ISSN: 2574-1241
DOI: *10.26717/BJSTR.2018.11.002129*
Saima Majeed. Biomed J Sci & Tech Res

BIOMEDICAL
Journal of Scientific & Technical Research

Mini Review Open Access

Advancement of Bio inks in three Dimensional Bioprinting

Sumbul Ali[1] and Saima Majeed*[1,2]

[1]*Akhuwat Faisalabad Institute of Research, Pakistan*

[2]*National Institute for Biotechnology and Genetic Engineering (NIBGE), Pakistan*

Received: : November 20, 2018; **Published:** : December 03, 2018

***Corresponding author:** Saima Majeed, Akhuwat Faisalabad Institute of Research, Pakistan

Abstract

Three dimensional bioprinting is the modern technique extensively used in regenerative medicine and tissue engineering for the development of multifaceted biological structures such as complex tissues and organs. Computer aided design (CAD) is being used to design complicated three dimensional structures. After designing the desired structure, next step of bioprinting involves the deposition of “bio inks” in the designed shapes. These bio inks are enriched with living cells and any medium supporting and nourishing these cells. Various bioprinters and bio inks based on agarose, collagen, hyaluronic acid, fibrin, Matrigel and pluronic® F-12 are discussed with respect to the advantages, disadvantages and suitability in the development of complex 3D biostructures. 3D bioprinting technology is a futuristic approach for tissue engineering and synthesis of other biological structures with greater feasibility which will help to overcome the hurdles in all medical fields.

Abbreviations: CAD: Computer Aided Design; EBB: Extrusion Based Bioprinter; LIFT: Laser Induced Forward Transfer; HA: Hyaluronic Acid

Introduction

Three dimensional bioprinting is the modern technique extensively used in regenerative medicine and tissue engineering for the development of multifaceted biological structures such as complex tissues and organs. An American inventor named Chuck Hull coined the concept of three dimensional printing in early 80’s. Three dimensional bioprinting works by depositing cell-laden biomaterial in a predesigned architecture to engineer functional organs and tissues. Computer aided design (CAD) is being used to design complicated three dimensional structures by processing the data obtained from MRI, X-ray and other imaging techniques. In this way a more personalized, highly precise and patient specific structures could be created efficiently within minimum time and resources. After designing the desired structure, next step of bioprinting involves the deposition of “bio inks” in the designed shapes. These bio inks or biomaterials are enriched with living cells and medium supporting and nourishing these cells [1-2].

Rheological behavior, gelation kinetics, swelling properties and surface tension of bio inks are the key characteristics which influence printability. But the core aspect here is bio fabrication which mainly rely on bio ink dispensing. Thus it is necessary to choose appropriate dispensing technique for relevant bio ink. Three main methodologies vastly used for bioprinting includes; inkjet bioprinting, extrusion based bioprinting and laser assisted bioprinting [3]. Inkjet bioprinting is based on two techniques i.e. thermal inkjet bioprinting and piezoelectric bioprinting. Former vaporizes the bio ink using a heating element and creates pulses of pressure which expels the droplets out. While in piezoelectric bioprinting, acoustic waves are produced by piezoelectric crystals which forces the fluid out of the nozzle head. Droplet size of inkjet bioprinter is 10-50μm and its formation is mainly dependent on the surface tension which arises due to the cohesive forces in the molecules of the liquid. Inkjet bioprinters are vastly used for bioprinting owing to its precision and compatibility with various bio inks but on the other hand, nozzle blockage due to early gelation of bio ink and loss of viability of living cells due shear and heat stress reduces the efficiency of inkjet bioprinters [4].

