive than those generated using simpler culture platforms.[150]

Future work should move from demonstrating that microgels can support organoid growth to establishing when a defined microgel system produces a reproducible biological advantage. A first priority is to develop a reference formulation for one organoid type at a time. Investigators should specify polymer identity and molecular weight, functionalization, adhesive ligands, crosslinking chemistry, and any degradation or release mechanism. Each formulation should then be characterized in hydrated culture conditions for particle size, mechanical properties, and stability over the intended culture period. Its biological performance should be tested against the established tissue-specific matrix using the same cells, medium, and assessment time. Studies of defined bulk hydrogels show how controlled matrix composition can clarify organoid responses, but these findings require direct testing in microgel formats.[151]

A shared minimum quality-control workflow needs to be established. For every independently prepared batch, researchers should report particle size distribution, the fraction within the intended size range, cell occupancy, viable cell recovery, and any process-specific residues after purification. Organoid formation efficiency should be calculated using a stated denominator, such as viable initiating cells or occupied microgels. At a predefined endpoint, morphology and lineage markers should be paired with a tissue-specific functional assay. At least three independently prepared batches would provide an initial estimate of variation; subsequent sample sizes and acceptable ranges should be set from those data for the intended application. Recent pancreatic and intestinal organoid platforms demonstrate why control of initiating cell number and distribution must accompany control of droplet size.[49,115]

The development of stimuli-responsive microgels should be guided by clearly defined biological questions. One feasible experiment would compare morphogen-loaded microgels with otherwise matched unloaded particles and soluble-factor delivery. The study should measure loading, release in complete medium, local factor exposure, and a prespecified organoid response at several time points. Material response alone would not establish a benefit: the intervention should also improve a relevant outcome, such as spatial patterning or lineage-specific function, without reducing viability or organoid identity. Microgels with tunable VEGF affinity have already been used to alter local endothelial responses in kidney organoid culture, providing a starting point for such controlled studies.[55]

Finally, smart biomanufacturing should be evaluated by the quality of its output. An initial automated workflow could monitor particle size and occupancy during production, reject particles outside predefined limits, and record losses at each processing step. A subsequent closed-loop study could compare this workflow with fixed operating settings across independent runs. The primary endpoint should be the number of functionally qualified organoids per input cell and unit of production time. Secondary endpoints should include batch variation, reagent consumption, and operator time. These experiments would establish whether automation improves reproducibility and usable yield, rather than only increasing droplet generation rate.[115]

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Conflict of interest

The authors declare no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data

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References

1. Lancaster MA, Knoblich JA. Organogenesis in a dish: modeling development and disease using organoid technologies. *Science*. 2014;345(6194):1247125.

   doi: 10.1126/science.1247125

2. Takebe T, Wells JM. Organoids by design. *Science*.

2019;364(6444):956-959.

doi: 10.1126/science.aaw7567

3. Lancaster MA, Renner M, Martin CA, *et al.* Cerebral organoids model human brain development and microcephaly. *Nature*. 2013;501(7467):373-379.

doi: 10.1038/nature12517

4. Takasato M, Er PX, Chiu HS, *et al.* Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis. *Nature*. 2015;526(7574):564-568.

doi: 10.1038/nature15695

5. Takebe T, Sekine K, Enomura M, *et al.* Vascularized and functional human liver from an iPSC-derived organ bud transplant. *Nature*. 2013;499(7459):481-484.

doi: 10.1038/nature12271

6. Sachs N, Papaspyropoulos A, Zomer-van Ommen DD, *et al.* Long-term expanding human airway organoids for disease modeling. *EMBO J*. 2019;38(4):e100300.

doi: 10.15252/embj.2018100300

7. Lee J, Rabbani CC, Gao H, *et al.* Hair-bearing human skin generated entirely from pluripotent stem cells. *Nature*. 2020;582(7812):399-404.

doi: 10.1038/s41586-020-2352-3

8. Sato T, Vries RG, Snippert HJ, *et al.* Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. *Nature*. 2009;459(7244):262-265.

doi: 10.1038/nature07935

9. Salewskij K, Penninger JM. Blood Vessel Organoids for Development and Disease. *Circ Res*. 2023;132(4):498-510.

doi: 10.1161/CIRCRESAHA.122.321768

10. Nwokoye PN, Abilez OJ. Bioengineering methods for vascularizing organoids. *Cell Rep Methods*. 2024;4(6):100779.

doi: 10.1016/j.crmeth.2024.100779

11. Ahn Y, An JH, Yang HJ, *et al.* Human Blood Vessel Organoids Penetrate Human Cerebral Organoids and Form a Vessel-Like System. *Cells*. 2021;10(8):2036.

doi: 10.3390/cells10082036

12. Hong ZX, Zhu ST, Li H, *et al.* Bioengineered skin organoids: from development to applications. *Mil Med Res*. 2023;10(1):40.

doi: 10.1186/s40779-023-00475-7

13. Wimmer RA, Leopoldi A, Aichinger M, *et al.* Human blood vessel organoids as a model of diabetic vasculopathy. *Nature*. 2019;565(7740):505-510.

doi: 10.1038/s41586-018-0858-8

14. Nikolova MT, He Z, Seimiya M, *et al.* Fate and state transitions during human blood vessel organoid development. *Cell*. 2025;188(12):3329-3348.e31.

