Bioprinting in ophthalmology: current advances and future pathways

Nataraj Poomathi
Centre for Nanofibers and Nanotechnology Initiative, National University of Singapore, Singapore and Organic and Bioorganic Chemistry Division, CSIR-Central Leather Research Institute, Chennai, India
Sunpreet Singh
School of Mechanical Engineering, Lovely Professional University, Phagwara, India
Chander Prakash
School of Mechanical Engineering, Lovely Professional University, Jalandhar, India
Rajkumar V. Patil
Singapore Eye Research Institute, Singapore and Okyo Pharma Ltd., Doylestown, Pennsylvania, USA
P.T. Perumal
Organic and Bioorganic Chemistry Division, CSIR-Central Leather Research Institute, Chennai, India
Veluchamy Amutha Barathi
Translational Preclinical Model Platform, Singapore Eye Research Institute, Singapore and Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore and Ophthalmology Academic Clinical Research Program, DUKE-NUS Graduate Medical School, Singapore
Kalpattu K. Balasubramanian
Department of Biotechnology, Indian Institute of Technology Madras, Guindy, India
Seeram Ramakrishna
Centre for Nanofibers and Nanotechnology Initiative, National University of Singapore, Singapore, and
N.U. Maheshwari
Organic and Bioorganic Chemistry Division, CSIR-Central Leather Research Institute, Chennai, India

Abstract

Purpose – Bioprinting is a promising technology, which has gained a recent attention, for application in all aspects of human life and has specific advantages in different areas of medicines, especially in ophthalmology. The three-dimensional (3D) printing tools have been widely used in different applications, from surgical planning procedures to 3D models for certain highly delicate organs (such as: eye and heart). The purpose of this paper is to review the dedicated research efforts that so far have been made to highlight applications of 3D printing in the field of ophthalmology.

Design/methodology/approach – In this paper, the state-of-the-art review has been summarized for bioprinters, biomaterials and methodologies adopted to cure eye diseases. This paper starts with fundamental discussions and gradually leads toward the summary and future trends by covering almost all the research insights. For better understanding of the readers, various tables and figures have also been incorporated.

Findings – The usages of bioprinted surgical models have shown to be helpful in shortening the time of operation and decreasing the risk of donor, and hence, it could boost certain surgical effects. This demonstrates the wide use of bioprinting to design more precise biological research models for research in broader range of applications such as in generating blood vessels and cardiac tissue. Although bioprinting has not created a significant impact in ophthalmology, in recent times, these technologies could be helpful in treating several ocular disorders in the near future.

Originality/value – This review work emphasizes the understanding of 3D printing technologies, in the light of which these can be applied in ophthalmology to achieve successful treatment of eye diseases.

Keywords Advanced manufacturing technologies, Health, Medical care, Body systems and organs

Paper type Literature review

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1. Introduction

Three-dimensional (3D) printing in the area of rapid prototyping, rapid manufacturing and rapid tooling (Ho *et al.*, 2015; Jerez-Mesa *et al.*, 2017) has provided excellent service since 30 years. Owing to tremendous benefits offered by 3D printers, now, its accessibility for industrial and hobbyist users has drastically increased during the recent decade (Stansbury and Idacavage, 2016). Globally, the sale of printing devices, their workhorse materials and utility with respect to industries has also grown over 33 per cent in past three years (Wohlers and Caffrey, 2015). The IDTechEx report in *The Guardian* highlighted that the medical market is expected to grow about $867m by 2025, wherein the inclusion of 3D printed organs and tissues would be of average potential of $6bn in a decade (Butler, 2014; IDtechex, 2014). Interestingly, evolutions of 3D printer are not only limited to the manufacturing hubs but also are becoming the parts of educational institutes, public libraries and research laboratories (Jerez-Mesa *et al.*, 2017). The 3D printing process works on the lines of the additive manufacturing (AM) principle which illustrates the layer-upon-layer joining of feedstock with the help of external stimulation (ASTM F2792-12a, 2012; Slotwinski, 2014; Sood *et al.*, 2009). The functional and non-functional parts are built using computer-aided design (CAD)/computer-aided manufacturing (CAM)-based software packages that transform a computer design into physical part in an additive manner.

This technique is widely adopted similar to 2D printing on the surface of paper. Using 3D printing, it is possible to print guns, clothing and designer jewelry and car parts. These technologies are more advent in the medical fields and have the possibilities to revolutionize surgical and medical fields. Ample numbers of literature reports are investigated on both cell culture and 3D printing in terms of vascular networks, fabrication of blood vessels, bandages, ears, bones, exoskeletons, dental prosthetics and windpipes (Schubert *et al.*, 2014; Fedorovich *et al.*, 2011; Mannoor *et al.*, 2013). Very soon, the potential of emerging 3D printing technologies will be witnessed in materials science and cell biology. Furthermore, this technology is applied to manufacture medical devices such as splints and stents for clinical usage (Fielding *et al.*, 2012). This technology is also applied by the research communities to generate prototypes for all special parts, kinds and novel designs collectively with structural models with specific designs. 3D printing methods are fairly non-economical to obtain specific products, and the existing materials must meet certain specifications in accordance with the products.

