Korean J. Chem. Eng., 40(2), 267-275 (2023)
DOI: 10.1007/s11814-022-1310-1
pISSN: 0256-1115
eISSN: 1975-7220

INVITED REVIEW PAPER

Jammed microgels fabricated via various methods for biological studies

Dowon Moon*, Kwang Hoon Song,†, and Junsang Doh***,****,*****,†**

*Department of Mechanical Engineering, Pohang University of Science and Technology (POSTECH), Pohang, Gyeongbuk 37673, Korea
**Department of Nano-Bioengineering, Incheon National University, 119, Academy-ro, Yeonsu-gu, Incheon 22012, Korea
***Department of Materials Science and Engineering, Seoul National University, Seoul 08826, Korea
****Research Institute of Advanced Materials (RIAM), Institute of Engineering Research, Seoul National University, Seoul 08826, Korea
*****BioMAX Institute, Seoul National University, Seoul 08826, Korea
(*Received 23 July 2022 • Revised 29 September 2022 • Accepted 5 October 2022*)

Abstract−Microgels, hydrogels fabricated in microscale via various methods, can be jammed, and the jammed state can be influenced by some factors such as volume fraction (ϕ), pressure and temperature. Compared to bulk hydrogels, jammed microgels have distinct characteristics. Structures of jammed microgels, stable through a balance of effective forces applied to them, can be changed by application of forces or pressure, implying shear-thinnning properties. Additionally, the ability to maintain structures under a static condition and porous internal structures of them has been extensively exploited in researches. Additional materials can be involved in jammed microgels for additional features (e.g., conductivity), and overall mechanical properties can be also controlled. These characteristics have been used in diverse biological studies by developing them as injectable scaffolds, drug delivery vehicles and inks and support bath in 3D printing processes. In this review, jamming processes, characteristics of jammed microgels, fabrication methods of microgels and applications of jammed microgels are discussed to provide a comprehensive understanding of jammed microgels and promote their use in diverse researches.

Keywords: Jamming, Microgels, Shear-thinning

INTRODUCTION

Hydrogels are made of hydrophilic polymer networks containing a large amount of water and have been used in diverse research fields, exploiting their characteristics such as hydrophilicity, possibility of chemical modification and intrinsic features of polymers [1-3]. Recently, various attempts have been made to expand their applications, and a newly developed method is to use jammed microgels for biological studies [4-6].

Microgels are hydrogels produced at micro size [7] via various methods such as microfluidic, micro-droplet, batch emulsion and fragmentation methods (Fig. 1(a)) and have been already used for numerous applications. For example, microgels were involved in hydrogels to change their physical properties [8], and microgels with pH reactivity were used as drug-releasing particles [9]. Microgels with pores were also used as adsorbents to remove Cu(II) components [10]. The survival rate of lactic acid bacteria of food product can be increased by adding lactic acid bacteria to the microgel [11].

Unlike the researches using microgels in normal conditions, there have been efforts to study properties of jammed microgels [12-15]. Interestingly, microgels can maintain a densely compressed state under appropriate conditions, and the compressed microgels, also called jammed microgels, display macroscopically distinct properties from general bulk hydrogels (Fig. 1(b)) [12,16]. In particular, jammed microgels exhibit shear thinning properties, implying decreasing viscosity upon increasing shear rate. Thus, jammed microgels can be injected through needles, transformed by application of forces and structurally stabilized upon removal of the applied forces, enabling them to be used for 3D printing inks [17-19], support bath for 3D printing processes [20,21], injectable scaffolds [22-24] and drug carriers (Fig. 1(c)) [25,26].

Previously, macroporous hydrogels [27,28], shear-thinning hydrogels [29-31] and in situ gelling hydrogels [32-34] were developed (Table 1) and used as injectable hydrogels in various applications. Macroporous hydrogels formed via diverse materials can recover their original shape after injection and might not be useful as 3D printing inks because 3D-printed shapes can be deformed by a shape recovery feature. Shear-thinning hydrogels that maintain injected shapes after injection have been involved in various drug delivery [35,36] and 3D printing researches [30,31]. Precise control of gelation is required for application of in situ gelling hydrogels, and proper gelation might not be easily obtained when they are used as 3D printing inks. Compared to these conventional injectable hydrogels, jammed microgels can be formed via various materials [17,18,37] and involve porosity useful for cell culture [22,24,38]. Specifically, the viability of cells encapsulated in microgels printed and annealed was higher than that of cells in bulk hydrogels when they were compared on day 3 of cell culture [24]. As a limitation, the shape and size of microgels can influence resolution of 3D printing processes

†To whom correspondence should be addressed.
E-mail: khsong@inu.ac.kr, jsdoh@snu.ac.kr
Copyright by The Korean Institute of Chemical Engineers.