doi: 10.1016/j.cell.2025.03.037

15. Aisenbrey EA, Murphy WL. Synthetic alternatives to Matrigel. *Nat Rev Mater*. 2020;5(7):539-551.

doi: 10.1038/s41578-020-0199-8

16. Fang Y, Sun W, Zhang T, Xiong Z. Recent advances on bioengineering approaches for fabrication of functional engineered cardiac pumps: A review. *Biomaterials*. 2022;280:121298.

doi: 10.1016/j.biomaterials.2021.121298

17. Gjorevski N, Sachs N, Manfrin A, *et al.* Designer matrices for intestinal stem cell and organoid culture. *Nature*. 2016;539(7630):560-564.

doi: 10.1038/nature20168

18. Brown JW, Mills JC. Implantable synthetic organoid matrices for intestinal regeneration. *Nat Cell Biol*. 2017;19(11):1307-1308.

doi: 10.1038/ncb3635

19. Hernandez-Gordillo V, Kassis T, Lampejo A, *et al.* Fully synthetic matrices for in vitro culture of primary human intestinal enteroids and endometrial organoids. *Biomaterials*. 2020;254:120125.

doi: 10.1016/j.biomaterials.2020.120125

20. Broguiere N, Isenmann L, Hirt C, *et al.* Growth of Epithelial Organoids in a Defined Hydrogel. *Adv Mater*. 2018;30(43):e1801621.

doi: 10.1002/adma.201801621

21. Xuan LY, Hou YY, Liang L, *et al.* Microgels for Cell Delivery in Tissue Engineering and Regenerative Medicine. *Nano-Micro Letters*. 2024;16(1):218.

doi: 10.1007/s40820-024-01421-5

22. Mahdieh Z, Cherne MD, Fredrikson JP, *et al.* Granular Matrigel: restructuring a trusted extracellular matrix material for improved permeability. *Biomed Mater*. 2022;17(4).

doi: 10.1088/1748-605X/ac7306

23. Graham AJ, Khoo MWL, Srivastava V, *et al.* Stress-relaxing granular bioprinting materials enable complex and uniform organoid self-organization. *Nat Mater*. 2026;25(7):1239-1251.

doi: 10.1038/s41563-026-02519-4

24. Jin H, Xue Z, Liu J, Ma B, Yang J, Lei L. Advancing Organoid Engineering for Tissue Regeneration and Biofunctional Reconstruction. *Biomater Res*. 2024;28:0016.

doi: 10.34133/bmr.0016

25. Shao Y, Wang J, Jin A, Jiang S, Lei L, Liu L. Biomaterial-assisted organoid technology for disease modeling and drug screening. *Mater Today Bio*. 2025;30:101438.

doi: 10.1016/j.mtbio.2024.101438

26. Hsiung N, Ju Y, Yang K, *et al.* Organoid-based tissue

engineering for advanced tissue repair and reconstruction. *Mater Today Bio*. 2025;33:102093.

doi: 10.1016/j.mtbio.2025.102093

27. Du YA, Lo E, Ali S, Khademhosseini A. Directed assembly of cell-laden microgels for fabrication of 3D tissue constructs. *Proc Natl Acad Sci USA*. 2008;105(28):9522-9527.

doi: 10.1073/pnas.0801866105

28. Griffin DR, Weaver WM, Scumpia PO, Di Carlo D, Segura T. Accelerated wound healing by injectable microporous gel scaffolds assembled from annealed building blocks. *Nat Mater*. 2015;14(7):737-744.

doi: 10.1038/nmat4294

29. Mealy JE, Chung JJ, Jeong HH, *et al.* Injectable Granular Hydrogels with Multifunctional Properties for Biomedical Applications. *Adv Mater*. 2018;30(20):e1705912.

doi: 10.1002/adma.201705912

30. Daly AC, Riley L, Segura T, Burdick JA. Hydrogel microparticles for biomedical applications. *Nat Rev Mater*. 2020;5(1):20-43.

doi: 10.1038/s41578-019-0148-6

31. Asadikorayem M, Surman F, Weber P, Weber D, Zenobi-Wong M. Zwitterionic Granular Hydrogel for Cartilage Tissue Engineering. *Adv Healthc Mater*. 2024;13(25):e2301831.

doi: 10.1002/adhm.202301831

32. Tang G, Xiong R, Lv D, *et al.* Gas-Shearing Fabrication of Multicompartmental Microspheres: A One-Step and Oil-Free Approach. *Adv Sci*. 2019;6(9):1802342.

doi: 10.1002/advs.201802342

33. Ribezzi D, Gueye M, Florczak S, *et al.* Shaping Synthetic Multicellular and Complex Multimaterial Tissues via Embedded Extrusion-Volumetric Printing of Microgels. *Adv Mater*. 2023;35(36):e2301673.

doi: 10.1002/adma.202301673

34. Daly AC. Granular Hydrogels in Biofabrication: Recent Advances and Future Perspectives. *Adv Healthc Mater*. 2024;13(25):e2301388.

doi: 10.1002/adhm.202301388

35. Zhang S, Lin A, Tao Z, *et al.* Microsphere-containing hydrogel scaffolds for tissue engineering. *Chem Asian J*. 2022;17(20):e202200630.

