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REVIEW

A review on biocompatibility nature of hydrogels with 3D printing techniques, tissue engineering application and its future prospective

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Abstract

Recently, tissue engineering (TE) is one of the fast growing research fields due the accessibility of extra-molecular matrix (ECM) at cellular and molecular level with valuable potential prospective of hydrogels. The enhancement in the production of hydrogel-based cellular scaffolds with the structural composition of ECM has been accelerated with involvement of rapid prototyping techniques. Basically, the recreation of ECM has been derived from naturally existed or synthetic hydrogel-based polymers. The rapid utilization of hydrogels in TE puts forward the scope of bioprinting for the fabrication of the functional biological tissues, cartilage, skin and artificial organs. The main focus of the researchers is on biofabrication of the biomaterials with maintaining the biocompatibility, biodegradability and increasing growth efficiency. In this review, biological development in the structure and cross-linking connections of natural or synthetic hydrogels are discussed. The methods and design criteria that influence the chemical and mechanical properties and interaction of seeding cells before and after the implantations are also demonstrated. The methodology of bioprinting techniques along with recent development has also been reviewed. In the end, some capabilities and shortcomings are pointed out for further development of hydrogels-based scaffolds and selection of bioprinting technology depending on their application.

Keywords Hydrogels · Extra-molecular matrix (ECM) · Biocompatibility · Bioprinting · Tissue engineering

Introduction

Tissue engineering can simply be defined as a field of science having multi-disciplinary nature of combining life sciences and engineering technology together with molecular biological attributes to improve the structural regeneration and growth of tissues for malfunctioning and clinical applications. The approach of the tissue engineering is to develop new techniques for biocompatible seed cells and tissues for different transplants directly or indirectly in the body. The materials used for TE should be biocompatible which means that they should be compatible without affecting the biological and physical nature of the living tissues. These biomaterials influence the focus of TE toward the development of reparative cells to make an efficient matrix that is biologically suitable for implantation through appropriate supportive scaffold with biocompatible nature and improve the growth of the tissue [1]. Recently, the statistics released by US department of Health and Services show that from 2012 to 2017, the number of patients of transplants raised from 28,054 to 34,770, respectively, with more than 114,000 patients who are still are on the waiting list [2]. The history of tissue engineering moves back to early 1970s, when the demand of transplantation of organs in medical field rose with less number of donor's availability [3]. This leads to the combination of cell and organ developmental biology, implantation engineering, clinic medical and veterinary sciences, biomaterials and bio physics and mechanics [4]. Researchers started working on tissue engineering with combination of these fields for creating living tissues by utilizing the few cells from any particular body part and linking them with different biomaterials like polylactic acid [5], polyethylene glycol [6], hydrogel collagen [7] or different types of

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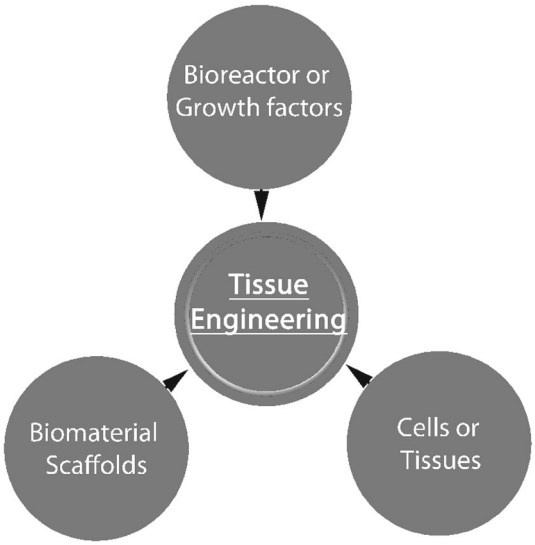

Fig. 1 Schematic representation of main elements of tissue engineering

extracellular matrix [8] for covering the shortage of donors with fast recovery, improved quality and less complications after transplantation [9].

Tissue engineering includes the development of appropriate 3D scaffolds that should have the ability to provide a regenerative environment for the growth of tissues and organs. Typical biomaterial scaffolds are stuffed with bioreactors having the function of mechanical support and chemical stimuli to growing cells. These scaffolds may be directly implanted to the infected part or kept in vitro environment for synthesizing cells for further implantation [10]. The essential factors of tissue engineering are shown in Fig. 1.

The implanted cells or tissues with the supporting matrix have the ability to reconstruct within the scaffolds and regenerate the infected parts of the body. But in doing so, there are many challenges of regeneration of seeded cells, and then, transplantation has its own complications. The homogenous growth of the seeded cells into their parents' cells within the scaffold is one of the biggest challenge. Secondly, the low-quality growth cells also affect the transplantation and badly influence the interaction of cell and supporting matrix. So to overcome these challenges of the tissue engineering, some natural or synthetic biopolymers are used in matrix interface to enhance the regeneration process [1, 11]. These matrix materials should pose the properties of reproducing themselves in different kinds of cells, and the process should be cost-effective and easily processed [12].

The main concept of this review is to explain the importance of hydrogels in the field of tissue engineering with the characteristics that enable such biomaterials to easily interact with particular tissues and can exist with normal working conditions in specific environment during direct implantations or in vivo/vitro. The stability and degradability of such materials are very important factors during tissue engineering applications. The classification of hydrogels is given on the basis of naturally and synthetically extracted biomaterials with recent development for improving the biocompatibility, biodegradability and mechanical properties. Further, additive manufacturing (AM) techniques for such biomaterials with their specific characteristics and design criteria are discussed. The characteristics of bioinks and criteria for selecting these bioinks for specific method of 3D printing with considerable limitations are also explained.