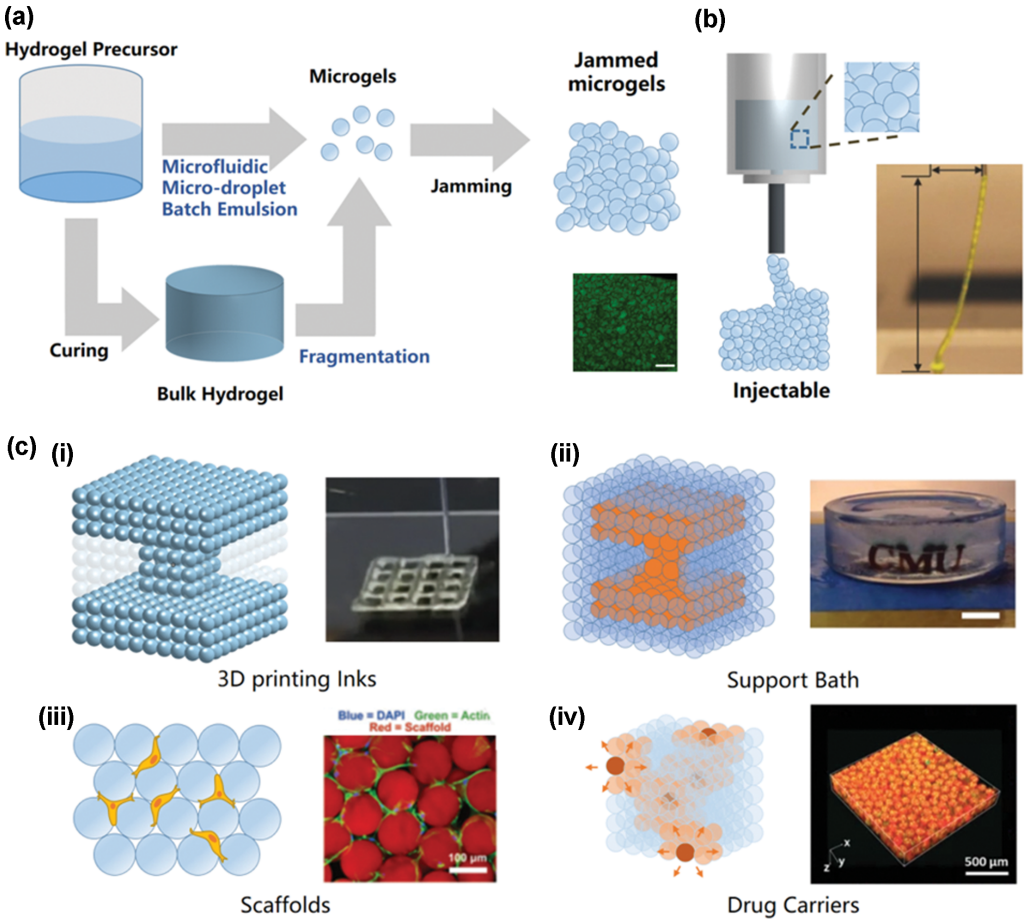


Fig. 1. Schematic illustration of jammed microgel preparations, injection and applications. (a) Microgel fabrication methods (Microfluidic, micro-droplet, batch emulsion, and fragmentation methods) and jamming processes. A scale bar indicates 200 μm. Reproduced from [18] with permission. Copyright 2018, John Wiley and Sons. Distributed under the Creative Commons Attribution 4.0 International License (CCBY4.0, http://creativecommons.org/licenses/by/4.0/). (b) Injection of jammed microgels. Reproduced from [17] with permission. Copyright 2018, John Wiley and Sons. Distributed under the Creative Commons Attribution 4.0 International License (CCBY4.0, http://creativecommons.org/licenses/by/4.0/). (c) Applications of jammed microgels. (i) 3D printing inks. Reproduced from [17] with permission. Copyright 2018, John Wiley and Sons. Distributed under the Creative Commons Attribution 4.0 International License (CCBY4.0, http://creativecommons.org/licenses/by/4.0/). (ii) Support bath. From [70]. Reprinted with permission from AAAS. (iii) Cell scaffolds. Reproduced from [38] with permission. Copyright 2019, John Wiley and Sons. Distributed under the Creative Commons Attribution 4.0 International License (CCBY4.0, http://creativecommons.org/licenses/by/4.0/). (iv) Drug carriers. Reproduced from [25] with permission. Copyright 2019, John Wiley and Sons. Distributed under the Creative Commons Attribution 4.0 International License (CCBY4.0, http://creativecommons.org/licenses/by/4.0/).

Table 1. Characteristics of conventional injectable hydrogels (Macroporous hydrogel, shear-thinning hydrogel, in vivo gelling hydrogel) and jammed microgels

Type	Material	Porosity	Injected shape	Parameters affecting rheology
Macroporous hydrogel	Any hydrogels [27,28]	Formed	Original shape	Ratio of porous and non-porous region
Shear-thinning hydrogel	Shear-thinning hydrogels (e.g., Alginate [29], pluronic F-127 [30], guest-host hydrogel [31])	Not formed	Free	Degree of shear-thinning properties
In situ gelling hydrogel	Hydrogels crosslinked on a target (e.g., N-isopropylacrylamide [32])	Not formed	Relatively free	Gelling speed
Jammed microgels	Any hydrogels [17,18]	Formed	Free	Microgel size, jamming degree

[39], although jammed microgels are useful as 3D printing inks or support bath.

To properly utilize the jammed microgels and expand their applications, it is important to understand the overall jamming process and characteristics of jammed microgels. In this review, therefore, microgel jamming conditions, diverse characteristics of jammed microgels, microgel fabrication methods with their features and current applications of jammed microgels in biological studies are discussed to provide insights of jammed microgels to future researches.

JAMMING CONDITIONS AND RHEOLOGICAL PROPERTIES OF JAMMED MICROGELS

Jammed microgels, densely compressed microscale hydrogel particles, display distinct properties, compared to bulk hydrogels larger than a millimeter, due to variation of effective forces applied to them. Typically, effects of forces on hydrogels can be altered by variation of hydrogel size and volume fraction (ϕ), implying packing density of hydrogel particles. As the size of hydrogels decreases, the effect of thermodynamic forces, unlike that of gravity, increases on hydrogels [40]. Additionally, friction and van der Waals force become effective via contact of hydrogel particles and greatly act on the particles at critical volume fraction (ϕ_c), where all the particles in a designated area are connected to each other (Fig. 2(a)). For microgels compressed beyond the critical volume fraction, frictional force affects more than van der Waals forces, although gravity is still more effective than thermodynamic energy. In this state, overall compressed microgels can be structurally stabilized via balance of these forces [41,42], which refers to jamming of microgels [15,42]. Thereby, forces will be transmitted throughout the jammed microgels, as indicated as positive (blue line) and negative (red line) contact forces, if a pressure is applied to a point of the jammed microgels (Fig. 2(b)) [43].

For jamming of microgels, various factors that can affect the forces effective on microgels, besides particle size, can be considered. As stated, friction can be effective via compression of microgels beyond the critical volume fraction, useful for jamming (Fig. 2(c)) [44]. Typically, values of volume fraction, 0.58, 0.64 and 0.74, indicate random loose packing, random closed packing and hexagonal closed packing, respectively [45]. On the other hand, a pressure exceeding friction at interfaces of microgels might break jammed microgels if applied to them [46]. Thus, pressures or loads enough to dominate friction at the interfaces should be avoided for the jamming process. Additionally, temperature needs to be controlled for the jamming state because relatively high thermodynamic energy can disperse jammed microgels (Fig. 2(c)) [14,44,46]. Other than these factors, aspect ratio of particles [47], activity of networks (thermal reactivity) [48,49], charge of polymer [20] can affect jamming state of microgels.

To understand properties of jammed microgels, useful for diverse applications, their rheological behavior was analyzed. Specifically,

