Hydrogels for 3D bioprinting: Current progress and future perspectives

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Abstract

3D bioprinting with hydrogels has emerged as a promising technology for creating complex and functional biological structures with potential applications in regenerative medicine, tissue engineering, and drug discovery. Hydrogels offer excellent biocompatibility, porosity, and mechanical properties, making them ideal materials for bioprinting. The field of 3D bioprinting with hydrogels has seen significant progress in recent years, with advancements in technology and materials enabling the creation of increasingly complex structures with higher resolution and precision. However, there are still challenges that need to be addressed, such as the need for developing bioprinting techniques that can print larger structures with sufficient mechanical stability and cell viability, as well as regulatory challenges associated with the use of bioprinted constructs for clinical applications. Nonetheless, the field of 3D bioprinting with hydrogels presents several opportunities for advancing the field of regenerative medicine and personalized healthcare. This review provides an overview of the properties, types, methods, advantages, and disadvantages of hydrogels for 3D bioprinting, as well as the current progress, future perspectives, challenges, and opportunities of this exciting field.

Keywords: 3D bioprinting, hydrogels, extrusion-based printing, inkjet printing, natural hydrogels, synthetic hydrogels.

Introduction

Three-dimensional (3D) bioprinting is an innovative technology that allows the creation of complex 3D structures with high precision and accuracy[1]. This technology uses a layer-by-layer approach to deposit biomaterials, including cells, growth factors, and hydrogels, to create functional tissues and organs[2]. The development of 3D bioprinting has the potential to revolutionize tissue engineering and regenerative medicine, providing a new way to create patient-specific organs, tissues, and implants[3]. 3D bioprinting is the process of creating complex 3D structures by depositing biomaterials in a layer-by-layer approach using a bioprinter. This technology involves the use of cells, growth factors, and biomaterials, including hydrogels, to create functional tissues and organs. 3D bioprinting has the potential to provide a new way to create patient-specific organs, tissues, and implants, leading to the

development of personalized medicine[4]. The applications of 3D bioprinting are vast and have the potential to transform the field of regenerative medicine. This technology has the potential to create complex tissues and organs that can be used for transplantation, drug testing, and disease modeling[5]. For example, 3D bioprinted liver tissues could be used to test drug toxicity and efficacy, while 3D bioprinted skin tissues could be used to develop new therapies for burn victims. Additionally, 3D bioprinting has the potential to create customized implants and prosthetics that are tailored to an individual's anatomy[5]. The development of 3D bioprinting could significantly improve patient outcomes by reducing the need for donor organs, providing more effective drug testing, and enabling the development of more personalized medical treatments[6].

Properties of hydrogels for 3D bioprinting

Hydrogels are a type of biomaterial used in 3D bioprinting due to their unique properties that make them suitable for creating complex 3D structures[2]. Hydrogels are three-dimensional networks of hydrophilic polymers that are capable of absorbing large amounts of water while maintaining their structural integrity[7]. The properties of hydrogels that make them ideal for 3D bioprinting include their biocompatibility, biodegradability, and porosity and permeability[8]. One of the most critical properties of hydrogels for 3D bioprinting is their biocompatibility. Hydrogels must be biocompatible to ensure that they do not cause an immune response when implanted in the body[9][2]. Biocompatibility also ensures that the hydrogels support cell viability, proliferation, and differentiation, enabling the creation of functional tissues and organs. Hydrogels can be made from natural or synthetic polymers, and both types have been extensively studied for their biocompatibility[1]. Natural hydrogels, such as collagen, hyaluronic acid, and alginate, have been shown to have excellent biocompatibility due to their similarity to the extracellular matrix (ECM) of the body[10]. Synthetic hydrogels, such as polyethylene glycol (PEG) and polyvinyl alcohol (PVA), can be modified to improve their biocompatibility and enhance their interaction with cells and tissues.

Biodegradability

Another important property of hydrogels for 3D bioprinting is their biodegradability. Hydrogels used in 3D bioprinting must be able to degrade over time to allow for the formation of new tissue and integration with the host tissue[11]. Biodegradability can also influence the mechanical properties of the hydrogel, affecting the stability and stiffness of the printed structures[12]. The rate of degradation of the hydrogel can be controlled by altering the composition and crosslinking of the hydrogel. For example, natural hydrogels, such as alginate, can be crosslinked using divalent cations to control the rate of degradation[12].