Hydrogels

Hydrogels belonged to hydrated polymeric materials having $\geq 90\%$ of water content by weight. As hydrogels have greater pervading quality for oxygen and also no response for foreign bodies, they were applied in the field of biomedical as contact and intraocular lens from 1960s [13]. Researchers always worked on finding the materials for some replacement of extracellular matrix (ECM) for structural support of the cells, and hydrogels are one of the best materials as they have great resemblance with natural ECM. Hydrogels have the great ability to control cellular and molecular attachments with structural and functional integrity. They are also biocompatible and biodegradable in nature [9]. The faculties which hydrogels provide during tissue engineering are similar to properties of natural ECM, which helps in the attachment and migration with retaining the biochemical nature of the cells [14], enables easy and fast diffusion of the nutrients [9] with mechanical and biological support to enhance the growth of seeded cells [15]. The scaffolds can be manufactured with natural or synthetic hydrogels having resemblance with natural ECM.

The general benefits of the hydrogels are biocompatible, biodegradable and easily injected in vitro for growth after specific conditions, great mean of transportation of the nutrients during development process and can easily be modified for the usage in different places [16]. It also has some limitations: It usually provides low mechanical strength, is very difficult to handle, needs high sterilized conditions and is expensive for treatment.

Types of hydrogels

Hydrogels, on the basis of their nature, place of transplantation and requirement of support, can be classified into two main categories as naturally existed and synthetically prepared hydrogels. Both the types have their own advantages and uses. Naturally existed hydrogels possess natural ligands which provide significant adhesion to the cells and usually was obtained from natural ECM, but some are extracted

Table 1 Types of cells and tissue engineering applications of naturally existed hydrogels

Hydrogels from natural polymers	Type of cells	TE applications	Study/references
Collagen	Astroglial cells, chondrocytes	Spinal cord, vocal cord, skin, cartilage, neural	[28, 30, 31, 21, 22, 32, 33, 34, 35]
Gelatin	Fibroblasts, chondrocytes	ECM, cartilage	[36, 37, 38, 39, 40]
Pullulan	Fibroblasts, mesenchymal stem cells, smooth muscle cells, human umbilical vein endothelial cells	Skin, cartilage, soft tissues stem cell culture, vascular	[41–43, 44, 45, 46, 47]
Hyaluronic acid	Fibroblasts, chondrocytes, human embryonic, stem cells	ECM, cartilage, skin, eye, facial, intraperitoneal, vascular, connective tissue	[48, 49–51, 52, 53, 54, 55]

from non-mammalian sources like brown seaweed alginate [17]. However, synthetically produced hydrogels can be customized chemically according to the application and usage of the material [18]. They lack the property of cell adhesion, but it can be improved through functionalization with ECM proteins.

Hydrogels with natural materials

The hydrogel polymers which originated from the national biomaterials are classified as natural hydrogels. Many hydrogels made of natural proteins such as collagen and gelatin are biodegradable, biocompatible with supportive nature during cellular attachment [16]. With these advantages, they also have some drawbacks like variation in properties during the preparation of every batch, difficult to synthesis and process and material properties are not constant [19]. In tissue engineering, the applications of naturally existed hydrogels are numerous as shown in Table 1.

Collagen

The most abundantly used protein as hydrogels is collagen, which is present almost 30% in the body of mammals [20]. In tissue engineering, collagen is the most important protein used because of its triple-standard helical structures with self-aggregating quality using covalent and hydrogen bonds. They construct different types of cartilages including fibrous or articular [4]. The quality of these proteins is the variation in their supportive linkage that can be changed according to the use in vivo [21] by utilizing their chemical [9] or physical cross-linking designs [22] or mixing with different polymers [23]. Collagen has the ability to form different kinds of gels, sponges, etc., which exist due to variation in strands of collagen and induction in the cross-linking.

It has a great potential for the production of hydrogels as it has resembling properties of natural ECM having the ability of enhancing cell functionality and adhesion properties. It can be used in the manufacturing of many types of artificial tissues like skin [24], cartilage [25], heart valves [26], breast reconstruction [27], vocal cord [9, 28] and spinal cord [29]. Recently, many researchers are working for the improvement in the use of collagen-based scaffolds. Calabrese worked a lot in the development of collagen and discussed the chondrogenesis process for converting collagen into cartilage and the full differentiation of bioactive factors during vivo stage [30]. He also worked on hydrogels bone formation with collagen/hydroxyapatite as biomaterial scaffolds in vitro and after implantation [31, 32].

Different techniques have been used for the fabrication of collagen hydrogels. The manufacturing of aligned wall composite fibers is done using electrospinning technique from collagen and other protein fibers because it became more biocompatible with the mixing with electrospun fibers [33]. Nakada et al. [34] also worked on the improving of biocompatibility of collagen with denaturizing the collagen at high temperature and low pressure to convert collagen fibers into cross-linkage structures. Some cross-linking of fibers like carbodiimide also elevate biocompatibility and stability of collagen–chitosan scaffolds [35].

Gelatin

Gelatin is another biomaterial used for the manufacturing of hydrogels. It can be obtained by partial hydrolysis of collagen which is a mixture of proteins and peptides usually obtained from skins, bones and connective tissues of the animals. Gelatin is also very important because of its degradability and compatibility nature in vitro as well as during direct implantation. It also retains its bioactive nature

including MMP-sensitive sites and RGD sequences with cost-effectiveness [56].

Gelatin can easily be obtained from different by-products of the animals, forming high strength and changeable natured hydrogels. Thermally, they are less stable at high temperatures with water-soluble property. They have wide range of applications in biomedical [36]. The capability of cross-linking for the gelatin is little less, but its mechanical supportive strength has been increased with the technique of double network of photo-cross-linking of gelatin and gellan gum [37]. As the strength of the DN hydrogels was not impressive as encapsulated cells and cell-compatible conditions, the model of micro-gel-reinforced hydrogels was suggested with the same products, gelatin and gellan gum for better biological and mechanical properties as compared to DN hydrogels [57]. Some researchers worked on improving biocompatibility of the gelatin by mixing other non-toxic and biocompatible materials like dextran aldehyde [58] or chitosan [59].