doi: 10.1002/asia.202200630

36. Scalia S, Young PM, Traini D. Solid lipid microparticles as an approach to drug delivery. *Expert Opin Drug Delivery*. 2015;12(4):583-599.

doi: 10.1517/17425247.2015.980812

37. Liu Z, Xu Z, Wang X, *et al.* Preparation and biocompatibility of core-shell microspheres for sequential, sustained release of BMP-2 and VEGF. *Biomed Res Int*. 2022;2022:4072975.

doi: 10.1155/2022/4072975

38. Ding Z, Liang Z, Rong X, *et al.* Janus-Structured Microgel Barrier with Tissue Adhesive and Hemostatic Characteristics for Efficient Prevention of Postoperative Adhesion. *Small*. 2024;20(50):e2403753.

doi: 10.1002/smll.202403753

39. Wu J, Li G, Ye T, *et al.* Stem cell-laden injectable hydrogel microspheres for cancellous bone regeneration. *Chem Eng J*. 2020;393:124715.

doi: 10.1016/j.cej.2020.124715

40. Gegg C, Yang F. Spatially patterned microribbon-based hydrogels induce zonally-organized cartilage regeneration by stem cells in 3D. *Acta Biomater*. 2020;101:196-205.

doi: 10.1016/j.actbio.2019.10.025

41. Zhang X, Li Y, Ma Z, He D, Li H. Modulating degradation of sodium alginate/bioglass hydrogel for improving tissue infiltration and promoting wound healing. *Bioact Mater*. 2021;6(11):3692-3704.

doi: 10.1016/j.bioactmat.2021.03.038

42. Conrad B, Han LH, Yang F. Gelatin-based microribbon hydrogels accelerate cartilage formation by mesenchymal stem cells in three dimensions. *Tissue Eng Part A*. 2018;24(21-22):1631-1640.

doi: 10.1089/ten.TEA.2018.0011

43. Wu MM, Zhao Y, Zhao RQ, *et al.* Chemical Design for Both Molecular and Morphology Optimization toward High-Performance Lithium-Ion Batteries Cathode Material Based on Covalent Organic Framework. *Adv Funct Mater*. 2022;32(11).

doi: 10.1002/adfm.202107703

44. Kessel B, Lee M, Bonato A, Tinguely Y, Tosoratti E, Zenobi-Wong M. 3D bioprinting of macroporous materials based on entangled hydrogel microstrands. *Adv Sci (Weinh)*. 2020;7(18):2001419.

doi: 10.1002/advs.202001419

45. Headen DM, Aubry G, Lu H, García AJ. Microfluidic-based generation of size-controlled, biofunctionalized synthetic polymer microgels for cell encapsulation. *Adv Mater*. 2014;26(19):3003-3008.

doi: 10.1002/adma.201304880

46. Xin S, Chimene D, Garza JE, Gaharwar AK, Alge DL. Clickable PEG hydrogel microspheres as building blocks for 3D bioprinting. *Biomater Sci*. 2019;7(3):1179-1187.

doi: 10.1039/c8bm01286e

47. Barati D, Watkins K, Wang Z, Yang F. Injectable and Crosslinkable PLGA-Based Microribbons as 3D Macroporous Stem Cell Niche. *Small*. 2020;16(22):e1905820.

doi: 10.1002/smll.201905820

48. Munger C, Kohler TN, Slatery E, *et al.* Microgel culture

and spatial identity mapping elucidate the signalling requirements for primate epiblast and amnion formation. *Development*. 2022;149(20):dev200263.

doi: 10.1242/dev.200263

49. Liu H, Tao T, Gan Z, *et al.* Organoid in droplet: Production of uniform pancreatic cancer organoids from single cells. *Mater Today Bio*. 2025;32:101765.

doi: 10.1016/j.mtbio.2025.101765

50. Qin X, Gan Z, Liu H, *et al.* A Pump-Free Strategy for the Controllable Generation of Alginate Microgels as Cellular Microcarriers. *ACS Biomater Sci Eng*. 2024;10(6):3958-3967.

doi: 10.1021/acsbiomaterials.4c00375

51. Rosas JM, Campanale JP, Harwood JL, *et al.* Differential Effects of Confinement on the Dynamics of Normal and Tumor-Derived Pancreatic Ductal Organoids. *ACS Appl Bio Mater*. 2024;7(12):8489-8502.

doi: 10.1021/acsabm.4c01301

52. Xu X, Li H, Chen J, *et al.* A Universal Strategy to Construct High-Performance Homo- and Heterogeneous Microgel Assembly Bioinks. *Small Methods*. 2024;8(12):e2400223.

doi: 10.1002/smtd.202400223

53. Roth JG, Brunel LG, Huang MS, *et al.* Spatially controlled construction of assembloids using bioprinting. *Nat Commun*. 2023;14(1):4346.

doi: 10.1038/s41467-023-40006-5

54. Ayan B, Heo DN, Zhang Z, *et al.* Aspiration-assisted bioprinting for precise positioning of biologics. *Sci Adv*. 2020;6(10):eaaw5111.

doi: 10.1126/sciadv.aaw5111

55. Kühn S, Magno V, Zimmermann R, *et al.* Microgels With Electrostatically Controlled Molecular Affinity to Direct Morphogenesis. *Adv Mater*. 2025;37(3):e2409731.

