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Microgels and Granular Gels: From Injectable Scaffolds and Bioinks to 3D Printing Supports

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Editorial

Microgel technology has emerged as a powerful and versatile tool for regenerative medicine and tissue engineering applications[1]. Just like their bulk counterparts, microgels are characterized by high water content, tunable physicochemical properties, and mimicry of the native extracellular environment. Owing to the advances in fabrication techniques, microgels can be produced in different shapes and sizes from a range of natural and synthetic polymers. They can also be utilized for controlled encapsulation of cells and therapeutics. One of the main advantages of microgels in comparison to traditional bulk hydrogels is that they are readily injectable thus allowing minimally invasive delivery of cellular cargo, drugs, or biological scaffolding for tissue repair. Furthermore, modular microgel systems are easily attainable by mixing microgel populations with distinct properties, while embedding microgels in conventional hydrogels provides a route toward soft matter composites. When many microgels are packed into a jammed state, they give rise to granular gels, bulk materials with dynamic macroscale properties that can be leveraged either as a support bath for embedded three-dimensional (3D) printing or as 3D printing inks. This collection of articles explores a wide range of methods for microgel formulation and fabrication, as well as their utilization for potential biomedical applications.

Cost-effective, emulsion-free, and technologically nondemanding approaches for the generation of microgels in large quantities are much needed. To address this, Muir et al. demonstrated an elegant protocol for the generation of norbornene-modified hyaluronic acid (HA) microgels via extrusion fragmentation[2]. Photo-crosslinked bulk hydrogels were extruded through a series of needles with sequentially smaller diameters. The resulting fragmented microgel particles were then jammed by vacuum-driven filtration to form a tightly packed granular hydrogel that can be used as an ink for extrusion-based 3D printing. Stager et al. presented another fragmentation approach where a crosslinked chitosan hydrogel was extruded through a mesh filter to generate microgel particles with controlled size[3]. Fragmented hydrogels were then shown to promote cartilage tissue regeneration when employed in a growth plate injury rat model.

Interlinking jammed microgel particles together gives rise to annealed granular hydrogels and porous bulk

scaffolds with unique microarchitectures. Anderson et al. provided a protocol for the microfluidic-based generation of photocrosslinkable HA microgels that are subsequently freeze-dried without damage to the polymer network[4]. Controlled rehydration of the lyophilized microgels and subsequent interlinking via a biorthogonal crosslinking scheme leads to the formation of porous HA scaffolds with controlled particle fraction, demonstrated by the authors to significantly influence cell infiltration and migration. Roosa et al. described a method for high throughput microfluidic synthesis of large volumes of polyethylene glycol (PEG) microgels[5]. The authors then demonstrate approaches for microgel purification, basic microparticle characterization, and particle annealing based on a secondary crosslinking mechanism to form a microporous scaffold. Rommel et al. showcased an approach for generating annealed scaffolds with increased porosity by utilizing anisotropic microgel particles[6]. They took advantage of the flow-focusing microfluidics to create microgel rods from star-PEG polymers with controllable aspect ratios. Annealed microgel rod scaffolds can be used as a 3D environment for cell experiments. Luo et al. demonstrated a method for the generation of highly open porous microspheres via a simple microfluidic approach that could be used for the delivery of cells or biologics[7].

The unique rheological properties of granular gels make them ideal supports for embedded 3D printing of soft hydrogels and cells[8]. Machour et al. combined an approach for embedded 3D printing inside gelatin granular gels with sacrificial mold-based 3D printing to create engineered tissue flaps[9]. This hybrid method was leveraged to create a hierarchical vascular network from collagen-based ink mixed with endothelial cells. The engineered flap was then directly implanted into a rat femoral artery. Jalandhra et al. demonstrated an approach for the creation of bone-mimicking constructs via embedded 3D printing of a calcium phosphate-based ceramic ink inside cell-laden granular gel made from gelatin methacrylate (GelMA) microgels[10]. The granular support was annealed post-printing to give support to cell growth around the engineered bone-mimicking structures. Kajtez et al. employed embedded 3D printing to create human stem cell-based neural tissue constructs[11]. They developed a composite printing support material that combines alginate microgels and collagen-based extracellular matrix solution. Gentle crosslinking of collagen anneals the printing support to provide a favorable environment for the differentiation of neural stem cells into functional neurons. Senior et al. took advantage of shear processing during gelation approach to generate an agarose-based support bath for embedded 3D printing[12]. The thermal properties of agarose make it possible for printed cell-laden hydrogel constructs to be cultured without melting the support bath.

Jammed microgel inks present a route for controllable 3D printing of possibly any hydrogel otherwise challenging to print due to its low viscosity or difficult-to-control crosslinking dynamics[13]. As microgel inks, hydrogels can be printed in a traditional layer-by-layer manner or in a suspension bath. They can also accommodate cells to form granular bioinks. As such, granular bioinks provide a solution for the bioprinting of materials not compatible with traditional methods that might require additives or crosslinking conditions harmful to cells. Zaman et al. provide a method that further enhances the printability of these inks by programming GelMA hydrogels with reversible interfacial nanoparticle self-assembly[14]. Due to altered interparticle interactions, the resulting nanoengineered granular bioinks can be printed at lower packing density which allows for the formulation of granular bioinks with increased microporosity well-preserved

throughout the printing process. Furthermore, the authors describe a methodology for high-throughput microfluidic hydrogel microparticle generation, conversion to micro-aerogels, and granular ink annealing using transglutaminase.

In summary, this collection of articles provides detailed practical guidance for a wide range of applications of microgel technology. The collection not only describes the use of different hydrogel materials and crosslinking mechanisms but also presents several fabrication techniques for hydrogel microparticle generation. Most importantly, the collection provides useful information on how to employ hydrogel microparticles for 3D printing and regenerative medicine, highly promising applications of microgel and granular gel technologies.

Disclosures

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