Research on gelatin also reveals that they do not influence the functional and physical conditions of antigenic response toward the body, but they affect macrophages to activate them [60]. Development has also been done to improve the biocompatibility of gelatin and related biomaterials by combining sponge scaffolds of hydroxyapatite with different modified surfaces [38, 61]. The altering of soaking process by depositing the nano-hydroxyapatite helps to improve the growth of seeded cells and increase their adhesive bonding properties [39]. For the additive manufacturing techniques, a 3D scaffold has been developed with PCL placed between gelatin–chitosan hydrogels for congenital heart defects. They are biodegradable patches containing a thin PCL-layer self-assembled core which provide significant strength to the ventricular walls for proper function. This novel research helps the doctors to facilitate patients more efficiently [40].

Pullulan

Another kind of hydrogel is pullulan, usually manufactured from the yeast such as fungus *Aureobasidium pullulans*. In 1958, Bernier was the first scientist to extract the pullulan and tried to understand its chemical structure. Pullulan is a type of exopolysaccharide (EPS) formed as thick sledge in amorphous form on the surface of bacterial infected cells [62–64]. The appearance of the pullulan powder is white with no taste and odor. It is not soluble in any organic or inorganic solvents except water. Due to the properties of water-soluble and toxic nature, pullulan is used in medical application such as drugs carrier, preparation of syrups [41–43] and packaging material [44].

Pullulan can also be manufactured by fermentation of different waste materials [45]. Machy also worked on the extraction of pullulan and dextran which improves the rapid growth of cells located in endothelium region [46]. Similarly, Amrita et al. [47] utilized pullulan and their derivatives as scaffolds for tissue engineering by pore wall mineralization method with enhanced osteo-conductive properties. To improve the mechanical properties of the pullulan, Aschenbrenner employed cross-linking technique to combine pullulan and dextran [65]. Therefore, different types of pullulan including nanoparticles and nano-gels can be used in drug delivery systems, curing of tumor cells and supporting normal cells for toxicity of drugs.

Hyaluronic acid

Hyaluronic acid (HA) chemically known as hyaluronan naturally was found in the body of mammals having non-sulfated glycosaminoglycan and extensively found in the different body parts including neural, epithelial and connective tissues, eye and joint fluids [48, 66]. They are very essential part of different human body mechanisms such as cell growth, wound healing, embryonic and tumor development [49–51].

On the basis of cross-linkage variation, HA can be divided into two categories such as monophasic or biphasic [52]. Both of them are toxic-free fillers, and biphasic HA mostly is used in hyaluronidase resistance and syringeability [53]. Molecular weight is an important factor in changing the properties and application of HA with other materials. Similarly, HA is water-soluble, helps in the process of angiogenesis, biodegradability and does not provoke any immunogenic response with higher molecular weight. HA with lower molecular weight displays angiogenic, immunogenic and inflammatory response [54]. HA hydrogels are covalent bonded cross-linked manufactured by different methods including esterification [67], electrospinning cryogelation [68] and annealing [69]. The properties like biocompatibility and biodegradability of hyaluronic acid have been enhanced by photo-polymerization of UV-initiators during cross-linking process [70]. Recently, researchers are focusing on the biomedical applications of HA and its derivatives like visco-supplementation [55], wound healing [71], tissue engineering [72] and therapeutics [50].

Hydrogels with synthetic materials

Synthetic polymers have great influence for the researchers to be utilized in the field of biomedical and pharmaceutical applications because of their wide availability, biocompatibility, biodegradable nature and easy to handle. It also provides wide range of material selection with different physical and chemical behavior suitable for various applications as shown in Table 2. For the first time in 1954, Wichterle and Lim worked for the development of polymeric hydrogel biomaterial using 2-hydroxyethyl methacrylate (HEMA) and ethylene dimethacrylate (EDMA) as copolymers to use

Table 2 Biocompatibility nature of different types of synthetically manufactured hydrogels and their tissue engineering applications

Hydrogels from synthetic polymers	Biocompatibility nature	TE applications	Study/references
Poly (lactic and glycolic) acid	Products degrade during metabolic pathway, localized inflammation	Bone, nerves, skin, ligament, tendon, vessels, cartilage, kidney, tumor, bladder, liver cells	[74, 75, 76, 77, 79, 80, 81, 82]
Polyethylene oxide and polyethylene glycol	Hydrolysis, mild foreign in PEO and minimal foreign in PEG body reaction, no inflammation	Bone, skin, muscles, vessels, cartilage, nerves, cardiovascular, intraperitoneal, liver cells	[83, 84, 85, 86, 87, 88, 89]
Polycaprolactone	Hydrolysis, minimal inflammation	Skin, ligament, tendon, vessels, nerves, cartilage, bone, retina	[90, 91, 92, 93, 94]

as contact lenses [73]. Generally polymeric hydrogels are bonded with covalent or ionic bonds and show less biocompatibility nature as compared to the naturally derived polymers. However, the prominent advantages of synthetic polymers are comparatively high degradation and mechanical properties [74] with simple structure and monomeric unit constituency [75].

Poly(lactic and glycolic) acid-based hydrogels

Poly(lactic and glycolic) acid (PLGA) has influence for the extraction of hydrogels because of considerable properties including biocompatibility, biodegradation rate, clinical applications at human level, highly allowable for modifications in surface properties and ease of transportation with handling [76]. PLGA and their copolymers are exclusively used in tissue engineering [75] especially for bones and cartilages due to their impressive strength and biodegradable nature [76, 77]. A rapid increase has been found for the usage of polymeric biomaterials in medical applications with the combination of tri- and multi-block copolymers of PLA for hydrogel preparation [78]. Similarly, the mixture of hydrophilic PLA polymers exhibits specific and useful properties with variable concentration ratios and possibilities.