doi: 10.1002/adma.202409731

56. Birgul Akolpoglu M, Inceoglu Y, Kizilel S. An all-aqueous approach for physical immobilization of PEG-lipid microgels on organoid surfaces. *Colloids Surf B Biointerfaces*. 2020;186:110708.

doi: 10.1016/j.colsurfb.2019.110708

57. Chen J, Liu Z, Wang Z, *et al.* One-step biofabrication of liquid core-GelMa shell microbeads for in situ hollow cell ball self-assembly. *Regen Biomater*. 2024;11:rbae021.

doi: 10.1093/rb/rbae021

58. Zhang X, Wang Z, Chen J, Xu T. A high-throughput microfluidic platform for functional hiPSC-derived liver organoids with bile duct- and lobule-like structures. *Lab Chip*. 2025;25(10):2475-2490.

doi: 10.1039/d5lc00154d

59. Joshi S, Maan M, Barman P, *et al.* Advances in biomaterials for wound care management: Insights from recent developments. *Adv Colloid Interface Sci*. 2025;343:103563.

doi: 10.1016/j.cis.2025.103563

60. Chaudhuri O, Cooper-White J, Janmey PA, Mooney DJ, Shenoy VB. Effects of extracellular matrix viscoelasticity on cellular behaviour. *Nature*. 2020;584(7822):535-546.

doi: 10.1038/s41586-020-2612-2

61. Yang X, Xu Y, Zhu D, Mi X. GelMA Core-Shell Microgel Preparation Based on a Droplet Microfluidic Device for Three-Dimensional Tumor Ball Culture and Its Drug Testing. *Molecules*. 2025;30(15):3305.

doi: 10.3390/molecules30153305

62. Huch M, Dorrell C, Boj SF, *et al.* In vitro expansion of single Lgr5+ liver stem cells induced by Wnt-driven regeneration. *Nature*. 2013;494(7436):247-250.

doi: 10.1038/nature11826

63. Han K, Cheng Y, Han Q, Chen J. Extraction of type I collagen and development of collagen methacryloyl (ColMA)/PEGDA ink for digital light processing printing. *Int J Biol Macromol*. 2024;282(Pt 6):137253.

doi: 10.1016/j.ijbiomac.2024.137253

64. Fredrikson JP, Roth DM, Cosgrove JA, *et al.* Engineering neuronal networks in granular microgels to innervate bioprinted cancer organoids on-a-chip. *Lab Chip*. 2025;25(14):3467-3481.

doi: 10.1039/d5lc00134j

65. Zhang T, Zhang H, Zhou W, *et al.* One-Step Generation and Purification of Cell-Encapsulated Hydrogel Microsphere With an Easily Assembled Microfluidic Device. *Front Bioeng Biotechnol*. 2021;9:816089.

doi: 10.3389/fbioe.2021.816089

66. Pittermannová A, Ruberová Z, Lizoňová D, *et al.* Functionalized hydrogel microparticles prepared by microfluidics and their interaction with tumour marker carbonic anhydrase IX. *Soft matter*. 2020;16(37):8702-8709.

doi: 10.1039/d0sm01018a

67. Tan S, Zhong C, Langrish T. Microencapsulation of pepsin in the spray-dried WPI (whey protein isolates) matrices for controlled release. *J Food Eng*. 2019;263:147-154.

doi: 10.1016/j.jfoodeng.2019.06.005

68. Lee KY, Mooney DJ. Alginate: properties and biomedical applications. *Prog Polym Sci*. 2012;37(1):106-126.

doi: 10.1016/j.progpolymsci.2011.06.003

69. Yue K, Trujillo-de Santiago G, Alvarez MM, Tamayol A, Annabi N, Khademhosseini A. Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. *Biomaterials*. 2015;73:254-271.

doi: 10.1016/j.biomaterials.2015.08.045

70. Cho AN, Jin Y, An Y, *et al.* Microfluidic device with brain extracellular matrix promotes structural and functional

maturation of human brain organoids. *Nat Commun*. 2021;12(1):4730.

doi: 10.1038/s41467-021-24775-5

71. Giobbe GG, Crowley C, Luni C, *et al.* Extracellular matrix hydrogel derived from decellularized tissues enables endodermal organoid culture. *Nat Commun*. 2019;10(1):5658.

doi: 10.1038/s41467-019-13605-4

72. Shen C, Wang J, Li G, *et al.* Boosting cartilage repair with silk fibroin-DNA hydrogel-based cartilage organoid precursor. *Bioact Mater*. 2024;35:429-444.

doi: 10.1016/j.bioactmat.2024.02.016

73. Deng A, Zhang H, Hu Y, *et al.* Microsphere Strategy to Generate Conformal Bone Organoid Units with Osteoimmunomodulation and Sustainable Oxygen Supply for Bone Regeneration. *Adv Sci (Weinh)*. 2025;12(32):e01437.

doi: 10.1002/advs.202501437

74. Feng Q, Li D, Li Q, Cao X, Dong H. Microgel assembly: Fabrication, characteristics and application in tissue engineering and regenerative medicine. *Bioact Mater*. 2022;9:105-119.

doi: 10.1016/j.bioactmat.2021.07.020

75. Luo Y, Wang Q. Recent development of chitosan-based polyelectrolyte complexes with natural polysaccharides for drug delivery. *Int J Biol Macromol*. 2014;64:353-367.