It is widely adopted for designing complex parts and it can replace a congregated device as a single fabricated device. In addition, 3D printing has a significant impact on manufacturing sector mainly to improve reliability, build speed and intuitive user interfaces. Different materials have been designed based on 3D printing to meet the manufacturing scope especially for research institutions; independent materials supply companies and machine manufacturers (Zopf *et al.*, 2013). The most difficult situation in developing a new material is the requirement of processing conditions along with phase change. Currently, AM techniques are regarded as one of the latest and the best ways available for building human specific structures via using biological/biocompatible materials (Fahad *et al.*, 2013). In case of AM, problems in placing multiple cells, biomaterials and active molecules within defined contours is one of the critical barriers in controlling the architecture of the resulting products. As an answer to aforementioned barriers, the latest bioprinting technology has the ability to construct 2D and 3D structures with high precision and proper placement of cells, biomaterials and bio-molecules at decided sites (Hoch *et al.*, 2014).

The 3D bioprinter can print liquids mixtures within 50°C-150°C temperature frame and also print a wider range of biomaterials, including ceramics, cells, proteins, hydrogels, biodegradable polymers, etc. In the history of bioprinting, the step was taken by Thomas Boland in 2000, at Clemson University, as he positioned bacteria mixture inside an ink cartridge and then followed by printing a bio structure using an ordinary ink-jet printer. Upon successful achievement, he filed and granted a patent in 2003 and 2006. Further, Dr Gabor Forgacs (Professor of Missouri University, USA) defined the development of cellular bio-ink and established Novogen bioprinting platform (Seol *et al.*, 2014). Noticeably, the development of various bio-ink materials enabled the scientists to precisely manipulate the biological and biochemical *in-vivo* environments of living beings to create the complex biological constructs through cells (Hospodiuk *et al.*, 2017).

In 2007, the first advanced bioprinter, NovoGen MMX, was constructed by his group and commercialized by Orgonovo Inc. This printer was very costly that affected its sale. The first publication on bioprinting of organ was made in 2003 by Thomas Boland, Dr Forgacs and Dr Mironov (Beaman *et al.*, 2004; Mironov *et al.*, 2003). During 2003-2011, various developments in bioprinting application domain have been made as indicated by Dababneh and Ozbolat (2014). Song *et al.* (2010) developed three-axes bioprinting system consisting of system controlled injection syringe. As used in various fields, 3D printing technology could also be beneficial in ophthalmology. This technique is likely to be applied to design different varieties from printing of spectacles to printing of ocular tissues such as cornea and sclera for the research purposes (Shim *et al.*, 2012). According to Yap *et al.* (2017), 3D printing has the potential to produce life like bio-models with true physical characteristics to enhance the study of human anatomy and analysis of diseases. In addition, the combination of 3D printing and 3D scanning technology customization of prosthetic 3D printed eye could be designed in just few weeks. The 3D printing technology may adopt in the future for the production of entire new organs to cure specific diseases. The possible ophthalmology applications of 3D printing could be in corneal surgical planning, glaucoma valve design and patient-specific prosthetic ocular implants (Ji *et al.*, 2018).

2. Three-dimensional printing technologies

A numerous number of 3D printing techniques are available based on their classes (liquid, solid and powder), as cited by Moroni *et al.* (2004), Turner *et al.* (2014), Shirazi *et al.* (2015), Singh and Ramakrishna (2017). Apart from the commercialized techniques, there are numerous in-house developed systems that failed to maintain their market values, for example, layer beams, solid ground curing, Teijin Seiki's solid form system, Meiko's AM system for the jewelry industry, SLP, computer-

assisted laser-active modeling machine, layer modeling system, light sculpting, Plastic Sheet lamination by Solidimension, Paper lamination technology by KIRA, CAM-LEM'S CL 100, ENNEX corporation's offset fabbers, Shape deposition manufacturing process, Direct shell production casting by Soligen, Multiphase jet solidification by Fraunhofer and LASFORM technology by Aeromet corporation.

