MINI-REVIEW

Granular hydrogels for 3D bioprinting applications

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Abstract
Granular hydrogels are the conglomerations of micrometer-sized hydrogel particles that have recently become promising in tissue growth and three-dimensional (3D) bioprinting. Recent advances in the use of jamming transition of granular hydrogels represent a potential paradigm shift in the extrusion-based 3D bioprinting. These dynamic granular hydrogels are shear thinning and self-healing, enable higher printing performance, and the creation of better physiological conditions for heterocellular constructs. Here, we review the current efforts to explore materials to produce granular hydrogels with novel functional properties, focusing on the granular hydrogels that can be used for supporting baths and bioinks in the extrusion-based 3D bioprinting. The recent advances, benefits, and challenges in this emerging area are highlighted.

KEYWORDS
3D printing, bioinks, extrusion-based 3D bioprinting, granular hydrogels, self-healing, shear-thinning

1 | INTRODUCTION

The motivation and the demand for building living tissues or organs lead to loads of technology innovations in biomedical engineering.1-3 As a cellular-assembly method, three-dimensional (3D) bioprinting has been extensively used in the fabrication of cell-laden 3D scaffolds to replicate the tissue architectures.4-9 The principle of the 3D bioprinting can be defined as the placement of living cells within biomaterials into preprogrammed structures and geometries using automated fabrication processes.4 The earliest work of the 3D bioprinting was initiated by Kelbe in 1988, who demonstrated the precise deposition of cells on a substrate using an inkjet printer or a graphics plotter.10 As more research groups and industry bodies joined, 3D bioprinting is expanding at a rapid rate to the fields of tissue engineering and regenerative medicine, transplantation, drug testing and high-throughput screening, and cancer research.11

Current 3D bioprinting technologies for fabricating of artificial tissues or organs that mimic their native prototypes include droplet-based, extrusion-based, laser-induced forward transfer, and stereolithography bioprinting.12 Among them, extrusion-based 3D
bioprinting has been the most preferred one due to its ease of use, compatible with a great variety of cells, wide adoption of already established materials, precision manipulation of bioinks, and flexibility printing of complex geometries.\(^{13-16}\) During this bioprinting process, it extrudes inks to form continuous building blocks for fabricating constructs, which requires a delicate balance between ink solidification rates and deposition rates so that achieving intricate structures and excellent performance. The preventing printed material from changing shape after placement is a critical challenge that can affect extrusion-based 3D printing. To address it, many hydrogel bioinks have been developed with specific characteristics, either in the form of liquid precursors or as solid-gel materials.\(^{17-20}\) The hydrogel materials offer a highly hydrated environment that is biocompatible to the encapsulated cells and usually provide shape retention to maintain the form of the bioprinted constructs. The liquid precursors should be able to transit into a solid status immediately after extrusion, and this usually archived by fast gelation under polymerization or phase change.\(^{21,22}\) The preformed solid-gel materials should exhibit shear-thinning properties, which experiences a transition from solid to fluidic states under applied stress, allowing them to be positioned in space against physical spreading.\(^{23,24}\) However, either fast gelation or increased extrusion pressures might reduce the cell viability and can also impact on cellular phenotype, as the cells require softer substrates for survival.

Recently, granular hydrogels have emerged as a powerful platform for the 3D bioprinting, due to the dynamic structures, unique shear-thinning, and self-healing properties.\(^{25-27}\) They inherently behave as a solid to liquid transitions under the changing of the jamming and unjamming status. The shear-thinning property is originated predominately from the physical interactions between the hydrogel particles, which should expand the variety of cells and materials that are suitable for extrusion-based 3D printing. In this Minireview, we briefly introduce the jamming transition of granular hydrogels. We then highlight some milestone in the use of granular hydrogels to construct 3D objects. The focus is on two roles of granular hydrogels in extrusion-based 3D bioprinting including granular hydrogels for supporting baths and granular hydrogels for bioinks. Finally, we provide our summary on the remaining challenges and the perspective on how these granular hydrogels can be further exploited for 3D bioprinting.

1.1 Jamming of granular hydrogels

Granular hydrogels are microscaled hydrogel particles, each of which is comprised of a crosslinked polymer network and a tremendous amount of water. The dispersion of hydrogel particles in aqueous medium forms a heterogeneous suspension system, where the property is depending on the composition of individual particles and their packing density. However, reducing the amount of the dispersion phase can turn the hydrogel particles into a jamming state, showing dominantly elastic responses to small levels of shear deformation.