doi: 10.1016/j.ijbiomac.2013.12.017

76. Highley CB, Song KH, Daly AC, Burdick JA. Jammed microgel inks for 3D printing applications. *Adv Sci (Weinh)*. 2019;6(1):1801076.

doi: 10.1002/advs.201801076

77. Muir VG, Qazi TH, Shan J, Groll J, Burdick JA. Influence of microgel fabrication technique on granular hydrogel properties. *ACS Biomater Sci Eng*. 2021;7(9):4269-4281.

doi: 10.1021/acsbiomaterials.0c01612

78. Liu T, Huang X, Luo C, Wang D. The formation mechanism of the double gas layer in gas-assisted extrusion and its influence on plastic micro-tube formation. *Polymers (Basel)*. 2020;12(2):355.

doi: 10.3390/polym12020355

79. Kubota T, Kurashina Y, Zhao J, Ando K, Onoe H. Ultrasound-triggered on-demand drug delivery using hydrogel microbeads with release enhancer. *Mater Des*. 2021;203:109580.

doi: 10.1016/j.matdes.2021.109580

80. Umbanhowar PB, Prasad V, Weitz DA. Monodisperse emulsion generation via drop break off in a coflowing stream. *Langmuir ACS J Surf Colloids*. 2000;16(2):347-351.

doi: 10.1021/la990101e

81. Alzanbaki H, Moretti M, Hauser CAE. Engineered microgels-their manufacturing and biomedical applications. *Micromachines (Basel)*. 2021;12(1):45.

doi: 10.3390/mi12010045

82. Darling NJ, Sideris E, Hamada N, Carmichael ST, Segura T. Injectable and spatially patterned microporous annealed particle (MAP) hydrogels for tissue repair applications. *Adv Sci (Weinh)*. 2018;5(11):1801046.

doi: 10.1002/advs.201801046

83. Toprakcioglu Z, Challa PK, Morse DB, Knowles T. Attoliter protein nanogels from droplet nanofluidics for intracellular delivery. *Sci Adv*. 2020;6(6):eaay7952.

doi: 10.1126/sciadv.aay7952

84. Naqvi SM, Vedicherla S, Gansau J, McIntyre T, Doherty M, Buckley CT. Living cell factories - electrosprayed microcapsules and microcarriers for minimally invasive delivery. *Adv Mater*. 2016;28(27):5662-5671.

doi: 10.1002/adma.201503598

85. Lüken A, Stüwe L, Rauer SB, Oelker J, Linkhorst J, Wessling M. Fabrication, Flow Assembly, and Permeation of Microscopic Any-Shape Particles. *Small*. 2022;18(15):e2107508.

doi: 10.1002/smll.202107508

86. Xie J, Marijnissen JCM, Wang CH. Microparticles developed by electrohydrodynamic atomization for the local delivery of anticancer drug to treat C6 glioma in vitro. *Biomaterials*. 2006;27(17):3321-3332.

doi: 10.1016/j.biomaterials.2006.01.034

87. Qayyum AS, Jain E, Kolar G, Kim Y, Sell SA, Zustiak SP. Design of electrohydrodynamic sprayed polyethylene glycol hydrogel microspheres for cell encapsulation. *Biofabrication*. 2017;9(2):025019.

doi: 10.1088/1758-5090/aa703c

88. Gansau J, Kelly L, Buckley CT. Influence of key processing parameters and seeding density effects of microencapsulated chondrocytes fabricated using electrohydrodynamic spraying. *Biofabrication*. 2018;10(3):035011.

doi: 10.1088/1758-5090/aacb95

89. Wang H, Zhao Z, Liu Y, Shao C, Bian F, Zhao Y. Biomimetic enzyme cascade reaction system in microfluidic electrospray microcapsules. *Sci Adv*. 2018;4(6):eaat2816.

doi: 10.1126/sciadv.aat2816

90. John JV, McCarthy A, Wang H, *et al.* Engineering biomimetic nanofiber microspheres with tailored size, predesigned structure, and desired composition via gas bubble-mediated coaxial electrospray. *Small*. 2020;16(19):e1907393.

doi: 10.1002/smll.201907393

91. Song T, Zhang H, Luo Z, Shang L, Zhao Y. Primary human pancreatic cancer cells cultivation in microfluidic hydrogel microcapsules for drug evaluation. *Adv Sci (Weinh)*. 2023;10(12):e2206004.

doi: 10.1002/advs.202206004

92. Sun LL, Li TB, Zhang BJ, Zhang M, Xu J, Wang JY. An off-the-shelf microfluidic device for the controllable fabrication of multiple-holed hollow particles and their cell culture applications. *Mater Chem Front.* 2021;5(7):3149-3158.

doi: 10.1039/d0qm01014f

93. Qazi TH, Wu JY, Muir VG, *et al.* Anisotropic Rod-Shaped Particles Influence Injectable Granular Hydrogel Properties and Cell Invasion. *Adv Mater.* 2022;34(12).

doi: 10.1002/adma.202109194

94. Park SY, Lee S, Yang J, Kang MS. Patterning Quantum Dots via Photolithography: A Review. *Adv Mater.* 2023;35(41):2300546.

doi: 10.1002/adma.202300546

95. Martino C, Vigolo D, Solvas XCI, Stavrakis S, deMello AJ. Real-Time PEGDA-Based Microgel Generation and Encapsulation in Microdroplets. *Adv Mater Technol.* 2016;1(2).