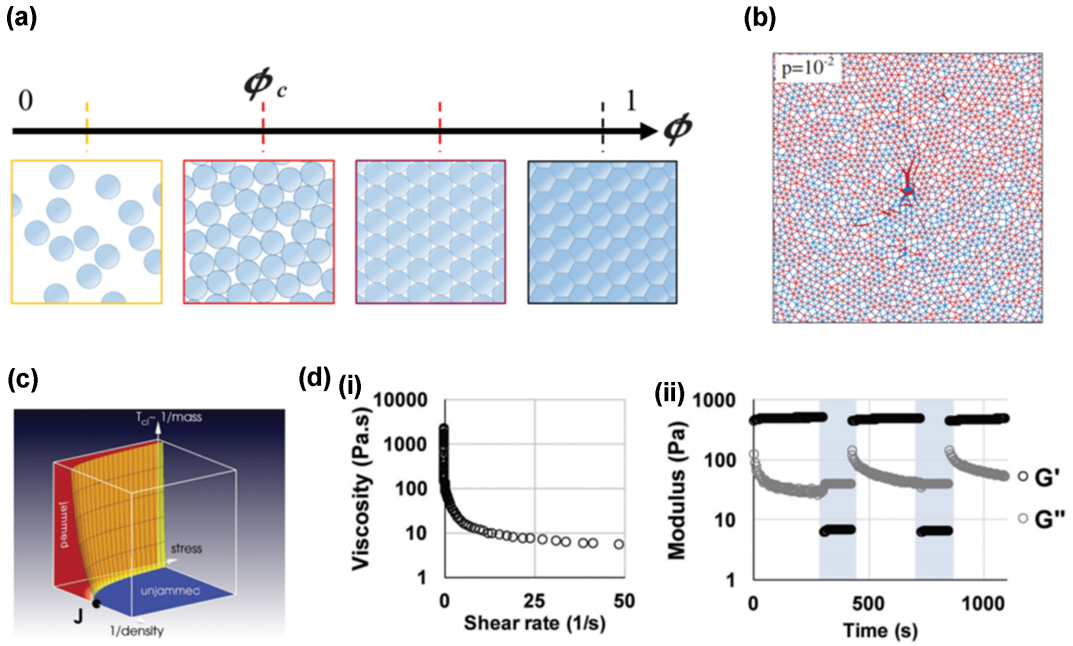


Fig. 2. Jamming conditions and rheological properties of jammed microgels. (a) An illustration of volume fraction (ϕ). Critical volume fraction (ϕ_c) indicates a state that all particles in the area are connected. (b) Transmission of a force from one point to all jammed microgels. Blue and red lines indicate positive and negative contact force change, respectively. Reprinted figure with permission from [43]. Copyright 2006 by the American Physical Society. (c) A graph describing influence of volume fraction (1/density), temperature (T_{eff}: effective temperature of the classical system) and stress to a jamming state. Reprinted figure with permission from [46]. Copyright (2013) by the American Physical Society. (d) Rheological properties of jammed microgels. (i) Viscosity decreased in response to increasing shear rate, indicating shear thinning property. (ii) Repeated switches of elastic and viscous states under repeated switches of low and high (shaded) strains, indicating shear-thinning and self-healing properties. Reproduced from [17] with permission. Copyright 2018, John Wiley and Sons. Distributed under the Creative Commons Attribution 4.0 International License (CCBY4.0, http://creativecommons.org/licenses/by/4.0/).

viscosity of jammed microgels decreased when shear rates of them increased (Fig. 2(d)-(i)). Additionally, jammed microgels were elastic and viscous under low (unshaded) and high (shaded) strains, respectively, and those states were repeatedly switched with strain changes (Fig. 2(d)-(ii)). These together verified shear-thinning and self-healing properties, implying that jammed microgels are deformable via pressure and become stable with removal of the applied pressure. These rheological properties are similar to those of other types of injectable hydrogels such as poly(acrylamide)-based jammed microgels [18], hyaluronic acid-based guest-host hydrogels [31] and hybrid hydrogels consisting of polyvinyl alcohol and κ-carrageenan [50].

CHARACTERISTICS OF JAMMED MICROGELS IN APPLICATIONS

In addition to rheological properties, jammed microgels used in previous applications showed diverse characteristics that can be further developed in the future. For example, jammed microgels were injected or sprayed through a nozzle, and the extruded jammed microgels maintained their shapes, allowing fabrication of user-defined hydrogel structures, such as a hollow cylinder and a rat-

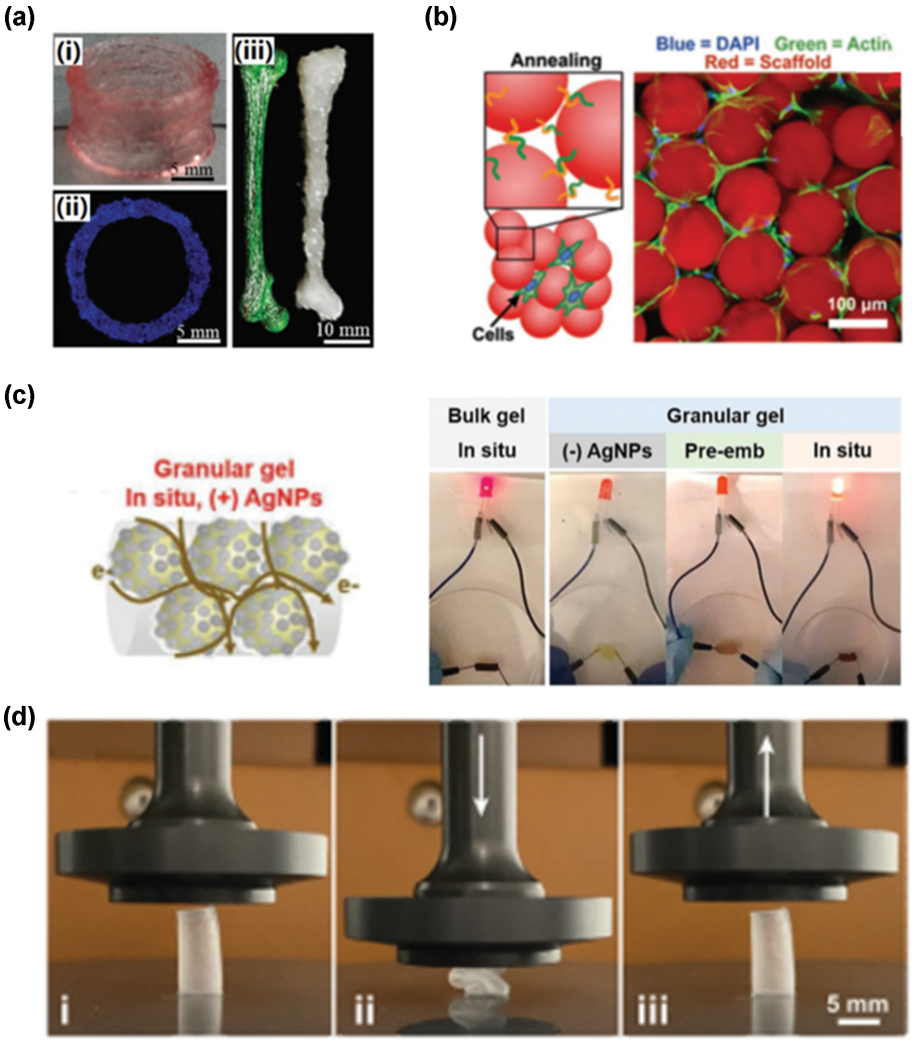


Fig. 3. Characteristics of jammed microgels used in previous researches. (a) Jammed microgels maintained 3D-printed structures. Images indicate (i) a photo of a cylinder-shape, (ii) a fluorescent image of a cylinder-shape and (iii) a photo of a rat-size thigh bone-shape. Reproduced from [51] with permission. Copyright 2019, John Wiley and Sons. Distributed under the Creative Commons Attribution 4.0 International License (CCBY4.0, http://creativecommons.org/licenses/by/4.0/). (b) Jammed microgels containing pores were used as a porous and injectable scaffolds. Reproduced from [38] with permission. Copyright 2019, John Wiley and Sons. Distributed under the Creative Commons Attribution 4.0 International License (CCBY4.0, http://creativecommons.org/licenses/by/4.0/). (c) Jammed microgels involving silver nanoparticles at interfaces of microgels showed conductivity. Reproduced from [54] with permission. Copyright 2019, John Wiley and Sons. Distributed under the Creative Commons Attribution 4.0 International License (CCBY4.0, http://creativecommons.org/licenses/by/4.0/). (d) A hollow cylinder structure composed of jammed microgels and stabilized by double polymer networks recovered its original shape after compression. Reproduced from [55] with permission. Copyright 2020, John Wiley and Sons. Distributed under the Creative Commons Attribution 4.0 International License (CCBY4.0, http://creativecommons.org/licenses/by/4.0/).