The jamming transition of granular hydrogels is often found when the particle-to-volume fraction reaches (\(\Phi\)) to approximately 0.58, while the hydrogel particles are random loose packing.\(^{25}\) With increasing packing concentration of the hydrogel particles, the interparticle friction increases, and the external force-induced particle deformation also happens. As a result, the hydrogel particles will be packed closely, and the granular hydrogels can be considered as a bulk hydrogel possessing conventional gel properties. In theory, the monodispersed hard-spherical particles should be maximally jammed in a random configuration at \(\Phi = 0.64\) and be perfectly packed at \(\Phi = 0.74\).\(^{25}\) However, the packing of soft hydrogel particles is much more complicated due to the interparticle friction, the charge, the stiffness, and the heterogeneous population of the microgels.

Whatever the packing density of granular hydrogels is, the unique physical properties of shear-thinning and self-healing are more or less able to present. Especially, when the hydrogel particles are concentrated at particle-to-volume fraction between 0.58 and 0.64, the granular hydrogels experience stronger gravitational forces relative to thermal effect.\(^{25}\) Also, the van der Walls force between the adjacent microgels is negligible compared to the friction force. Therefore, the jamming granular hydrogels behave as viscous fluids under the shearing, then return to a viscoelastic solid after releasing the external load. Such shear-thinning-like behavior of granular hydrogels inspired researchers to employ them as supporting materials or bioinks for extrusion-based 3D printing.

1.2 Granular hydrogels for supporting baths

The usage of granular hydrogels as supporting baths is a way to place them in a container, followed by applying a nozzle of the 3D printer to deposit the desired bioink into the granular hydrogels.\(^{28}\) As the nozzle draws a spatial path by the bioinks, the granular hydrogels fluidics at the point of the injection and then rapidly jam into a solid-like state, fixing the injected bioinks in place (Figure 1A and 1B). When the materials are held within the jammed hydrogels, the instabilities arising from surface tension, gravitational sag, and interfacial wetting are eliminated, allowing several elements can be written in this process.
1.2.1 Carbopol-based granular hydrogels

In 2015, Angelini and co-workers pioneered the extrusion-based 3D printing by using the commercialized granular hydrogels as supporting baths. They took Carbopol ETD 2020 polymer as the granular hydrogel medium, which is a type of poly (acrylic acid) polymer particles with a diameter of approximately 7 µm. When those particles were dispersed in a certain amount of water, they swell to form a jammed hydrogel exhibiting a yield point. The applying 1 to 200 Pa shear stresses would permit easy insertion and rapid motion of nozzles within the Carbopol granular hydrogels. A variety of materials, including silicones, hydrogels, colloids, and living cells, have been used as inks...
for the writing in those granular hydrogels with several complex and multiscale structures, while other 3D printing methods are not able to produce (Figure 1C to E). Importantly, Angelini et al. demonstrated the stability provided by the granular hydrogels allowed the uncrosslinked structure to be retained without visible changes over 6 months (Figure 1E). This level of the stability illustrates the writing in the granular hydrogels is not dominated by the rheological behaviors of the printing inks.

Following up on these examples, more details of works have been done to understand the using of the Carbopol support baths.32,33 For example, a two-step gelation-based “printing-then-gelation” approach was developed to fabricate 3D alginate structures using filament extrusion.34 The Carbopol granular hydrogels supported alginate structure has been printed, avoiding the instantaneous gelation to stop nozzle clogging. After removing the Carbopol granular hydrogels, the alginate carrying cells was ionically crosslinked by calcium chloride, resulting in cell-laden constructs. In contrast to conventional 3D bioprinting requires biocompatible materials to encapsulate cells for writing, the Carbopol granular hydrogels made it possible to direct print cells without additional supporting matrix (Figure 1F and 1G). Angelini et al. reported an integrated approach for 3D bioprinting multicellular structures while taking the same platform for 3D cell culture, experimentation, and assay development. The Carbopol granular hydrogels allowed molecular diffusion for the delivery of nutrients or small molecules for fluorescence-based assays.30 The same group also introduced a simple laboratory testing system that could translate the 3D printing nozzle through the printing medium at a speed over 1 m/s.35 However, the limits are remaining by a selection of the printing materials. Recently, Tibbits, Laucks, and co-workers reported the usage of a six-axis industrial robotic arm and three-axis computer numerically controlled machines would scaling up and speeding up the spatial printing process in the Carbopol granular hydrogels supporting baths.36 Upon testing a range of materials, including plaster, concrete, urethane expanding foam, epoxy, UV curable resin, marine sealants, casting alloys, silicones, and metal-filled epoxy, silicones, have proved to be very successful.