Researchers worked for the degradation of poly(lactic and glycolic) acid polymers which have been considered as one of the main concerns for tissue engineering because intermediate degradation leads to decrease the pH value of the implanted cells and this action reduces the mechanical properties in newly generated bone [79]. The concentrations of lactic and glycolic acid may also affect the degradation process such as higher concentration of lactic acid take more time for biodegradation that will prolong the support for tissue regeneration [80].

Recently, more work has been done on biocompatibility of PLA-based scaffolds like bovine amniotic epithelial stem cells [95], osteoblast-like human bone fibroblast (MG-63) cells [81, 96] and nano-hydroxyapatite/PLA scaffolds with human bone marrow-derived mesenchymal stem cells (hMSCs) [82]. Biocompatibility of PLA scaffolds has also been enhanced by employing the techniques like organic solvent-free extraction [97], room temperature ionic liquids (RTILs) [98] and electrospinning technique [99]. The scaffolds of such polymers (PLA, PGA and PLGA) also provide mechanical support, guidance for the growth of new tissues and help in the complete degradation in the body for pathologically altered tissue structures such as skin, ligaments, skeletal muscles and vascular tissues [74].

Polyethylene oxide- and polyethylene glycol-based hydrogels

Polyethylene oxide (PEO) and polyethylene glycol (PEG) are also abundantly used as biomaterials for extracting hydrogels [100]. The functional attributes of PEO and PEG hydrogels are photo-polymerization capability, suitable mechanical properties, easy to handle for scaffold structures and chemical composition. All these characteristics make them suitable for 3D models for tissue development. The drawback of these hydrogels is that they do not provide sufficient adhesive support to the cells due to the limited antigenicity, immunogenicity, cell adhesion and protein binding [83].

The major properties that researchers wanted to achieve with the hydrogels are biodegradability, biocompatibility, thermo-sensitivity and easy handling for biomedical applications, and polyethylene glycol (PEG)-based copolymers are perfect biomaterial for such attributes. PEG and PEO are also permitted by FDA for pharmacological applications [84]. Combination of copolymers of PEO [101] and PEG [102] with PLLA produced polycaprolactone hydrogels with thermal reversibility. Degradability of these hydrogels has also been enhanced by combining them with oligopeptides [103], hydrolytically degradable PLA [104] and carboxymethyl cellulose [105] and PLLA for the reduction of tumor growth

factor (TGF-β) [78]. PLGA showed great biocompatibility with both PEO and PEG as compared to other biomaterials like poloxamer [84]. Hou et al. [85] employed different bioactive and compatible PEG-scaffolds for tissue engineering applications with new designs and manufacturing techniques.

PEG has great compatibility nature which helps to reduce the growth of thrombus and damage caused to the tissues in vitro/vivo because PEG suppresses the platelet adhesion process. Secondly, it is also used as coating material for drugs carrier delivery purposes [83]. Incorporation of RGD sequences into PEG enhances the cell growth and attachment [86]. Similarly, Acr–PEG–RGD has also helped to improve the mineral distribution and osteoblast attachment for rat caldaria [106]. The mixture of PEG–RGD leads to the improvement of implanted seed cells in their growth and reduces the danger of thrombus formation by non-specific absorbing of fibrinogen and proteins from plasma and serum, respectively [87]. Recently, researchers have also worked for more biocompatible synthetic PEG, PEG–chitosan, PEG–polypeptides and multi-arm PEG hydrogels [88, 89].

Polycaprolactone-based hydrogels

Polycaprolactone (PCL), biodegradable, semicrystalline and hydrophobic polyester, allowed by the Food and Drug Administration (FDA) is used as drug delivery and in medical devices [107]. The application of PCL in bone tissue engineering is an integration of bioactive glasses and calcium phosphate-based ceramics which improves its mechanical properties, bioactive nature and degradation rates [108] because PCL lacks such properties originally [109, 110]. Some other applications of the PCL-based products are correction of facial aging including long-lasting and nourishing effects, decrease in volume and enhancing the clearness of skin via tissue engineering [90, 91]. The biocompatibility response of PCL for periosteal cell culture systems and human fibroblasts is outstanding [92].

The combination of PCL and other biomaterials also provides a great degree of range for the researchers to provide more suitable environment for protein growth and other bioactivities. The blend of PCL and chitosan at a ratio of 3:1 with 8% and 1%, respectively, improves the response of seeded tissues and enhances the protein observing capacity of mixture [93]. The blend of heparin and curdlan sulfate with PCL efficiently reduces thrombus formation due to the surface engineering, and similarly, biocompatibility can also be improved by combining PCL with PEG employing the techniques of electrospinning and cross-linking [94]. However, further enhancement in biocompatibility of PCL can be done via two-step modification using air plasma and carbodiimide [67].