sized thigh bone (Fig. 3(a)) [51,52]. Additionally, overall structures were permanently stabilized through annealing to avoid unexpected pressure-induced structure deformation. Other than use as 3D printing inks, porous structures of annealed jammed microgels, formed via gaps between microgels, could permit them to be used as scaffolds. The jammed microgel-based scaffolds could be delivered via injection and colonized by cell infiltration through the gaps (Fig. 3(b)) [22,53]. A feature could be added by involving new materials in jammed microgels. Previously, it was reported that metal nanoparticles were involved at interfaces of microgels, introducing conductivity to overall jammed microgels (Fig. 3(c)) [54]. Conductivity of the jammed microgels involving metal nanoparticles at interfaces of microgels was statistically greater than that of bulk hydrogels containing metal nanoparticles inside, due to large surface area of microgel interfaces. Mechanical properties of overall microgel-based structures could also be increased by introducing double networks (Fig. 3(d)) [55]. For instance, a cylinder-shaped object fabricated with jammed poly(2-acrylamido-2-methylpropane sulfonic acid) (PAMP) microgels containing acrylamide (AM) monomers was stabilized and further strengthened by polymerizing AM monomers.

MICROGEL FABRICATION METHODS AND APPLICATIONS OF JAMMED MICROGELS

1. Microfluidics method

Various microfluidic channels generating emulsion with immiscible fluids have been used to fabricate diverse microgels (Fig. 4(a)) [56]. Specifically, when hydrogel precursors and fluids immiscible to the precursors, separately injected through microfluidic channels via syringe pumps, meet at intersection of the channels, continuous flow of the hydrogel precursors is cut off, creating hydrogel precursor emulsions dispersed in the other fluid [57]. Then, stimulation such as ultraviolet (UV) [17] or temperature variation [58], varied by components of precursors, is applied to polymerize the emulsions, followed by washing steps to remove the other fluid.

In this way, size and shape of microgels can be precisely controlled because manipulation of flow rates through microfluidic channels and modification of channel geometry/size are available. Upon the changes of flow rates and microfluidic channel geometry/size, microgels ranging from 2 to 1,000 μm [59] and microgels in complex shapes such as microgels containing microgels inside [60] were fabricated. Although general microgel production rates are relatively

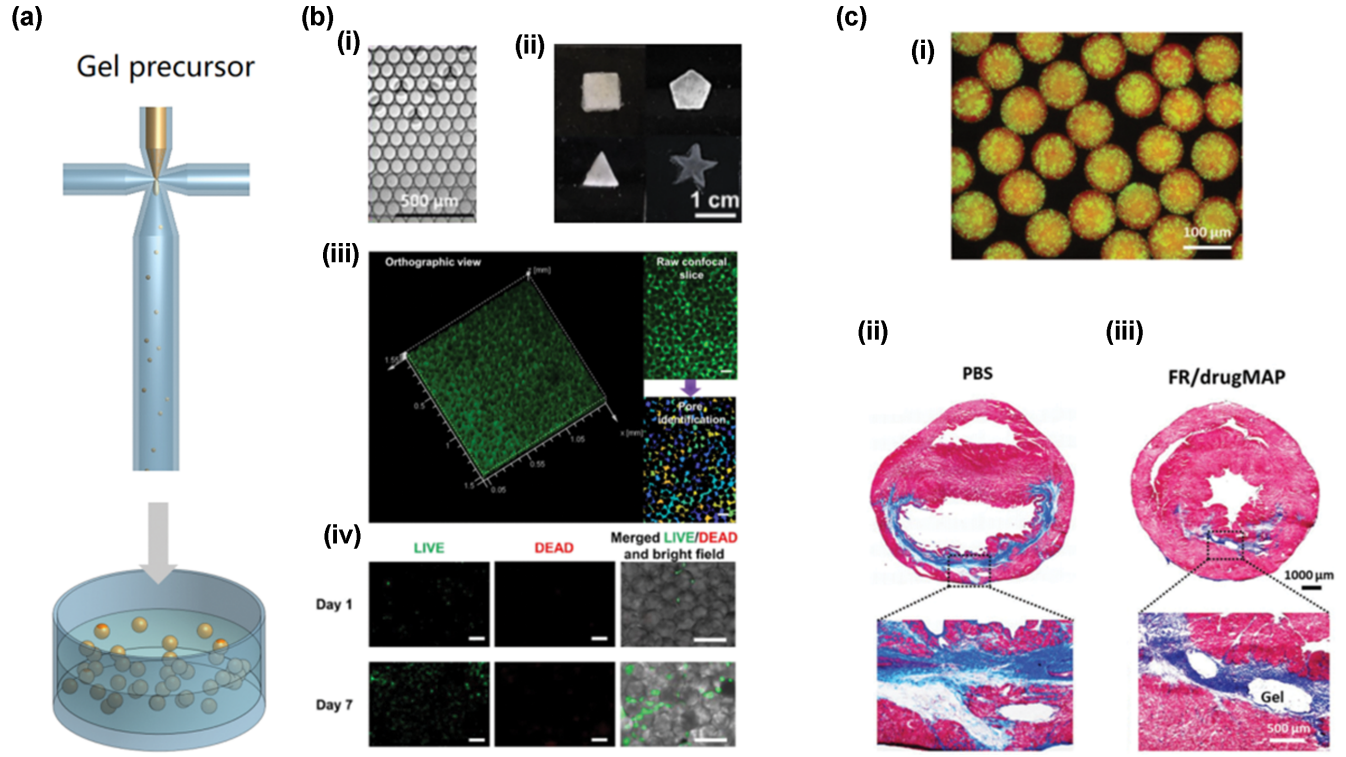


Fig. 4. Microfluidic methods to fabricate microgels and applications of the jammed microgels. (a) Illustration of microfluidic methods. Hydrogel precursors and immiscible fluids are flowed into microchannels to form precursor emulsion, and the emulsion is cured. (b) Jammed microgels containing pores were used to culture cells. (i) Microgels produced in uniform size and shape. (ii) Jammed microgels in diverse shapes formed by molding. (iii) Visualization of pores formed at interfaces of jammed microgels. (iv) Images of live/dead NIH/3T3 cells grown within jammed microgels. Scale bars indicate 200 μm. Reproduced from [58] with permission. Copyright 2020, John Wiley and Sons. Distributed under the Creative Commons Attribution 4.0 International License (CCBY4.0, http://creativecommons.org/licenses/by/4.0/). (c) Jammed microgels were used to deliver cellular metabolism-affecting drugs to ischemia-reperfusion injury. (i) Jammed microgels developed as drug carriers. Cross-sectional images of the injury treated with jammed microgels containing (ii) phosphate buffered saline (PBS) only and (iii) Forskolin and Repsox drugs. Reproduced from [25] with permission. Copyright 2019, John Wiley and Sons. Distributed under the Creative Commons Attribution 4.0 International License (CCBY4.0, http://creativecommons.org/licenses/by/4.0/).

low, due to low flow rates through microfluidic channels, they could be improved by development of parallel production strategies [38,61].