1.2.2 Biocompatible natural polymers based granular hydrogels

Despite their accessibility to commercialized Carbopol sources, the interactions between charged poly (acrylic acid) polymer particles and ions present in cell growth media may lead to changes in rheological behavior or causing negative effects on cell performance.37 To grow complex tissues, some efforts have been focused on the use of biocompatible natural polymers based granular hydrogels.31,38–40 Those materials usually are formed in bulk, and they are blended into a slurry that behaves like a Bingham plastic. Feinberg and his co-workers reported one of the earliest examples of development of freeform reversible embedding of suspended hydrogels (FRESH) within gelatin: these researches demonstrated the 3D bioprinting of biological hydrogels composed of polysaccharides and proteins that are challenging or impossible to build using traditional fabrication methods.39 As a proof of concept, 3D internal and external anatomical architectures based on femurs, branched coronary arteries, trabeculated embryonic hearts, and human brains were recreated. The same research group recently made a breakthrough in this method, with a printing parts at a resolution of 20 µm, which exceeds the resolution of 100 to 500 µm obtained with previous extrusion-based 3D bioprinting techniques.41 In contrast to previous granular hydrogels consisted of irregularly shaped microparticles, the improved gelatin hydrogel particles are with uniform spherical morphology, reduced polydispersity, and tunable storage modulus and yield stress. In the updated supporting bath, ventricles were constructed by a dual-material printing strategy with a structural component of collagen in combination with a high-density cell bioink (Figure 1I–K). When embryonic stem cells were printed, the resulting tissues showed functions similar to the real heart such as synchronized beating and the valves on-off under the pulsatile flow. There are still a lot of challenges to overcome, however, this work brought on-demand tissues and organs bioprinting closer to reality. More examples by using gelatin granular hydrogels as supporting baths have been reported by several groups.39,42 One exciting research is the simultaneous solidification of bioinks during the bioprinting process, taking the advantages of the Schiff base crosslinking between the carbohydrazide-modified gelatin bioink and oxidized alginate medium (with aldehyde moieties) suspending the gelatin microgels.43 As an alternative to gelatin, there are other granular hydrogel supporting baths that are made of agarose,44 gellan,45,46 or alginate.47,48 Those materials are cytotocompatible, easy to remove without leaving significant amount residues, and not interfere with the printed cells or materials. One attempt using agarose granular hydrogels as a “bed” gives the production of multiple cell structures of closely defined morphology, mechanical properties, and chemistry.44 The scaffolds are potentially able to produce the osteochondral plugs for the augmentation of full-thickness cartilage defects. For gellan granular hydrogels, they could supply crosslinking agent of the enzyme to the printed precursors for hydrogel mild crosslinking.45 In this respect, a crosslinkable gellan granular hydrogels
have been developed as a supporting matrix bath. The printed materials are serving as sacrificial materials to generate engineered tissue constructs with perfusible internal channels.\textsuperscript{46} As reported by several research groups, the use of alginate granular hydrogels also allows the bio-printing of either cells-containing biomaterials or cell-only bioinks.\textsuperscript{47,48}

### 1.3 Granular hydrogels for bioinks

In conventional extrusion-based 3D bioprinting, the bioinks are extruded from the printing nozzle like a liquid under high shear stress, then turn into a solid status to maintain the shape. On account of the shear-thinning behavior, the jammed granular hydrogels can form intact long filaments when injected under optimal conditions,\textsuperscript{49,50} making them as promising bioinks for extrusion-based 3D bioprinting. While particulate materials have been used as inks for 3D printing previously,\textsuperscript{51–53} Burdick et al. reported the first example of printing granular hydrogels both with layer-by-layer depositing and within a supporting material.\textsuperscript{54} The monodispersed hydrogel particles were prepared by a droplet-based microfluidic method, forming water-in-oil emulsions (Figure 2A). The water phase could be the materials of norbornene-modified hyaluronic acid, poly (ethylene glycol) diacrylate, or agarose. After solidification, the hydrogel particles were washed out from the oil and packed into a jammed state (Figure 2B). Those granular hydrogels show shear-thinning behavior, behaving as an elastic hydrogel at low strains but they are yielded at high strains. With loading granular hydrogels as inks, a regular filament has been extruded and it is retained after breaking away from the nozzle (Figure 2C–E). Standard layer-by-layer printing was carried out to build a lattice of up to four layers, of which the mechanical property was further enhanced by postcrosslinking (Figure 2F). High cell viability was observed by using cell encapsulated granular hydrogels inks. This is because the encapsulation of the cells opens up a possibility for shielding them from shear stresses usually experienced during the extrusion process. More complex and anatomically relevant 3D structures were produced with the bioinks consisting of poly (ethylene glycol) granular hydrogels prepared via off-stoichiometry thiolene click chemistry, where the thiolene annealing reaction allowed the cell incorporation during printing with high viability (Figure 2G).\textsuperscript{55} In contrast to the encapsulation of the cells inside the hydrogel particles, the bioinks are made by mixing the cells with granular hydrogels, allowing the cells to spread and proliferate in the interstitial spaces.