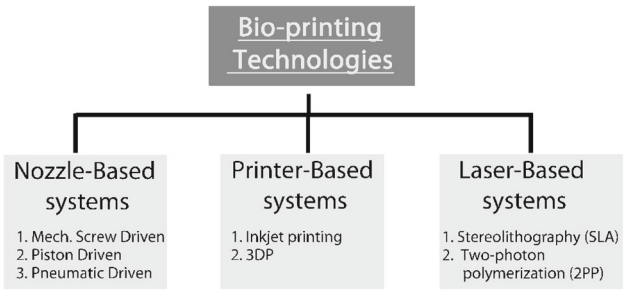

Fig. 2 Overview of different types of bioprinting techniques

Overview of hydrogel bioprinting technologies

The fabrication of biological organs and artificial tissue with the help of additive manufacturing (AM) is one the greatest milestone achieved by the researchers. Three dimensional (3D) printing of biomaterials commonly known as bioinks is to manufacture 3D structures like bones and tissues. These bioinks are composed of specific biocompatible materials so that they can support cellular attachments, proper growth and their function during and after printing. Biocompatibility of these materials is very important for the bioprinting because they are supposed to interact directly during extrusion, so the main focus of the researchers is on the rheological behaviors and cross-linking methods for these materials to get precise and accurate deposition [111, 112]. The combination of biomaterials with living cells also provides a potential mixture for the bioprinting of self-supporting designs. Secondly, the biocompatible materials also support cell viability as non-cytotoxic and show appropriate swelling properties for short term [113]. Hydrogels are the best selection for bioinks as they are biocompatible, biodegradable and structurally similar to naturally existing extracellular matrix (ECM) with hydrophilic environment which promote the cell growth. Due to hydrophilic nature, hydrated structures and channels are created with help in encapsulation of cells.

Both types of hydrogels including naturally existed or synthetically prepared can be employed for biofabrication. Collagen [114], gelatin [115], alginate [116] and chitosan [117] are efficiently used for bioprinting because of their high biocompatibility. But, structurally they are naturally very weak which limits their application in biofabrication [118]. On the other hand, synthetic hydrogels have better mechanical support, but degradation may prevent their utilization for bioprinted products [118, 119]. Bioprinting is divided three main categories: inkjet bioprinting, robotic dispensing and laser-assisted bioprinting [120, 121] on the basis of printing processes as shown in Fig. 2 and further explained by rheological, biological, interfacial and degradation properties.

Along with the characteristics of the bioinks and their biocompatibility, bioprinting also depends on the different parameters which decide the printing technique and suitable

Table 3 Different characteristics and parameters of bioprinting techniques

Types of bioprinting	Working principle	Cell viability (%)	Size of the nozzle	Resolution (μm)	Study/references
Robotic dispensing	Contact	40–95	20 μm–mm	>100	[118, 120, 122]
Inkjet	Non-contact	>85	20–150 μm	50–300	[111, 118, 122, 123, 124]
Laser-assisted	Non-contact	>95	Nozzle-free	20–80	[111, 118, 122]

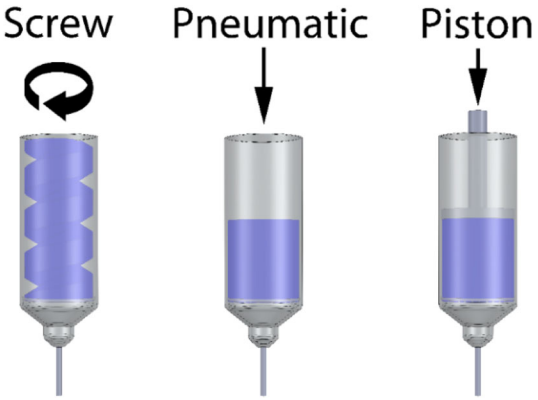

Fig. 3 Schematic demonstration of three robotic dispensing systems [120]

optimization needed for successful fabrication of tissue constructions. Some parameters of the respective techniques are listed in Table 3.

Robotic dispensing

Robotic dispensing 3D printer with a disposable syringe (plastic or metallic depending on the bioink) extrudes the biomaterial (bioink) through the nozzle with the help of mechanical screw or piston mechanism or pneumatic system as shown in Fig. 3. The pneumatic control system allows the pressurized air to extrude the bioink which may show some delay time during the compression of air [122], but the piston-driven system provides direct interaction of pressurized surface and bioink material which provides sufficient control and smooth printing. Both of these systems are very feasible for the printing of cells and tissues [121, 122]. In mechanical driven screw system, the extrusion and feed of the bioink is controlled with the rotational motion of the screw having specialized designs [120]. High-viscosity bioinks are favorable for printing through screw control system, but the problem of pressure drop may harm the cells. Main feature of these systems is the continuous extrusion of the material in the form of filaments.

The important hydrogels typically used as bioinks in robotic dispensing 3D printing are collagen [125], fibrin [126], alginate [116, 127, 128], GelMA [129, 130] and hydrogel blends [131, 132]. The application of such hydrogels for biological means is difficult because they changed into gel form so quickly and collapse due to their own weight after printing [133]. The researchers have worked to improve the supporting techniques by fast curing [134, 135] and using support baths during the printing of such biomaterials [133, 136]. Geo et al. [137] employed robo-dispensing technique to manufacture an organ with micro-channels inside it as shown in Fig. 4.

The design of the nozzle is coaxial, and alginate of 2% solution and solution of $CaCl_2$ of 4% were extruded with varying flow rates. The hollow filament was extruded due the coaxial arrangement with an average inner diameter of 892 μm. Further, the results of perfusion test explained that the printed structure provides sufficient perfusion without any blockage. Another alginate-based material prepared by adding methylcellulose (MC) in 3% alginate solution having improved viscosity characteristics is used for bioprinting via robotic dispensing 3D plotting technique [138], and these scaffolds showed high elasticity, stability, microporosity with cross-linkage. Lee et al. [139] demonstrated an innovative technique with the combination of robot-dispensing system and aerosol spraying of surface gelation to fabricate 3D alginate hydrogel scaffold with 100% connected pores in a controlled fashion as shown in Fig. 5. The alginate-based scaffold implanted with cell-laden micro-beads showed cell viability more than 90% after several days of periodic culture. Ang et al. [140] utilized the robotic dispensing technique equipped with pneumatic system to manufacture 3D scaffolds of chitosan–hydroxyapatite solution. The bioink was prepared by mixing chitosan and chitosan–hydroxyapatite solution with acetic acid and extruded through teflon-lined nozzle to fabricate the scaffold according to CAD model with layer deposition. The results showed that good adhesive forces are present between the layers which enable the chitosan matrix to create well-interconnected layering pattern.