Unlike inkjet bioprinter, extrusion based bioprinter (EBB) dispenses filaments of hydrogel which are 150-300 micrometer in diameter. Bio ink is fed to plastic syringes and it is extruded out via piston (pneumatic) or screw-driven (mechanical) assembly. Pneumatic bioprinting provides better control of flow rate of bio ink whereas mechanical assembly aids the spatial control and printing of viscous bio inks. Major drawback of this methodology is poor resolution and like inkjet bioprinting; compromised cell viabity and nozzle clogging also occurs [5-6]. Another methodology used for bioprinting is LIFT (Laser induced forward transfer) which is orifice free bioprinting technique. The assembly of LIFT consists of three layers i.e. donor substrate, an absorbing layer made up of gold or titanium and bio ink layer. Laser beam is focused on the absorbing plate which creates a pressure bubble due to local evaporation thus impelling a small quantity of hydrogel towards the collector platform by leaving the donor layer although a loose connection remains. This methodology addresses the nozzle clogging, shear and heat stress [7].

Bio inks for 3D Bioprinting

Raw material used for the manufacturing of 3D printed complex biological structures are considered as bio inks which the substances are mainly comprised of living viable cells or tissues and the matrix which holds these cells together and provide nutrition and support to the cells. Bio inks imitates extracellular matrix which allows adhering, proliferating and differentiating of bio printable cells. Selection of bio inks for 3D printing of the biomaterials is an imperative task. There is a pool of physical and chemical aspects of bio inks to be considered for bioprinting. Basic requirements for bio inks include bio printability, in situ gelation, viscoelasticity, biocompatibility with live cells, tissue regeneration, permeability of oxygen, nutrients and metabolic wastes, biodegradation and sheer thinning [8]. Recent studies have reported various biomaterials can be manipulated as bio inks. An overview of these materials will be discussed in following section. These biomaterials are categorized into two main classes; natural biomaterials and synthetic biomaterials. Both have their own distinct properties such as natural biomaterials show high degree of biomimicking and ability of self-assembling whereas stability, controllability and photo crosslinking are the key features of synthetic polymers.

Agarose Based Bio inks

Agarose is a polysaccharide which is derived from marine algae and has diverse application in biomedical field due its property of gel formation [9]. Agarose based bio inks imparts stability to the 3D structures and it can be used in conjunction with other biomaterials to increase the efficiency. A study has manipulated alginate, agarose and carboxymethyl-chitosan to develop functional neurons from neural cells derived from humans and printed the stable structures by encapsulating the cells [10]. A study has made a comparison between agarose and other hydrogels based on biocompatibility and printability by loading the gels with mesenchymal cells and 3D printed cartilage to examine the differentiation of cartilage to fibrocartilage. All the gels showed viability of around 80% while agarose and alginate showed higher cell differentiation [11,12]. Rapid gel formation, high degree of biocompatibility and rheological properties make it highly preferable for bioprinting. However, owing to its viscous nature it is not commonly used in inkjet bioprinters as it causes nozzle clogging [7].

Collagen-Based Bio inks

Collagen is a protein which is obtained naturally from the extra cellular matrix of many mammals and it is extensively used as bio ink for tissue regeneration, tumor modeling and other tissue engineering techniques. Owing to integrin-binding domains of collagen it facilitates cell adhesion, attachment and proliferation. It is most suitable for extrusion based bioprinting but due to the presence of high degrees of fibrous micro-architecture its use in inkjet bioprinter is limited. Other limitations of collagen based bio inks include, slow gelation rates, instability and formation of fibrous structure at high temperature [13]. A study has reported that cell attachment and cell proliferation of chondrocytes was enhanced by using collagen in conjunction with sodium alginate moreover it has also suppressed the differentiation of the incorporated cells and it is also suggested that the combination has also increased the mechanical strength of the structure thus it is preferred choice for the tissue engineering of the cartilage [14]. In another study has reported that viability and differentiation of human hepatocytes stem cells is improved when collagen was used in varying concentrations in lieu of alginate [15]. Engineered structures have shown enhanced biological and physical properties and a greater number of cells remained after printing. Moreover, engineered tissues and complex models of tumors were also developed by using the transglutaminase-crosslinked gelatin [16].