doi: 10.1002/admt.201600028

96. Stornello DE, Kim J, Chen Z, Heaton K, Qazi TH. Controlling microparticle aspect ratio via photolithography for injectable granular hydrogel formation and cell delivery. *ACS Biomater Sci Eng.* 2025;11(2):1242-1252.

doi: 10.1021/acsbiomaterials.4c02102

97. Sadeghi D, Solouk A, Samadikuchaksaraei A, Seifalian AM. Preparation of internally-crosslinked alginate microspheres: Optimization of process parameters and study of pH-responsive behaviors. *Carbohydr Polym.* 2021;255:117336.

doi: 10.1016/j.carbpol.2020.117336

98. Zarzar LD, Sresht V, Sletten EM, Kalow JA, Blankschtein D, Swager TM. Dynamically reconfigurable complex emulsions via tunable interfacial tensions. *Nature.* 2015;518(7540):520-524.

doi: 10.1038/nature14168

99. Miras J, Vílchez S, Bouju C, *et al.* Formation of water-in-water emulsions and microgels in nonionic surfactant + gelatin aqueous mixtures. *J Colloid Interface Sci.* 2025;684(Pt 1):319-330.

doi: 10.1016/j.jcis.2024.12.240

100. Pan Z, Bui L, Yadav V, Fan F, Chang HC, Hanjaya-Putra D. Conformal single cell hydrogel coating with electrically induced tip streaming of an AC cone. *Biomater Sci.* 2021;9(9):3284-3292.

doi: 10.1039/d0bm02100h

101. Jaberi A, Kedzierski A, Kheirabadi S, *et al.* Engineering microgel packing to tailor the physical and biological properties of gelatin methacryloyl granular hydrogel scaffolds. *Adv Healthcare Mater.* 2024;13(25):e2402489.

doi: 10.1002/adhm.202402489

102. Wang Z, Xiang L, Lin F, Tang Y, Cui W. 3D bioprinting of emulating homeostasis regulation for regenerative medicine applications. *J Control Release.* 2023;353:147-165.

doi: 10.1016/j.jconrel.2022.11.035

103. Wang X, Liu X, Li K, *et al.* A Microgel-Hydrogel Hybrid for Functional Compensation and Mechanical Stability in 3D Printed Cell-Dense Vascularized Liver Tissue. *Adv Mater.* 2025;37(28):e2413940.

doi: 10.1002/adma.202413940

104. Flégeau K, Puiggali-Jou A, Zenobi-Wong M. Cartilage tissue engineering by extrusion bioprinting utilizing porous hyaluronic acid microgel bioinks. *Biofabrication.* 2022;14(3).

doi: 10.1088/1758-5090/ac6b58

105. Xie C, Liang R, Ye J, *et al.* High-efficient engineering of osteo-callus organoids for rapid bone regeneration within one month. *Biomaterials.* 2022;288:121741.

doi: 10.1016/j.biomaterials.2022.121741

106. Zhao H, Chen Y, Shao L, *et al.* Airflow-assisted 3D bioprinting of human heterogeneous microspheroidal organoids with microfluidic nozzle. *Small.* 2018;14(39):e1802630.

doi: 10.1002/smll.201802630

107. Bernal PN, Bouwmeester M, Madrid-Wolff J, *et al.* Volumetric bioprinting of organoids and optically tuned hydrogels to build liver-like metabolic biofactories. *Adv Mater.* 2022;34(15):e2110054.

doi: 10.1002/adma.202110054

108. Muir VG, Prendergast ME, Burdick JA. Fragmenting Bulk Hydrogels and Processing into Granular Hydrogels for Biomedical Applications. *Jove-J Vis Exp.* 2022;(183).

doi: 10.3791/63867

109. Sinclair A, O'Kelly MB, Bai T, Hung HC, Jain P, Jiang S. Self-healing zwitterionic microgels as a versatile platform for malleable cell constructs and injectable therapies. *Adv Mater.* 2018;30(39):e1803087.

doi: 10.1002/adma.201803087

110. Caldwell AS, Campbell GT, Shekiro KMT, Anseth KS. Clickable microgel scaffolds as platforms for 3D cell encapsulation. *Adv Healthcare Mater.* 2017;6(15):1700254.

doi: 10.1002/adhm.201700254

111. Guo J, Zhou Q, Liu YC, *et al.* Preparation of soy protein-based microgel particles using a hydrogel homogenizing strategy and their interfacial properties. *Food Hydrocoll.* 2016;58:324-334.

doi: 10.1016/j.foodhyd.2016.03.008

112. Sarkar A, Murray B, Holmes M, Ettelaie R, Abdalla A, Yang X. In vitro digestion of pickering emulsions stabilized by soft whey protein microgel particles: Influence of thermal treatment. *Soft Matter.* 2016;12(15):3558-3569.

doi: 10.1039/c5sm02998h

113. Zhang B, Wei B, Hu X, Jin Z, Xu X, Tian Y. Preparation and characterization of carboxymethyl starch microgel with different crosslinking densities. *Carbohydr Polym*. 2015;124:245-253.

doi: 10.1016/j.carbpol.2015.01.075

114. Cui Z, Wang W, Obeng M, *et al.* Using intra-microgel crosslinking to control the mechanical properties of doubly crosslinked microgels. *Soft Matter*. 2016;12(33):6985-6994.