2.1 Bioprinting techniques

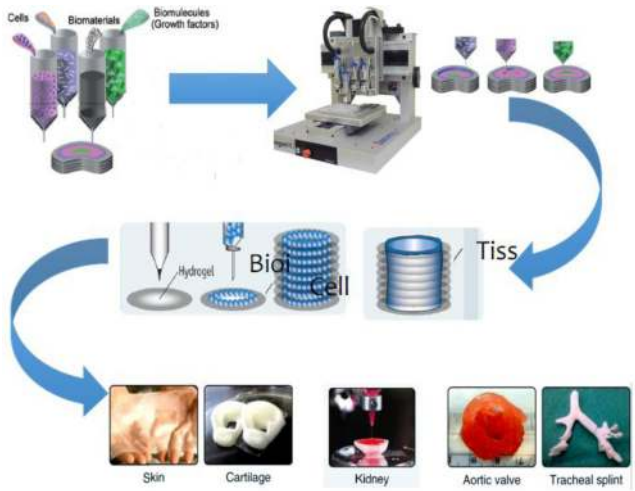
In today's time, bioprinting technologies are gaining much attention due to its ability to overcome many engineering challenges encountered in the field of tissue engineering (TE), Billiet *et al.* (2012), Xu *et al.* (2009). These technologies help in building key TE applications that involve cells, scaffolds and other biological molecules. Various challenges and problems of conventional TE approach, mainly in-terms of geometrical complexity and precision, can be readily solved through bioprinters. These computer-controlled methods have capabilities to assemble near-net shaped 3D objects through layer-wise deposition or layer-wise curing or layer-wise cross-linking of materials. For example, nozzle-based deposition techniques make use of hydro-gels and cells; dropping cell/bio-ink, as required, printers make cross-linking between adjacent layers; and layers-on-layer cross-linking of synthetic or natural polymers through selective light-based irradiation of single cells. Basically, the process of bioprinting mainly divided into three sequential technological steps (Billiet *et al.*, 2012): pre-processing, printing and post-processing. These technological steps start with pre-processing, in which a blueprint of tissue or organ design, using imaging and computer-aided design techniques, is drawn. During printing, cells are seeded onto solid and biodegradable scaffolds and formation of tissue is induced by bio-molecule growth factors. In the last part, the printed structure undergoes tissue remodeling and maturation in an especially designed chamber, bioreactor, which accelerates tissue maturation. Bioprinters can control the shape, size, internal porosity and interconnectivity of a TE services (Figure 1).

There are basically three types of biological printing systems (such as: laser based, extrusion based and inkjet-based), which vary in their ability to ensure the deposition accuracy, stability, and viability of cells (Dababneh and Ozbolat, 2014). The technologies can further divide into approaches used for fast-solidification of stimuli-sensitive (such as light, heat or chemical) bio-materials. There are three basic approaches, being used for almost all types of bioprinters (Ozbolat and Yu, 2013; Jakab *et al.*, 2010; Steer *et al.*, 2003; Mironov *et al.*, 2009): bio-mimicry, autonomous self-assembly and mini-tissue building. Table I compiles applications, capabilities, workhorse materials and the merits and demerits of available bioprinters, whereas Table II outlines the biomedical practices of bioprinters.

2.1.1 Jetting-based bioprinting

Jetting-based bioprinting (Figure 2) is a non-contact type printing technique which is used for generating 2D and 3D biomedical structures by using picolitre bio-ink droplets, layered on substrate (Wilson and Boland, 2003; Peltola *et al.*, 2008). The jet-based bioprinters can be categorized by the mechanism used to generate the bio-ink droplet (thermal

Figure 1 Step-by-step description of bioprinting



Note: Reproduced with permission from reference
Source: Murphy and Atala (2014)

method, piezoelectric actuator, laser-induced and pneumatic), Lee *et al.* (2009). The thermal method involves the use of a heat generator, which increases temperature locally within the bio-ink chamber, and this localized heat produces a bubble, ejected as a small droplet. The piezoelectric actuator utilizes piezocrystal pulse actuator triggered by current and finally ejects a small droplet. The thermal and piezoelectric methods are the most widely used phenomenon in jetting-based bioprinting, and due to this, only these delivery mechanisms are being used for commercial printers. In case of laser-induced method, relatively high-resolution patterns can be produced, but cell viability reduced in the printed hydrogels as delivered on the platform. The droplets are generated by an opening and closing of micro valve in case of pneumatic pressure systems. This method is simplest as compared to others and moreover is suitable to eject droplets of picolitre volume, with 20-100 μm resolution (Chang *et al.*, 2011).

Low viscous materials (such as: saline, $CaCl_2$, thrombin and fibrogen) have been used as bio-inks for these types of bioprinters (deGans and Schubert, 2004). Generally, the mechanical properties of jet-printed structures are weak and the fabrication of durable structures, that can maintain their structures and withstand loads after implantation is not optimal. In this technique, bio-ink is made of cells and biomaterials and used to print living cells in the form of droplets of 10,000-30,000 cells (Boland *et al.*, 2006). A group of researchers modified the inkjet printer to allow reproducible and precise arrangement of multiple cell types together within the specific matrices to create complex heterogeneous structures (Cui and Boland, 2009).