Hyaluronic Acid Based Bionks

Hyaluronic acid (HA) naturally occurs in all connective tissues and extra cellular matrix of cartilage of all mammals and shows the characteristics like collagen type I. HA is vastly used for tissue engineering as it is highly biocompatible and imparts flexibility to the hydrogels. Chemical modifications of HA increase its rheological properties and photo-cross linking. As HA plays a key role in embryonic development, thus it is favorable to the living cells in the hydrogels and structures bio printed using hyaluronic acid are more stable and mechanically controllable. However, owing to its slow gelation ability it is not suitable for extrusion based bioprinting, but it can be used efficiently by blending it with other hydrogels [1]. The adhesion property of hyaluronic acid based hydrogels was increased by the adding the oligopeptides having cell-adhesive properties while mechanical properties were not affected by this addition [17]. Moreover, Ruthenium-based complexes with visible light also polymerizes the hyaluronic acid-gelatin based bio inks. Owing to this ability cell differentiation and viability of adipose stem cells has been improved [18]. Additionally, hyaluronic acid-carboxymethyl cellulose increases the viability and stability of bioprinter structures, moreover the mechanical properties were also enhanced by modifying the HA based gels with methylcellulose [19].

Fibrin-Based Bio inks

Fibrin is the major clotting protein and can be transformed into hydrogel by the enzymatic reaction of thrombin and fibrinogen. It is highly biocompatible and possess biodegradation, but the structures formed using fibrin hydrogels are mechanically weak. It supports cell proliferation and growth. Due to its property of filaments formation the structures thus produced show high amount of deformation without breakage. It can be used with inkjet bioprinting, but it can cause nozzle blockage due to filament formation. In-vitro properties of fibrin has been investigated by developing a three dimensional structure of urethra [20]. Moreover, the combined effect of fibrin and hyaluronic acid by encapsulating the Schwan cells to investigate nerve regeneration [21].

Matrigel TM

Matrigel is a synthetic material and a commercial product mainly composed of gelatinous extra cellular material which promotes vascularization and outgrowth of cells from various tissue fragments, and promotes the differentiation of cultured cells, additionally complex cellular behavior is also observed when cells are cultured on Matrigel [22-23]. Matrigel imparts mechanical strength, stability and high survival rates to the 3D bioprinted structures as compared to alginate and agarose [24]. It is not a favorable choice as bio ink for extrusion based and droplet based bioprinters [25-26] but due to its optimal viscosity and thermal crosslinking ability it is widely used in laser based bioprinters [27]. Matrigel has been used as a vital instrument for the construction of rodent tumor xenograft models to develop innovative cancer treatments [28]. Moreover, Matrigel was used as a bio ink to print three dimensional biostructure using human osteosarcoma [29].

Pluronic® F-12

Pluronic® F-12 is a synthetic polymer having surfactant properties [30]. It is mostly used in combination with other bio ink materials e.g. PEG to deliver and slowed release of drugs [31] and with methacrylate hyaluronic acid to engineer biostructures with increased mechanical strength [32]. Complex structures can be engineered owing to the reversible properties of Pluronic® F-12. Moreover perusable channel like structures can also be constructed using this material [33]. This material is acceptable for bioprinting for extrusion based bioprinter and but not favorable for droplet based bioprinting due to high viscosity and thermosensitive nature. A study reported that interaction ability of mesenchymal stem cells derived from bone marrow was increased when bioprinted with Pluronic®.

Conclusion

3D bioprinting technology is a futuristic approach for tissue engineering and synthesis of other biological structures with greater feasibility. By improving the quality of bio inks and scaling up the commercialization of 3D products can open new horizons. It can facilitate the patients who are in dire need of specific organs and dependent on the organ donor moreover it can also address the emergency medical needs of patients. Various bio inks with their advantage and disadvantages and their suitable bioprinters for the development of complex 3D biostructures are discussed in this review which will improve the commercial application of 3D printing technology. Natural and synthetic bio inks such as agarose and fibrin based inks and other extracellular matrix based bio inks are showing promising results but there is need to address the problems arising in the printing process. Moreover it is required to modify these bio inks so that single bio ink should have the capability to be used with various bioprinters. 3D bioprinting is a modern technology which has the potential to form such complex biostructures which will help to overcome the hurdles in all medical fields.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2018.11.002129

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