Following this, Burdick and colleagues further developed an electroactive tissue support system by granular hydrogels containing in situ synthesized silver nanoparticles.\textsuperscript{56} The microfluidic prepared hydrogel particles were doped with silver nanoparticles by gallol redox chemistry coupled with situ metal reduction. On extrusion those granular hydrogels onto a surface, a free-standing conductive microgel pattern was observed, and the printed lattice could be transferred onto porcine myocardium tissue. The study highlighted that the large interfacial area in the granular hydrogels enhances the electrical conductivity, resulting in continuity of electrical flow. When bridging two freshly isolated skeletal muscles of the rat hind limb, noticeable contraction of the muscle was shown. Another interesting example is the development of chitosan methacrylate granular hydrogels and polyvinyl alcohol hybrid granular hydrogels as bioinks for the extrusion-based 3D bioprinting of scaffolds.\textsuperscript{57} For this work, nonspherical-shaped granular hydrogels were produced by fragmenting of bulk hydrogels into a slurry, showing typical shear thinning and yielding behavior. Various biomimetic constructs were built by extrusion-based 3D printing such as a rat-size thighbone or a human-size ear model (Figure 2H). Also, the scaffolds with chitosan methacrylate/polyvinyl alcohol granular hydrogels were demonstrated to modulate the growth of bone marrow-derived mesenchymal stem cells, which is promising for future tissue repairing applications (Figure 2I and J).

### 2 SUMMARY AND OUTLOOK

Following the development of granular hydrogels, their use for supporting baths and bioinks in the extrusion-based 3D bioprinting was a natural evolution. The unique rheological behavior of the granular hydrogels offers a new paradigm in the study of 3D bioprinting, introducing effective solutions to extend the type of materials or cells which are not able to print by the conventional method. Although this approach was tested with only a limited kind of hydrogel particle systems, the granular hydrogels should be useful throughout the biofabrication. The future controlled 3D bioprinting could be achievable by a number of chemically distinct granular hydrogel systems.

In the aspect of granular hydrogels for supporting baths, they allow the extruded material to be confined in the space without relying on the solidification of liquid ink. The resolution of extrusion-based bioprinting is usually in hundred micrometers, and it is mostly dominated by the printer nozzle. By choosing granular hydrogel baths, the construction of advanced biological parts with 20 \( \mu \text{m} \) is possible because of the smaller size of the produced filaments. Also, the supporting baths could store the nutrients and thus keep an appropriate physiological environment during a long time of cells printing process.
However, this platform is still at an early stage, and challenges are remaining, such as printing a large number of cells required for complex tissues, achieving fast manufacturing process, and fabricating fully functional tissues or organs.

In terms of granular hydrogels for bioinks, the dynamic rheological behavior enables them to be directly extruded by shearing from the printing nozzle, then the inks return to initial solid status and retain the shape. Although only a small number of examples has been reported on
this method, it shows the extruded-based 3D bioprinting should benefit a lot from the granular hydrogel bioinks. The cells could either be encapsulated in hydrogel particles before the bioprinting or be mixed along with the bioprinting. The encapsulation in hydrogel particles could shield the cells from the shear stress usually exited during the extruded-based 3D bioprinting; mixing the cells with hydrogel particles allows them to spread and the proliferate in the microspace between each granular hydrogel. While short-term cell viability studies have been presented, further exploration of long-term cell growth and metabolic activity are required.

In summary, we anticipate the two approaches of the granular hydrogels in 3D bioprinting will continue, and we expect to see a range of materials that can be processed into granular hydrogels for tissue engineering will likely expand. In the request to have tissue complexity, the development of basic biology is necessary. It should be given priority in the near future, alongside further technological improvements in 3D bioprinting approaches.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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