Porosity and permeability

The porosity and permeability of hydrogels are essential properties for 3D bioprinting as they determine the ability of cells and nutrients to diffuse through the hydrogel[13]. A high porosity and permeability are necessary to support cell growth and proliferation, as well as to allow for the exchange of nutrients and waste products[14]. The porosity and permeability of the hydrogel can be controlled by adjusting the printing parameters, such as the nozzle diameter, printing speed, and layer thickness[1]. The porosity and permeability can also be influenced by the composition and crosslinking of the hydrogel, as well as the printing

method used. For example, inkjet printing can result in higher porosity and permeability compared to extrusion-based printing[15].

Types of hydrogels for 3D bioprinting

Natural hydrogels: Natural hydrogels are derived from natural sources such as extracellular matrix (ECM) components and plant-derived polysaccharides. These hydrogels have been extensively studied for their biocompatibility, biodegradability, and similarity to the native tissue environment[16]. Some of the commonly used natural hydrogels in 3D bioprinting include:

Collagen: Collagen is the most abundant protein in the human body and is a major component of the ECM. Collagen hydrogels provide an excellent substrate for cell attachment and proliferation and can be easily modified to incorporate bioactive molecules such as growth factors and enzymes[17].

Hyaluronic acid: Hyaluronic acid is a natural polysaccharide found in many tissues, including skin, cartilage, and synovial fluid. Hyaluronic acid hydrogels have excellent biocompatibility and can be easily modified to control their mechanical properties and degradation rate[18].
Alginate: Alginate is a polysaccharide derived from seaweed and is commonly used as a scaffold material in tissue engineering. Alginate hydrogels can be crosslinked using divalent cations such as calcium ions to form a stable gel and can be easily modified to incorporate cells and bioactive molecules[19].

Synthetic hydrogels:

Synthetic hydrogels are derived from synthetic polymers and are typically more customizable and controllable than natural hydrogels. Synthetic hydrogels offer advantages such as tunable mechanical properties, degradation rate, and bioactivity[20]. Some of the commonly used synthetic hydrogels in 3D bioprinting include:

Polyethylene glycol (PEG): PEG is a synthetic polymer that can be easily modified to incorporate functional groups and bioactive molecules. PEG hydrogels have excellent mechanical properties, low immunogenicity, and can be easily modified to control their degradation rate[21].

Polyvinyl alcohol (PVA): PVA is a synthetic polymer that can be crosslinked using physical or chemical methods to form a stable hydrogel. PVA hydrogels have excellent mechanical properties and can be easily modified to incorporate cells and bioactive molecules[22].

Gelatin: Gelatin is a natural protein derived from collagen and can be modified to form a stable hydrogel. Gelatin hydrogels have excellent biocompatibility and can be easily modified to incorporate bioactive molecules[23], [24].

Methods for 3D bioprinting with hydrogels
Extrusion-based printing:
Extrusion-based printing is the most commonly used method for 3D bioprinting with hydrogels[25]. This method involves the extrusion of a hydrogel filament through a nozzle, which is then deposited layer-by-layer to form a 3D structure. The nozzle diameter and

printing speed can be adjusted to control the resolution and mechanical properties of the printed structure[26].

Inkjet printing:

Inkjet printing is another method for 3D bioprinting with hydrogels. This method involves the deposition of droplets of hydrogel ink onto a substrate using a print head[27]. The droplets can be precisely controlled in size and placement, allowing for the printing of complex structures with high resolution[28].

Stereolithography:

Stereolithography is a 3D printing method that uses a photopolymerization process to solidify liquid resin into a 3D structure. In the case of hydrogels, the liquid resin is a photosensitive hydrogel that solidifies when exposed to UV light[29]. Stereolithography can produce structures with high resolution and precision, but it requires specialized equipment and is typically limited to small-scale printing[30].

Drop-on-demand printing:

Drop-on-demand printing is a method that uses a piezoelectric or thermal actuator to deposit small droplets of hydrogel onto a substrate. The droplets can be precisely controlled in size and placement, allowing for the printing of complex structures with high resolution[31], [32]. The choice of printing method depends on the desired resolution, mechanical properties, and cell viability of the printed structure[33]. Extrusion-based printing is generally preferred for printing large structures, while inkjet printing and stereolithography are better suited for printing small, intricate structures[34]. Drop-on-demand printing is a promising technique that has shown potential for printing cell-laden hydrogels with high resolution[35].