The microgels produced with microfluidic channels exhibited nice uniformity in size and shape (Fig. 4(b)-(i)), which permitted good shape fidelity when they were jammed and shaped by molding (Fig. 4(b)-(ii)) [17]. Additionally, jammed microgels included microscale gaps formed at interfaces of microgels (Fig. 4(b)-(iii)), and NIH/3T3 cells within the gaps showed high viability, possibly due to supply of nutrients and oxygen via diffusion (Fig. 4(b)-(iv)) [5,58]. Similarly, microgels containing cellular metabolism-affecting drugs such as Forskolin and Repsox were jammed and injected to ischemia-reperfusion injury in female Sprague-Dawley rats to use them as drug-releasing scaffolds. (Fig. 4(c)-(i)) [25]. As a result, the size of the wound was reduced rapidly and rate of remodeling increased.

2. Micro-droplet Method

A small amount of liquid falling in the air forms a droplet, due to its surface tension. Likewise, various microgels can be fabricated by curing microscale droplets formed by dropping hydrogel precursors in the air although there can be variations in production methods (Fig. 5(a)) [62]. For instance, alginate microgels were formed when droplets of alginate precursor that could be crosslinked with Ca^{2+} ions were immersed in Ca^{2+} bath [63]. Similarly, polyethylene glycol microgels were collected by curing the hydrogel precursor droplets dispersed in a non-hydrophilic fluid by electro spraying [64].

Size of microgels could be adjusted in micro-droplet methods by controlling strength of air flow where monomer solutions drip down [65] and adjusting voltage applied on electrospray [52], although there exists low uniformity in microgel size in some methods [64]. Speed of microgel production is also relatively low, due to a feature of sequential droplet forming processes, which could be improved via methods exploiting centrifugal forces [66].

In a previous research, alginate microgels containing human mesenchymal stem cells were obtained by dropping alginate precursors with cells into Ca^{2+} bath, a relatively fast fabrication process increasing survival rates of encapsulated cells (Fig. 5(b)-(i)). The microgels involving cells were then jammed and printed into a star-shape within a gelatin slurry bath, followed by UV light exposure for annealing of microgels (Fig. 5(b)-(ii)) [67]. The cell-containing hydrogel in a star shape maintained its structure well. Additionally, the process showed possibility of preserving cell-containing microgels for a long time because cells in microgels, cryopreserved for 1 month, showed high viability (Fig. 5(b)-(iii)) [37].

3. Batch Emulsion Method

Microgels could be obtained by curing hydrogel precursor emersions dispersed within a hydrophobic liquid via a flow generated through rotating forces (Fig. 5(c)) [68]. Although the microgels were not uniformly generated in size (Fig. 5(d)-(i)), a large amount of them could be generated rapidly via this method. Additionally, high density particles (e.g., graphene oxide) that could sink within precursor immersions could be involved in microgels with relatively even distribution because they could be dispersed in the emulsions through continuously supplied energy [26]. Similar to other meth-

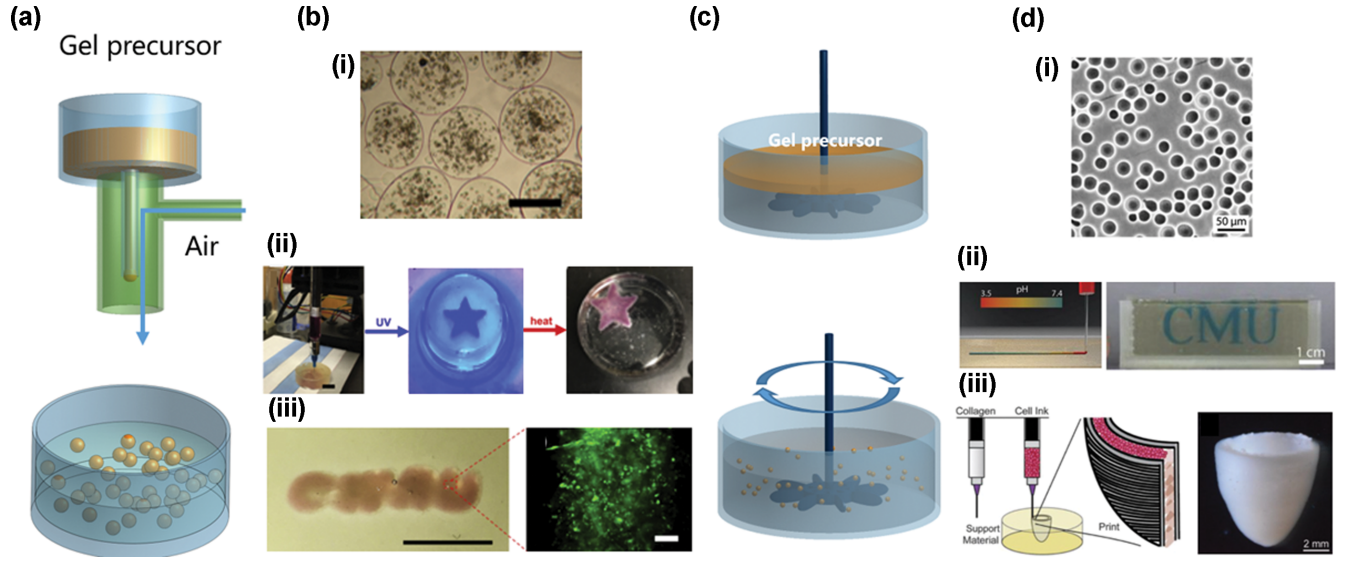


Fig. 5. Micro-droplet and batch emulsion methods to fabricate microgels and applications of the jammed microgels. (a) Illustration of micro-droplet methods. Hydrogel precursors were dropped as microscale droplets, and those droplets were cured. (b) Jammed microgels containing cells were used for 3D printing processes. (i) Alginate microgels involving human mesenchymal stem cells were formed. (ii) The jammed microgels were 3D-printed in a gelatin slurry bath to form a star-shape, and the shape was stabilized by UV-mediated annealing processes. (iii) After using cryopreserved microgels for 3D printing processes, cells showed high viability. A black and a white scale bar indicate 1 cm and 100 μm, respectively. Reprinted from [37]. Copyright 2019, with permission from Elsevier. (c) Illustration of batch emulsion methods. Emulsions of hydrogel precursors, dispersed within hydrophobic liquid, were cured. (d) Gelatin microgels were used as a support bath during 3D printing processes. (i) Gelatin microgels were formed. (ii) An acidic collagen ink was 3D-printed within a support bath composed of jammed microgels, and the deposited ink was stabilized by pH neutralization. (iii) A ventricle model was obtained by 3D printing of a collagen ink and a cell ink within jammed microgels. From [70]. Reprinted with permission from AAAS.

ods, the curing system of hydrogel precursors could vary such as temperature [69]- or UV [55]-mediated crosslinking.