doi: 10.1039/c6sm01337f

115. Lavickova B, Kronabitter H, Cervera-Negueruela M, *et al.* Integrated Microfluidic Platform for High-Throughput Generation of Intestinal Organoids in Hydrogel Droplets. *Adv Sci (Weinh)*. 2026;13(13):e16507.

doi: 10.1002/advs.202516507

116. Pal V, Singh YP, Gupta D, *et al.* High-throughput microgel biofabrication via air-assisted co-axial jetting for cell encapsulation, 3D bioprinting, and scaffolding applications. *Biofabrication*. 2023;15(3):035001.

doi: 10.1088/1758-5090/acc4eb

117. Panda P, Ali S, Lo E, *et al.* Stop-flow lithography to generate cell-laden microgel particles. *Lab Chip*. 2008;8(7):1056-1061.

doi: 10.1039/b804234a

118. Kang SM, Lee GW, Huh YS. Centrifugal Force-Driven Modular Micronozzle System: Generation of Engineered Alginate Microspheres. *Sci Rep*. 2019;9(1):12776.

doi: 10.1038/s41598-019-49244-4

119. Wu J, Chen L, Xiao C, *et al.* Scalable and oil-free fabrication of monodisperse microgels via all-aqueous microfluidics. *Cell Rep Phys Sci.* 2026;7(4):103253.

doi: 10.1016/j.xcrp.2026.103253

120. An C, Zhou R, Zhang H, *et al.* Microfluidic-templated cell-laden microgels fabricated using phototriggered imine-crosslinking as injectable and adaptable granular gels for bone regeneration. *Acta Biomater*. 2023;157:91-107.

doi: 10.1016/j.actbio.2022.11.034

121. Bhatt A, Dhiman N, Giri PS, Kasinathan GN, Pati F, Rath SN. Biocompatibility-on-a-chip: Characterization and evaluation of decellularized tendon extracellular matrix (tdECM) hydrogel for 3D stem cell culture in a microfluidic device. *Int J Biol Macromol*. 2022;213:768-779.

doi: 10.1016/j.ijbiomac.2022.06.010

122. Ali-Jerman H, Al-Quraishi Z, Muglikar A, *et al.* Enhancing transfection efficacy in glioma cells: A comparison of microfluidic versus manual polypropylenimine dendriplex formation. *Int J Nanomed*. 2024;19:12189-12203.

doi: 10.2147/IJN.S490936

123. Ferrante M, Gallo MB, Gende LB, Consolo VF, Álvarez VA, González JS. Synthesis and characterization of gelatin/chondroitin sulfate microgels with NaCl: Preliminary research toward wound healing applications. *Int J Biol Macromol*. 2025;290:138953.

doi: 10.1016/j.ijbiomac.2024.138953

124. Reineke B, Paulus I, Löffelsend S, *et al.* On-chip fabrication and in-flow 3D-printing of microgel constructs: from chip to scaffold materials in one integral process. *Biofabrication*. 2024;16(2):025038.

doi: 10.1088/1758-5090/ad3318

125. Schlosser CS, Morris CJ, Brocchini S, Williams GR. Hydrophobic ion pairing as a novel approach to co-axial electrospraying of peptide-PLGA particles. *Int J Pharm*. 2024;667(Pt B):124885.

doi: 10.1016/j.ijpharm.2024.124885

126. Sun Z, Zhou J, Sheng L, *et al.* Microfluidic engineering of microgels: Fabrication methods, structural design, assembly strategies, and biomedical applications. *Acta Biomater*. 2025;207:142-173.

doi: 10.1016/j.actbio.2025.10.017

127. Del Giudice F, Curtis DJ, Aufderhorst-Roberts A. A new approach for on-chip production of biological microgels using photochemical cross-linking. *Anal Chem*. 2024;96(25):10140-10144.

doi: 10.1021/acs.analchem.4c01574

128. Li Y, Chen R. Photolithographic patterning of organic semiconductors for organic field-effect transistors. *Chem Rev*. 2025;125(10):4933-4973.

doi: 10.1021/acs.chemrev.4c00446

129. Ling SD, Liu Z, Ma W, Chen Z, Du Y, Xu J. A novel step-T-junction microchannel for the cell encapsulation in monodisperse alginate-gelatin microspheres of varying mechanical properties at high throughput. *Biosensors*. 2022;12(8):659.

doi: 10.3390/bios12080659

130. Buritica S, Gutteriez J, Lapeyre V, *et al.* Inter cross-linking microgels by superchaotropic nano-ions at interface: Controlled stabilization of emulsions. *J Colloid Interface Sci*. 2025;699(Pt 2):138257.

doi: 10.1016/j.jcis.2025.138257

131. Jiang W, Wang J, Yuan D, *et al.* Fabrication, characterization and emulsifying properties of agarose microgel. *Int J Biol Macromol*. 2023;241:124565.

doi: 10.1016/j.ijbiomac.2023.124565

132. Wang K, Lan X, Chen J, *et al.* One-Step Coaxial 3D Printing of Pre-Vascularized Skin Organoid Models with ADSC Microspheres for Enhanced Wound Healing. *Adv Sci (Weinh)*. 2026;13(9):e17409.