The mechanical strength of hydrogel scaffolds is also one of the issues which limits their applications. To improve the mechanical properties, reinforcement materials are coated on

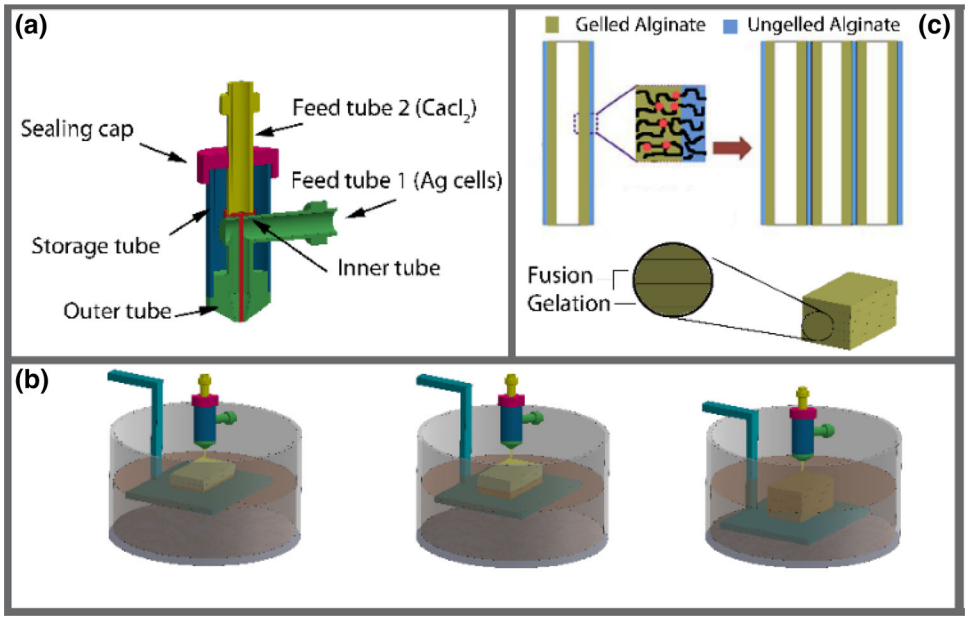

Fig. 4 Schematic explanation of **a** cross-sectional view of the coaxial nozzle assembly, **b** manufacturing process of a 3D alginate structure with built-in micro-channels and **c** networks formed after fabrication [137]

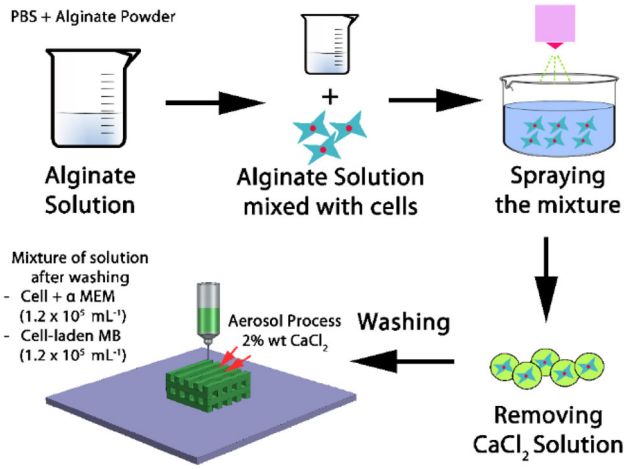

Fig. 5 Schematic diagram of fabrication process of micro-bead (MB) and cell-laden 3D scaffolds using a three-axis robot system supplemented with an aerosol process [139]

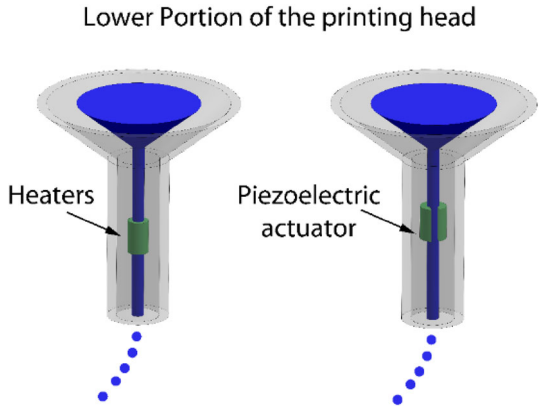

Fig. 6 Schematic drawing of inkjet printing with two different types [120]

the scaffolds. Kim et al. [141] employed the robotic dispensing bioprinting method to fabricate PCL (cell-laden)/alginate scaffolds with reinforced coating of alginate-based biomaterial. The results revealed great improvement in mechanical strength with homogeneous dispersal of cells.

Inkjet bioprinting

Inkjet bioprinting enables the printing of low-viscosity biomaterials in small fractions nearly 1–100 picolitres on the substrate [142]. Inkjet printing is droplet deposition-based process using piezoelectric actuators [143, 144] or thermal heaters [123] as driving force as shown in Fig. 6. Generally, these printers have two operating modes including continuous and drop on demand inkjet bioprinting [122]. In piezoelectric-based inkjet printers, the pulses generated by the piezoelectric actuators apply a voltage change according to computerized design, which extrude the biomaterial according to computerized design in drop-wise manner [145]. But in thermal-based inkjet printers, the heaters are utilized to convert the biomaterial into droplets by evaporating and then ejecting it on the printing-base platform [146]. The resolution of inkjet bioprinting ranges from 50 to 300 μm [111, 124] with the advantages of cost-effectiveness [111, 147] and high printing speeds [111, 120].