In a previous research, gelatin microgels fabricated via the batch emulsion method were jammed and used as support bath for 3D printing of complex collagen structures (Fig. 5(d)-(i)) [70]. Specifically, an acidic collagen ink was 3D-printed within the jammed gelatin microgels, forming complex structures and stabilized by pH neutralization (Fig. 5(d)-(ii)). In this way, a ventricle model consisting of internal and external collagen shells and a cell layer in between those shells was 3D-printed with a collagen ink and a cell ink (Fig. 5(d)-(iii)). Human embryonic stem cell-derived cardiomyocytes (hESC-CMs) and cardiac fibroblasts were used for the cell ink, and the bottom of the model was 3D-printed only with the collagen ink.

In other researches, this method was also used to fabricate microgels containing dispersed graphene oxide for poly(N-Isopropylacrylamide) photothermal reactions [26] and polydimethylsiloxane particles that required relatively large amount of time for curing [71].

4. Fragmentation Method

Microgels can also be obtained by grinding bulk hydrogels with a blender or fragmenting them with sieves containing microscale pores (Fig. 6(a)) [72]. These fragmentation methods require only little equipment and allow mass production of microgels via relatively simple processes. On the other hand, microgels fabricated through them are generally not uniform in size and shape, which might lead to 3D printing of structures with rough outlines and eventually hinder 3D printing of small features comparable to microgels in size. Thus, it can be very useful for 3D printing of relatively large structures that are less influenced by 3D printing resolutions and requires large amount of microgels as 3D printing inks.

For example, gelatin microgels were fabricated by crosslinking gelatin with transglutaminase (TG) and blending the gelatin hydrogel (Fig. 6(b)-(i)) [73]. Although those microgels were in relatively irregular size and shape, jammed microgels displayed shear-thinning behavior useful as a bioink in extrusion-based 3D printing systems. Thus, jammed microgels were extruded as a filament and printed into multiple connected lines (Fig. 6(b)-(ii)). Additionally, a cup-shape in millimeter scale was 3D-printed with the jammed microgels as an example of complex structures and further stabilized with TG-mediated post-crosslinking (Fig. 6(b)-(iii)). Resolution of the 3D printing process could be improved by filtering microgels with a sieve [74]. Ground microgels were also used as support bath that actually preserved 3D-printed structures of other materials via shear-thinning properties (Fig. 6(c)-(i)) [75]. Specifically, gelatin slurry prepared by grinding gelatin bulk hydrogels was filled in support bath and an ink was extruded within the slurry supporting printed structure. Eventually, the printed structure stabilized by post-crosslinking could be obtained by releasing the slurry with increased temperature. Although the particles in gelatin slurry were in irregular shape and size (Fig. 6(c)-(ii)), alginate was 3D-printed within gelatin slurry bath to form complex and hollow blood vessel structure (Fig. 6(c)-(iii)).

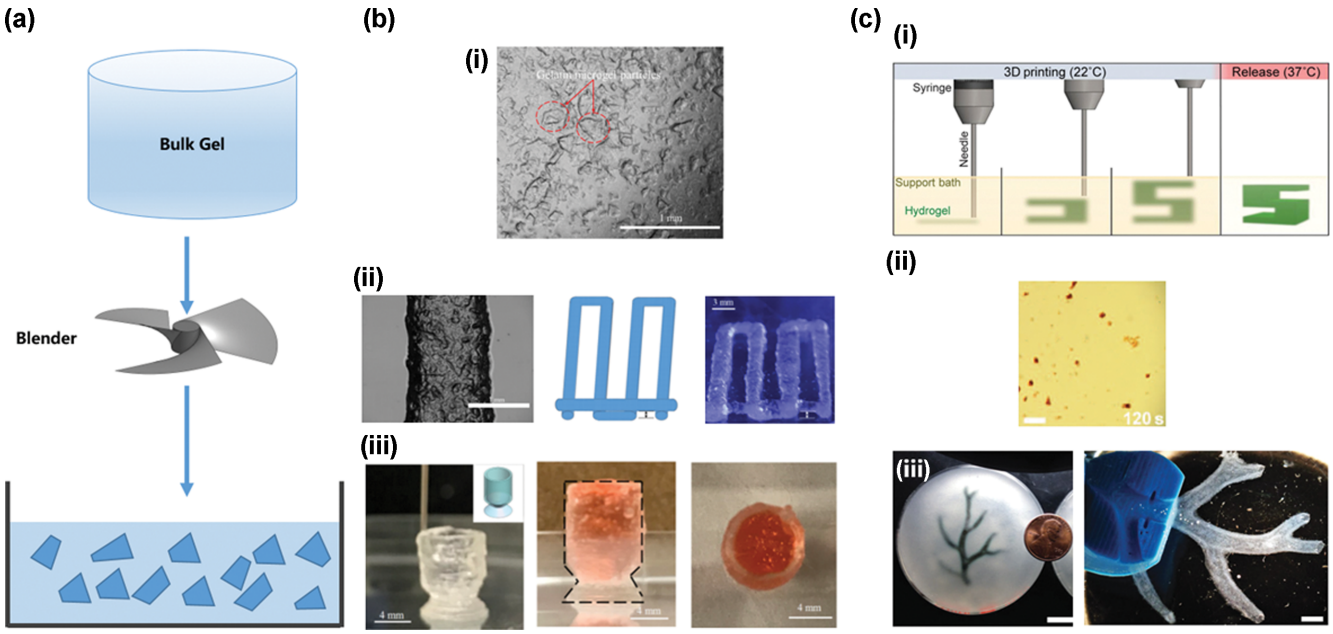


Fig. 6. Fragmentation methods to fabricate microgels and applications of the jammed microgels. (a) Illustration of fragmentation methods. Bulk hydrogels were fragmented into microgels. (b) Jammed gelatin microgels were used as 3D printing inks. (i) Gelatin microgels obtained by blending gelatin hydrogels. (ii) Jammed microgels were 3D-printed as a line and multiple connected lines. (iii) A cup-shape was obtained by 3D printing of jammed microgels. Reprinted figure with permission from [73]. Copyright 2020, American Chemical Society. (c) Gelatin slurry were used as support bath during 3D printing processes. (i) An ink was 3D-printed in support bath, and the printed structure was stabilized. By increasing temperature, the structure was obtained from the support bath. (ii) Gelatin slurry formed by grinding bulk hydrogels. A scale bar indicates 1 mm. (iii) An alginate ink was 3D-printed in support bath to form blood vessel structures. Both scale bars indicate 2.5 mm. Reproduced from [75] with permission. Copyright 2015. Distributed under the Creative Commons Attribution 4.0 International License (CCBY4.0, http://creativecommons.org/licenses/by/4.0/).