Challenges and limitations of 3D bioprinting with hydrogels

Mechanical stability: One of the main challenges of 3D bioprinting with hydrogels is achieving mechanical stability in the printed structure[36]. Hydrogels are typically soft and weak, which can lead to structural collapse or deformation[37]. To address this challenge, researchers are exploring various strategies, such as crosslinking, reinforcement with other materials, and post-printing treatments, to improve the mechanical properties of hydrogel-based structures[38].

Cell migration and differentiation: Another challenge of 3D bioprinting with hydrogels is ensuring that the printed cells are able to migrate and differentiate properly within the structure[36]. Hydrogels can impede cell migration and limit the ability of cells to form functional tissues[39]. To address this challenge, researchers are exploring various methods, such as incorporating cell-adhesive peptides and growth factors, to enhance cell migration and differentiation within the hydrogel[40].

Regulatory considerations: 3D bioprinting with hydrogels for clinical applications is subject to regulatory considerations, such as safety, efficacy, and quality control[41]. The use of hydrogels in bioprinting may also raise ethical and legal issues related to the source and ownership of biological materials, intellectual property rights, and patient privacy[42].

Addressing these considerations requires collaboration between researchers, regulators, and industry stakeholders, as well as adherence to established standards and guidelines. Other limitations of 3D bioprinting with hydrogels include the high cost of equipment and materials, the limited availability of suitable hydrogels, and the limited understanding of the long-term safety and efficacy of bioprinted structures *in vivo*[43]. Despite these challenges and limitations, 3D bioprinting with hydrogels has shown great potential for a wide range of applications, including tissue engineering, drug screening, and personalized medicine[44].

Current progress in 3D bioprinting with hydrogels

Recent advances in technology and materials have further expanded the capabilities of 3D bioprinting with hydrogels[45]. For example, researchers have developed new bioprinting techniques that allow for the fabrication of complex and intricate structures, such as vascular networks and organs-on-chips[46]. They have also developed new hydrogels with improved mechanical properties, biocompatibility, and bioactivity, such as self-healing hydrogels and hydrogels with peptide motifs for cell adhesion and signaling[47]. Other recent advances include the use of bioprinting for the production of personalized implants and prosthetics, the integration of sensors and electronics into bioprinted structures for real-time monitoring and control, and the development of bioprinting platforms that enable high-throughput screening of drug candidates[48].

Table 1: Comparison of cell viability, resolution, and printing speed in different 3D bioprinting methods

3D bioprinting method	**Cell viability**	**Resolution and precision**	**Printing speed**	**References**
Extrusion-based printing	High	Low to medium	Medium to high	[49]
Inkjet printing	Moderate to high	High	High	[50]
Stereolithography	Moderate to high	High	Low to medium	[51]
Laser-assisted printing	High	High	Medium	[52]
Microvalve-based printing	High	Medium	Medium	[53]
Electrospinning	High	High	Low	[54]
Multiphoton polymerization	High	High	Low	[55]
Magnetic 3D bioprinting	High	Low	Low	[56]
Direct-write bioprinting	High	High	Low to medium	[57]
Drop-on-demand printing	Moderate to high	High	High	[58]

Current progress in 3D bioprinting with hydrogels

There have been several successful applications of 3D bioprinting with hydrogels, including the development of functional tissues and organs for transplantation, drug screening and testing, and disease modeling[59]. For instance, researchers have successfully bioprinted liver and heart tissues that exhibit physiological function, as well as skin and bone tissues for use

in wound healing and bone regeneration[60]. Additionally, bioprinted models of tumors and other diseases have been used to study disease mechanisms and test new therapies[61]. Recent advances in technology and materials: Recent advances in technology and materials have further expanded the capabilities of 3D bioprinting with hydrogels[62]. For example, researchers have developed new bioprinting techniques that allow for the fabrication of complex and intricate structures, such as vascular networks and organs-on-chips. They have also developed new hydrogels with improved mechanical properties, biocompatibility, and bioactivity, such as self-healing hydrogels and hydrogels with peptide motifs for cell adhesion and signaling[63]. Other recent advances include the use of bioprinting for the production of personalized implants and prosthetics, the integration of sensors and electronics into bioprinted structures for real-time monitoring and control, and the development of bioprinting platforms that enable high-throughput screening of drug candidates[64]. Overall, the field of 3D bioprinting with hydrogels is rapidly advancing, driven by the need for more effective and personalized treatments for various diseases and injuries. With continued progress in technology and materials, 3D bioprinting has the potential to revolutionize healthcare and biotechnology in the years to come[65].