doi: 10.1002/advs.202517409

133. Kim W, Gwon Y, Park S, Kim H, Kim J. Therapeutic strategies of three-dimensional stem cell spheroids and organoids for tissue repair and regeneration. *Bioact Mater.* 2023;19:50-74.

doi: 10.1016/j.bioactmat.2022.03.039

134. Fumadó Navarro J, Crilly S, Chan WK, *et al.* Cerebral Organoids with Integrated Endothelial Networks Emulate the Neurovascular Unit and Mitigate Core Necrosis. *Adv Sci.* 2025;12(43):e07256.

doi: 10.1002/advs.202507256

135. Abeta S, Masuda A, Hioki A, Hirayama-Shoji K, Onoe H. Cell-Encapsulating Hollow Collagen Microgel Beads for the Construction of Hollow Organ Tissue Model in Vitro. *Annu Int Conf IEEE Eng Med Biol Soc*. 2025;2025:1-4.

doi: 10.1109/EMBC58623.2025.11253712

136. Ju J, Fang H, Jie J, *et al.* Modular living assembly of bone organoids with in situ guided vascularization. *Bioact Mater*. 2026;64:510-528.

doi: 10.1016/j.bioactmat.2026.04.020

137. Zhu M, Zhang H, Zhou Q, *et al.* Dynamic GelMA/DNA Dual-Network Hydrogels Promote Woven Bone Organoid Formation and Enhance Bone Regeneration. *Adv Mater*. 2025;37(24):e2501254.

doi: 10.1002/adma.202501254

138. Shen CY, Zhou QR, Wu X, *et al.* Accelerating cartilage regeneration with DNA-SF hydrogel sustained release system-based cartilage organoids. *Military Med Res*. 2025;12(1):39.

doi: 10.1186/s40779-025-00625-z

139. Lee SJ, Jeon O, Lee YB, *et al.* In situ cell condensation-based cartilage tissue engineering via immediately implantable high-density stem cell core and rapidly degradable shell microgels. *Adv Compos Hybrid Mater*. 2025;8(4):330.

doi: 10.1007/s42114-025-01406-x

140. Lin Z, Li Q, Han X, *et al.* An injectable and degradable heterogeneous microgel assembly capable of forming a “micro-nest group” for cell condensation and cartilage regeneration. *Mater Horiz*. 2024;11(21):5438-5450.

doi: 10.1039/D4MH00724G

141. Gao Y, Li Q, Du Z, *et al.* HAMA-SBMA hydrogel with anti-inflammatory properties delivers cartilage organoids, boosting cartilage regeneration. *J Nanobiotechnol*. 2025;23(1):401.

doi: 10.1186/s12951-025-03475-y

142. Xiong M, Yang X, Shi Z, *et al.* Programmable Artificial Skins Accomplish Antiscar Healing with Multiple Appendage Regeneration. *Adv Mater.* 2024;36(50):2407322.

doi: 10.1002/adma.202407322

143. Xie J, Yang Q, Zhang Y, Zheng K, Geng H, Wu Y. The Bioengineering of Microspheric Skin Organoids and Their Application in Drug Screening. *Adv Sci*. 2025;12(22):2416863.

doi: 10.1002/advs.202416863

144. Kim S, Yeop Baek S, Cha C. Bioactive Microgels with Tunable Microenvironment as a 3D Platform to Guide the Complex Physiology of Hepatocellular Carcinoma Spheroids. *ChemBioChem*. 2024;25(23):e202400482.

doi: 10.1002/cbic.202400482

145. Song H, Jiang H, Hu W, *et al.* Cervical extracellular matrix hydrogel optimizes tumor heterogeneity of cervical squamous cell carcinoma organoids. *Sci Adv*. 2024;10(20):eadl3511.

doi: 10.1126/sciadv.adl3511

146. Wang L, Riediger L, Rao Q, *et al.* Tunable Synthetic Hydrogel Modulates Hepatic Lineage Specification of Human Liver Organoid. *Adv Funct Mater.* 2026;36(7):e08430.

doi: 10.1002/adfm.202508430

147. Gnecco JS, Brown A, Buttrey K, *et al.* Organoid co-culture model of the human endometrium in a fully synthetic extracellular matrix enables the study of epithelial-stromal crosstalk. *Med*. 2023;4(8):554-579.e9.

doi: 10.1016/j.medj.2023.07.004

148. Andersson-Rolf A, Clevers H. New developments and applications of human organoids. *Nat Rev Mol Cell Biol.* 2026;27(7):543-558.

doi: 10.1038/s41580-026-00974-0

149. Wang D, Villenave R, Stokar-Regenscheit N, Clevers H. Human organoids as 3D in vitro platforms for drug discovery: opportunities and challenges. *Nat Rev Drug Discov*. 2026;25(3):204-226.

doi: 10.1038/s41573-025-01317-y

150. Sljukic A, Green Jenkinson J, Niksic A, Prior N, Huch M. Advances in liver and pancreas organoids: how far we have come and where we go next. *Nat Rev Gastroenterol Hepatol.* 2026;23(1):44-64.

doi: 10.1038/s41575-025-01116-1

151. Hushka EA, Blatchley MR, Macdougall LJ, *et al.* Fully Synthetic Hydrogels Promote Robust Crypt Formation in Intestinal Organoids. *Adv Mater*. 2025;37(43):e09672.

doi: 10.1002/adma.202509672