CONCLUSION

Microgels are hydrogels fabricated at micron scale via various methods and can be jammed under proper conditions. Jammed microgels exhibiting some interesting characteristics have been used for diverse biological studies. The shear-thinning property of jammed microgels allows their transformation via application of forces that exceed friction between microgels, while structures of bulk hydrogels generally cannot be changed by application of force. In addition, the jammed microgels maintain their shape under a static condition and involve numerous pores formed at interfaces of microgels. Additional features can be added by involving additional materials within jammed microgels, and their mechanical properties can also be modulated. These microgels can be fabricated by microfluidics, micro-droplet, batch emulsion and fragmentation, and the size, shape and production rate of microgels can be influenced by the fabrication methods. To date, jammed microgels prepared with these methods have been used as injectable scaffolds, drug carriers and inks/support bath for 3D printing processes. In the future, the application of jammed microgels can be expanded via understanding of jamming processes and characteristics of jammed microgels.

ACKNOWLEDGEMENTS

Kwang Hoon Song and Junsang Doh contributed equally to this work as corresponding authors. This research was financially supported by the Ministry of Trade, Industry and Energy (MOTIE) and Korea Institute for Advancement of Technology (KIAT) through the International Cooperative R&D program (p0011266), the National Research Council of Science & Technology (NST) grant by the Korea government (CAP-18-02-KRIBB), and the National Research Foundation of Korea (NRF) grant (No. NRF-2021R1 C1C1010633, No. NRF-2020R1A2B5B03001747).

REFERENCES

1. W. Cai and R. B. Gupta, *Kirk-Othmer Encycl. Chem. Technol.* 1 (2012). doi:https://doi.org/10.1002/0471238961.0825041807211620.a01.pub2.
2. K. Y. Lee and D. J. Mooney, *Chem. Rev.*, **101**, 1869 (2001).
3. A. S. Hoffman, *Adv. Drug Deliv. Rev.*, **64**, 18 (2012).
4. A. C. Daly, L. Riley, T. Segura and J. A. Burdick, *Nat. Rev. Mater.*, **5**, 20 (2020).
5. L. Riley, L. Schirmer and T. Segura, *Curr. Opin. Biotechnol.*, **60**, 1 (2019).
6. W. Cheng, J. Zhang, J. Liu and Z. Yu, *View*, **1**, 20200060 (2020).
7. J. R. Purdon Jr. and R. D. Mate, *J. Polym. Sci. Part A-1 Polym. Chem.*, **8**, 1306 (1970).
8. W. Richtering and B. R. Saunders, *Soft Matter*, **10**, 3695 (2014).
9. N. Gogoi and D. Chowdhury, *J. Mater. Chem. B*, **2**, 4089 (2014).
10. X. Hu, L. Long, T. Gong, J. Zhang, J. Yan and Y. Xue, *Chemosphere*, **240**, 124860 (2020).
11. A. Sohail, M. S. Turner, E. K. Prabawati, A. G. A. Coombes and B. Bhandari, *Int. J. Food Microbiol.*, **157**, 162 (2012).
12. R. J. Ketz, R. K. Prud'homme and W. W. Graessley, *Rheol. Acta*, **27**, 531 (1988).
13. M. E. Cates, J. P. Wittmer, J. P. Bouchaud and P. Claudin, *Phys. Rev. Lett.*, **81**, 1841 (1998).
14. C. S. O'Hern, L. E. Silbert, A. J. Liu and S. R. Nagel, *Phys. Rev. E - Stat. Physics, Plasmas, Fluids, Relat. Interdiscip. Top.*, **68**, 19 (2003).
15. A. J. Liu and S. R. Nagel, *Nature*, **396**, 21 (1998).
16. T. H. Qazi, V. G. Muir and J. A. Burdick, *ACS Biomater. Sci. Eng.*, **8**, 1427 (2022).
17. C. B. Highley, K. H. Song, A. C. Daly and J. A. Burdick, *Adv. Sci.*, **6**, 1801076 (2019).
18. D. Moon, M.-G. Lee, J.-Y. Sun, K. H. Song and J. Doh, *Macromol. Rapid Commun.*, e2200271 (2022). doi:10.1002/marc.202200271.
19. A. Charlet, M. Hirsch, S. Schreiber and E. Amstad, *Small*, **18**, 2107128 (2022).
20. C. S. O'Bryan, C. P. Kabb, B. S. Sumerlin and T. E. Angelini, *ACS Appl. Bio Mater.*, **2**, 1509 (2019).
21. E. Mirdamadi, N. Muselimyan, P. Koti, H. Asfour and N. Sarvazyan, *3D Print. Addit. Manuf.*, **6**, 158 (2019).
22. D. R. Griffin, W. M. Weaver, P. O. Scumpia, D. Di Carlo and T. Segura, *Nat. Mater.*, **14**, 737 (2015).
23. S. D. Edwards, S. Hou, J. M. Brown, R. D. Boudreau, Y. Lee, Y. J. Kim and K. J. Jeong, *ACS Appl. Bio Mater.*, **5**, 2786 (2022).
24. C. E. Miksch, N. P. Skillin, B. E. Kirkpatrick, G. K. Hach, V. V Rao, T. J. White and K. S. Anseth, *Small*, **18**, 2200951 (2022).
25. J. Fang, J. Koh, Q. Fang, H. Qiu, M. M. Archang, M. M. Hasani-Sadrabadi, H. Miwa, X. Zhong, R. Sievers, D.-W. Gao, R. Lee, D. Di Carlo and S. Li, *Adv. Funct. Mater.*, **30**, 2070289 (2020).
26. Q. Pang, J. Zhao, S. Zhang and X. Zhang, *J. Biomater. Sci. Polym. Ed.*, **31**, 2252 (2020).
27. S. A. Bencherif, R. Warren Sands, O. A. Ali, W. A. Li, S. A. Lewin, T. M. Braschler, T.-Y. Shih, C. S. Verbeke, D. Bhatta, G. Dranoff and D. J. Mooney, *Nat. Commun.*, **6**, 7556 (2015).
28. S. A. Bencherif, R. W. Sands, D. Bhatta, P. Arany, C. S. Verbeke, D. A. Edwards and D. J. Mooney, *Proc. Natl. Acad. Sci.*, **109**, 19590 (2012).
29. S. Duin, K. Schütz, T. Ahlfeld, S. Lehmann, A. Lode, B. Ludwig and M. Gelinsky, *Adv. Healthc. Mater.*, **8**, 1801631 (2019).
30. M. Müller, J. Becher, M. Schnabelrauch and M. Zenobi-Wong, *Biofabrication*, **7**, 035006 (2015).
31. L. Ouyang, C. B. Highley, C. B. Rodell, W. Sun and J. A. Burdick, *ACS Biomater. Sci. Eng.*, **2**, 1743 (2016).
32. Y. Cao, C. Zhang, W. Shen, Z. Cheng, L. (Lucy) Yu and Q. Ping, *J. Control. Release*, **120**, 186 (2007).
33. S. Ishii, J. Kaneko and Y. Nagasaki, *Biomaterials*, **84**, 210 (2016).
34. R. M. Desai, S. T. Koshy, S. A. Hilderbrand, D. J. Mooney and N. S. Joshi, *Biomaterials*, **50**, 30 (2015).
35. E. A. Silva and D. J. Mooney, *J. Thromb. Haemost.*, **5**, 590 (2007).
36. E. A. Silva, E.-S. Kim, H. J. Kong and D. J. Mooney, *Proc. Natl. Acad. Sci.*, **105**, 14347 (2008).
37. O. Jeon, Y. B. Lee, T. J. Hinton, A. W. Feinberg and E. Alsberg, *Mater. Today Chem.*, **12**, 61 (2019).
38. J. M. de Rutte, J. Koh and D. Di Carlo, *Adv. Funct. Mater.*, **29**, 1900071 (2019).
39. Z.-T. Xie, D.-H. Kang and M. Matsusaki, *Soft Matter*, **17**, 8769 (2021).
40. A. Basu, Y. Xu, T. Still, P. E. Arratia, Z. Zhang, K. N. Nordstrom, J. M. Rieser, J. P. Gollub, D. J. Durian and A. G. Yodh, *Soft Matter*, **10**, 3027 (2014).