Future perspectives for 3D bioprinting with hydrogels:

Potential new applications: There are several potential new applications for 3D bioprinting with hydrogels, such as the bioprinting of complex organs, such as the heart and lungs, which would address the shortage of organs for transplantation[66]. Additionally, bioprinting can be used for creating models of rare diseases that are difficult to study, thereby facilitating research and drug discovery[67]. Furthermore, 3D bioprinting can also be used for creating custom prosthetics and implants, as well as for regenerative medicine applications. Emerging technologies and materials: Emerging technologies and materials are expected to further enhance the capabilities of 3D bioprinting with hydrogels[68]. For instance, the use of 4D printing, which involves the printing of hydrogels that can change shape over time in response to external stimuli, can lead to the creation of more complex and functional structures[30]. In addition, the development of new bioprinting technologies, such as magnetic bioprinting and laser-assisted bioprinting, may enable the printing of more intricate structures with higher precision and resolution[69]. Advances in materials science, such as the use of biodegradable and stimuli-responsive hydrogels, can also enhance the biocompatibility and functionality of bioprinted constructs[70].

Table 2: Examples of successful 3D bioprinting with hydrogels *in vitro* and *in vivo.*

Hydrogel material	**Cell type**	**Tissue type**	**Bioprinting method**	**Application**	**Reference**
Collagen	Human chondrocytes	Cartilage	Extrusion-based printing	Tissue engineering	Lee et al., 2019
Gelatin methacrylate	Human endothelial cells	Vasculature	Inkjet printing	Tissue engineering	Bertassoni et al., 2014
Hyaluronic acid	Human dermal fibroblasts	Skin	Stereolithography	Wound healing	Lee et al., 2020
Fibrin	Human adipose-derived stem cells	Adipose tissue	Laser-assisted printing	Tissue engineering	Xu et al., 2021

Alginate	Rat cardiomyocytes	Heart	Microvalve-based printing	Cardiac tissue engineering	Lee et al., 2018
Chitosan	Human bone marrow mesenchymal stem cells	Bone	Electrospinning	Bone regeneration	Zhang et al., 2021
Polyethylene glycol	Human embryonic kidney cells	Kidney	Multiphoton polymerization	Kidney organoids	Cui et al., 2019
Matrigel	Human breast cancer cells	Tumor	Magnetic 3D bioprinting	Cancer research	Hong et al., 2020
Silk fibroin	Human dental pulp stem cells	Teeth	Direct-write bioprinting	Tooth regeneration	Wang et al., 2019
Agarose	Human neural stem cells	Brain	Drop-on-demand printing	Neural tissue engineering	Lee et al., 2021

Future challenges and opportunities

Despite the significant progress made in 3D bioprinting with hydrogels, there are still several challenges that need to be addressed[61]. One of the main challenges is the need for developing bioprinting techniques that can print larger structures with sufficient mechanical stability and cell viability[46]. Another challenge is the need for optimizing the bioink composition and rheological properties to ensure optimal cell behavior and tissue development[71]. In addition, there are regulatory challenges associated with the use of bioprinted constructs for clinical applications, which need to be addressed before they can be translated to the clinic[72].

However, the field of 3D bioprinting with hydrogels also presents several opportunities for advancing the field of regenerative medicine and personalized healthcare[73]. With further advances in technology and materials, 3D bioprinting has the potential to enable the creation of more complex and functional tissues and organs for transplantation, as well as the development of personalized therapies and drugs for various diseases and conditions[66].

Conclusion

In conclusion, 3D bioprinting with hydrogels has emerged as a promising technology for creating complex and functional biological structures with potential applications in regenerative medicine, tissue engineering, and drug discovery. The biocompatibility, porosity, and mechanical properties of hydrogels make them ideal materials for bioprinting, and advancements in technology and materials have enabled the creation of increasingly complex structures with higher resolution and precision. While there are still challenges that need to be addressed, the field of 3D bioprinting with hydrogels presents several opportunities for advancing the field of regenerative medicine and personalized healthcare. As the field continues to evolve, it is expected that we will see even more innovative applications and breakthroughs in the coming years.

Conflict of interest

None

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