Recently, a lot of work has been done on inkjet technique for cell printing which allows to manufacture 3D hydrogel structures. There are several examples of such printings which provided desired mechanical and chemical properties with efficient porosity factor. Boland et al. [148] employed

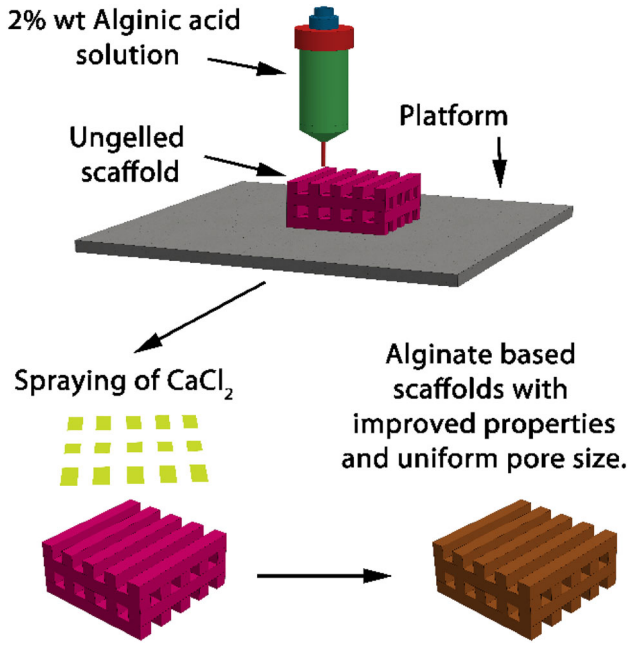

Fig. 7 Schematic view of manufacturing of alginate-based scaffolds using modified HP DeskJet [148]

inkjet printing method to 3D scaffolds of alginate/gelatin hydrogels by spraying $CaCl_2$ on to the alginic acid (ungelled) as shown in Fig. 7. The cartridge of the printer was filled with 2% alginic acid solution to fabricate the 3D printed scaffold which was further processed for specific properties by spraying 0.25 M $CaCl_2$ on the scaffolds. These printed scaffolds possess uniform pore size and well-adhesion of endothelial cells. Many other biomaterials can also be used to manufacture such kind of scaffolds in the form of tubes, branched or unbranched [149].

Researchers worked on commercially available inkjet printers for modifying them for the bioprinting [150]. Xu et al. [123] worked on the modification of commercial inkjet printer for printing sterile hydrogel specimen. Before using the inkjet printer, the chamber was sterilized with UV light and then washed several times with 70% ethanol. The quality of the samples proved that these modifications were acceptable after number of sterilizations. These inkjet printing techniques are very advantageous because the desired factors including deposition of living cells, growth rates after printing, right printing on exact location cross-linking and transfer of nutrients could be achievable [151] with cost-effectiveness and high efficiency. Inkjet printing technique also integrates with fields of biomedical applications like biosensors, drug screening and genomics [152]. The physical structure of these hydrogels and DNA structures is very delicate, but these could be printed directly using inkjet printers on glass slides for study and analysis purposes [153].

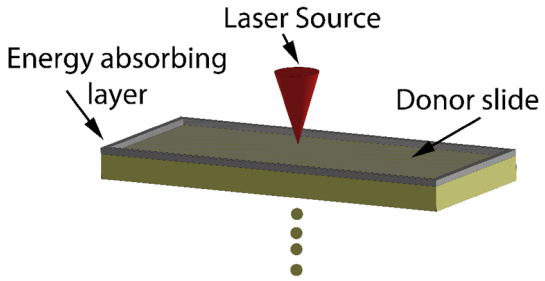

Fig. 8 Schematic illustration of laser-assisted bioprinting depositing bioink in the form of micro-droplets using pulsed laser source [111]

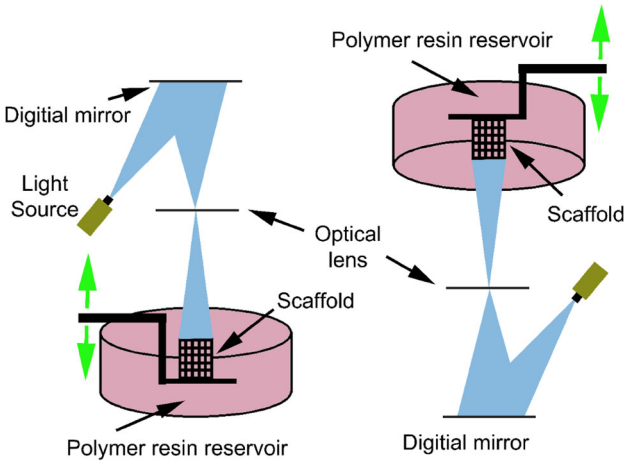

Fig. 9 Schematic representation of top–bottom and top–down visible light source for SLA

Laser-assisted bioprinting

The laser-assisted bioprinting employs laser beam to print biological structures [154]. The technique consists of main three components, the donor slide, pulsated laser beam source and a layer for absorbing laser energy [155] as shown in Fig. 8. The mechanism includes the deposition of the bioink on the donor slide which further converted into high-pressure bubbles through pulsed laser beam. When these micro-scale bubbles expand, they eject from the surface in the form of droplets [121]. There are two major AM techniques, stereolithography (SLA) [156] and two-photon polymerization (2PP) [122] which can be utilized for the fabrication of 3D biomaterial structures using laser assistance. SLA allows the printing of such structures range in centimeters and its resolution is very high up to 6 μm [157], while 2PP gives great resolution up to 100 nm which provides efficient interfaces between cells and printed substrate [156]. Usually two setups of light source are used in SLA including top–bottom and top–down as shown in Fig. 9.