41. A. Ikeda, L. Berthier and G. Biroli, *J. Chem. Phys.*, **138**, 12A507 (2013).
42. E. R. Weeks, *Stat. Phys. Complex Fluids*, **2**, 87 (2007).
43. W. G. Ellenbroek, E. Somfai, M. van Hecke and W. van Saarloos, *Phys. Rev. Lett.*, **97**, 258001 (2006).
44. M. van Hecke, *J. Phys. Condens. Matter*, **22**, 33101 (2009).
45. S. Torquato and F. H. Stillinger, *Rev. Mod. Phys.*, **82**, 2633 (2010).
46. Z. Nussinov, P. Johnson, M. J. Graf and A. V. Balatsky, *Phys. Rev. B*, **87**, 184202 (2013).
47. N. M. James, H. Xue, M. Goyal and H. M. Jaeger, *Soft Matter*, **15**, 3649 (2019).
48. A. Ghosh, G. Chaudhary, J. G. Kang, P. V. Braun, R. H. Ewoldt and K. S. Schweizer, *Soft Matter*, **15**, 1038 (2019).
49. G. M. Conley, C. Zhang, P. Aebischer, J. L. Harden and F. Scheffold, *Nat. Commun.*, **10**, 1 (2019).
50. P. Jiang, C. Yan, Y. Guo, X. Zhang, M. Cai, X. Jia, X. Wang and F. Zhou, *Biomater. Sci.*, **7**, 1805 (2019).
51. H. Zhang, Y. Cong, A. R. Osi, Y. Zhou, F. Huang, R. P. Zaccaria, J. Chen, R. Wang and J. Fu, *Adv. Funct. Mater.*, **30**, 1 (2020).
52. S. Xin, D. Chimene, J. E. Garza, A. K. Gaharwar and D. L. Alge, *Biomater. Sci.*, **7**, 1179 (2019).
53. P. Zhao, J. Wang, C. Chen, J. Wang, G. Liu, K. Nandakumar, Y. Li and L. Wang, *Micromachines*, **13**, 200 (2022).
54. M. Shin, K. H. Song, J. C. Burrell, D. K. Cullen and J. A. Burdick, *Adv. Sci.*, **6**, 1901229 (2019).
55. M. Hirsch, A. Charlet and E. Amstad, *Adv. Funct. Mater.*, **31**, 2005929 (2021).
56. A. Moreira, J. Carneiro, J. B. L. M. Campos and J. M. Miranda, *Microfluid. Nanofluidics*, **25**, 10 (2021).
57. A. B. Subramaniam, M. Abkarian and H. A. Stone, *Nat. Mater.*, **4**, 553 (2005).
58. N. Zoratto, D. Di Lisa, J. de Rutte, M. N. Sakib, A. R. Alves e Silva, A. Tamayol, D. Di Carlo, A. Khademhosseini and A. Sheikhi, *Bioeng. Transl. Med.*, **5**, 1 (2020).
59. S.-Y. Teh, R. Lin, L.-H. Hung and A. P. Lee, *Lab Chip*, **8**, 198 (2008).
60. S. Seiffert and D. A. Weitz, *Polymer (Guildf)*, **51**, 5883 (2010).
61. D. M. Headen, J. R. García and A. J. García, *Microsystems Nanoeng.*, **4**, 1 (2018).
62. J. Zhang, X. Li, D. Zhang and Z. Xiu, *J. Microencapsul.*, **24**, 303 (2007).
63. B. B. Lee, P. Ravindra and E. S. Chan, *Chem. Eng. Technol.*, **36**, 1627 (2013).
64. A. S. Qayyum, E. Jain, G. Kolar, Y. Kim, S. A. Sell and S. P. Zustiak, *Biofabrication*, **9**, 025019 (2017).
65. T. A. B. Bressel, A. H. Paz, G. Baldo, E. O. C. Lima, U. Matte and M. L. Saraiva-Pereira, *Genet. Mol. Biol.*, **31**, 136 (2008).
66. Y. Morimoto, M. Onuki and S. Takeuchi, *Adv. Healthc. Mater.*, **6**, 1 (2017).
67. P. H. Kim, H. G. Yim, Y. J. Choi, B. J. Kang, J. Kim, S. M. Kwon, B. S. Kim, N. S. Hwang and J. Y. Cho, *J. Control. Release*, **187**, 1 (2014).
68. T. G. Molley, G. K. Jalandhra, S. R. Nemec, A. S. Tiffany, B. A. C. Harley, T. Hung and K. A. Kilian, *bioRxiv*, 2020.08.30.274654 (2020).
69. W. Leong, T. T. Lau and D. A. Wang, *Acta Biomater.*, **9**, 6459 (2013).
70. A. Lee, A. R. Hudson, D. J. Shiwarski, J. W. Tashman, T. J. Hinton, S. Yerneni, J. M. Bliley, P. G. Campbell and A. W. Feinberg, *Science*, **365**, 482 (2019).
71. S. Roh, D. P. Parekh, B. Bharti, S. D. Stoyanov and O. D. Velev, *Adv. Mater.*, **29**, 1 (2017).
72. D. B. Gehlen, N. Jürgens, A. Omidinia-Anarkoli, T. Haraszti, J. George, A. Walther, H. Ye and L. De Laporte, *Macromol. Rapid Commun.*, **41**, 1 (2020).
73. K. Song, A. M. Compaan, W. Chai and Y. Huang, *ACS Appl. Mater. Interfaces*, **12**, 22453 (2020).
74. D. Zhao, Y. Liu, B. Liu, Z. Chen, G. Nian, S. Qu and W. Yang, *ACS Appl. Mater. Interfaces*, **13**, 13714 (2021).
75. T. J. Hinton, Q. Jallerat, R. N. Palchesko, J. H. Park, M. S. Grodzicki, H.-J. Shue, M. H. Ramadan, A. R. Hudson and A. W. Feinberg, *Sci. Adv.*, **1**, e1500758 (2015).