For the very first time, Odde demonstrated the 3D printing of biological structures with laser assistance using fibronectin clustering the individual cells [158]. There are many other

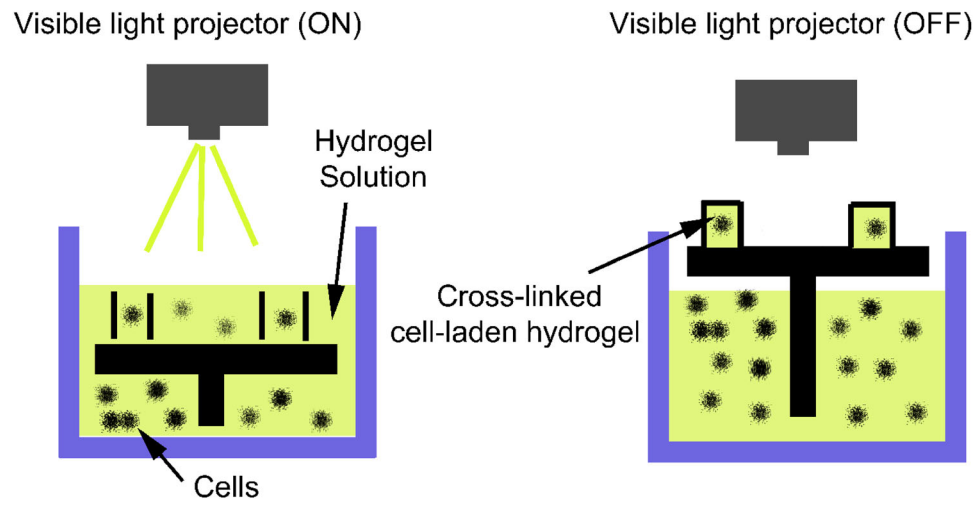

Fig. 10 Schematic demonstration of bioprinting of cross-linked cell-laden hydrogel cells [166]

biomaterials that can be used for such kind of printings including living cells [155], DNA [159] and peptides [160]. Karina et al. [161] fabricated the complex 3D structures of polyethylene glycol (PEG) hydrogels using stereolithography (SLA). The utilization of such cross-linked photo-active polymer PEG-dma MW 1000 up to 10% (w/v) with 0.5% of I-2959 enhanced the biofabrication attributes. These scaffolds had great importance in tissue engineering applications because SLA provides strong, smooth and precise structures with accurate placement of cells and other biological agents during fabrication. Some other biomaterials like photo-curable polymers offer controllable adhesive bonding between the cells because they can cure easily during the process of SLA [162]. PEG hydrogels also provide suitable strength for soft tissue and swelling due to their hydrophilic nature [163].

The light source of the SLA technique can also affect the cells composition and damage them. The main mutations and disorders are produced by UV light and laser lights. SLA techniques that employ visible light as a source are useful for tissue engineering application because they eliminate the dangerous effects of UV light and help in homogenous dispersion of polymers [164, 165]. Few polypeptides-based scaffolds also showed improved mechanical properties fabricated using SLA technique. Elomaa et al. [166] fabricated poly(ethylene glycol-co-depsipeptide) (PEG-co-PDP) scaffolds employing SLA with visible light source as shown in Fig. 10. The cross-linking between PEG-co-PDP and RGD-functionalized PEG acrylate enhanced the proliferation and cellular adhesive bonding. The results showed that mechanical stiffness depends on the curing time of the layer and the values range from 3 ± 1 to 38 ± 13 kPa. In another study, for semilunar cartilage structures, MeGEL is utilized to fabricate porous scaffolds [167].

Conclusion and future outlooks

The potential of the hydrogels is very positive for the future development of tissue engineering because they possess the resemblance with naturally existed ECM chemically as well as structurally. The innovation in the methodologies and conditions for providing biocompatible environments would be the key to success in future. The major focus of the researchers is to increase the biocompatibility of these hydrogels as this is the most important factor for developing new hydrogel-based scaffolds. Still, we have to understand the complexities of the process by which these hydrogel ECM seeded cells mediate their composition with the existing living cells. Exploring more information about ECM hydrogels could provide new possibilities to architecture and reprogram the chemical nature of hydrogels so that after implantation they should have the ability to repair and reconstruct the tissues if some variation happens in the actual living tissues. Secondly, the improvement in the fabrication methods of these hydrogel-based scaffolds is also developing very rapidly. These improvements could lead us to incorporate advanced manufacturing techniques like big data to optimize the process parameters [168] and designs of these hydrogel-based scaffolds to be more effective and sustainable. Some novel and innovative designs with their functional applications are reviewed above. The gradient techniques could provide more accurate and precise methods for the production of mimic ECM with enhanced biocompatibility and mechanical strength. As it is an innovative method that will change the mechanical properties of scaffolds patterns, researchers attempted to test these methods experimentally [169, 170], but still for functional applications and best approaches, they need more investigation [171]. There could be a possibility for analyzing the details about the interaction forces and cross-linking structures of hydrogels at nanoscale that can influence polymerization processes and drive the

self-assembling mechanism. Multiple cells printing at one time is still a challenge for researchers and scientists which can be done through combination of materials or employing different printing techniques spontaneously. This combination of various printing methods will provide a facility for more innovative designs and structures. For example, Kim et al. [172] explained the technique for printing the scaffold with combination of electrospinning and bioplotting techniques.

Despite this development in the field of tissue engineering, including reproduction of ECM using hydrogels and implantations, there are enormous factors yet to be explored that will allow TE to broad range of biomedical and clinical applications. The properties of hydrogel-based scaffolds can be improved through combination of different natural existing or synthetic hydrogels and fabricating the structures using different 3D printing techniques.

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