Researchers have examined the drawbacks of this printer of blood vessels and heart valves as the hydrogels used in inkjet printers are soft enough to withstand the physiological conditions (Xu *et al.*, 2011; Hockaday *et al.*, 2012). Notwithstanding these limitations, this printer offers numerous benefits, which involves low cost, high resolution, high

Table I A Comprehensive specification list of bioprinters

Characteristics/specification	Type of bioprinter		
	Ink-jet based	Extrusion based	Laser based
Mechanism of printing	Deposition of droplets (contact-type)	Pressurized deposition of biomaterials (contact-type)	Light or heat evaporation and thereafter deposition (non-contact type)
Printing speed	Fast (<10,000 droplets/s)	Slow	Medium
Droplet size	50–300lm	100lm–1mm	>20lm
Material viscosities	3.5–12mPa/s	30 mPa/s to >6 × 107mPa/s	1–300mPa/s
Cell densities	Low, <106 cells/ml	High, cell spheroids	Medium, 108 cells/ml
Cell viability	>85%	40–80%	>95%
Resolution	Medium	Medium to low	High
Multi-cellular feasibility	Yes	Yes	Yes
Throughput	High	Medium-low	Low
Mechanical/structural integrity	Low	High	Low
Fabrication time	Medium	Short	Long
Processing modes	Mechanical and thermal	Mechanical, thermal and chemical	Optical
Control of single-cell printing	Low	Medium	High
Gelation speed	High	Medium	High
Materials	Low-viscosity suspension of living cells, bio-molecules and growth factors	Hydrogel, melt, cells, proteins and ceramic materials, solutions, pastes, or dispersions of low to high viscosity, PLGA, tricalcium phosphate (TCP), collagen and chitosan, collagenalginate-silica composites coated with HA, and agarose with gelatin	Hydrogel, media, cells, proteins and ceramic materials of varying viscosity
Printer cost	Low	Medium	High
Advantageous	Affordable and versatile	Multiple compositions and good mechanical Properties	High accuracy, single cell manipulation and high-viscosity material
Disadvantageous	Low viscosity prevents build-up in 3D and low strength	Shear stress on nozzle tip wall, limited biomaterial used and relatively low accuracy	Cell-unfriendly, low scalability and low viscosity prevents build-up in 3D

Source: Malda *et al.* (2013), Wu and Ringeisen (2010), Raof *et al.* (2011), Keriquel *et al.* (2017), Moon *et al.* (2011), Duan *et al.* (2013), Chien *et al.* (2013), Guillemot *et al.* (2010), Lim *et al.* (2010), Ali *et al.* (2014), Xu *et al.* (2014), Bernhard *et al.* (2016), Sawkins *et al.* (2015)

speed and compatibility with many biological materials. Applications of jetting-based 3D printers in ophthalmology are not new, but the growth of this technology in this particular field of application is very slow due to numerous facts which include unavailability of the suitable workhorse materials, precision while printing, change in the chemical and physical properties of materials upon exposure to heat or pneumatic pressure and majorly cost constraints associated with printers. Half a decade ago, researchers at Princeton University demonstrated the solution for fabricating micrometer scale mid infra-red lenses of 10-350 μm diameter and 10-700 focal lengths, especially for integrated optics using inkjet printer (Sanchez *et al.*, 2011). Similarly, Sung *et al.* (2015) fabricated flexible optical lenses by *in situ* curing liquid polydimethylsiloxane droplets on a preheated smooth surface with an inkjet printing process. Recently, researchers outlined the detailed study of fabrication ARPE-19 and photo-receptors retina for the treatment of various retina problems.

In 2013, an inkjet-based printer was first time used for printing of the adult eye cells for producing customized tissue implants with the hope of curing various types of genetic and accidental blindness. The research team faced failures at the first instance as the optic nerves cells of the rats, which they tried as a pilot experimentation, failed due to fragility issues (Jose *et al.*, 2016). It seems logical if one could use the category of those materials that can provide ease of jetting along with precision with minimal aid of heating or pressure (Bakhshinejad and D'souza, 2015) for reducing collapsibility and discontinuity in the bio-ink stream (Castrejon-Pita *et al.*, 2013). However, the development of such materials is itself a virgin field of study and would take lot of expertise, time and expenditures. Furthermore, manufacturing with jetting-based bioprinters challenge the chemists and materials scientists to find out the ways of delivering both structural and functional materials in liquid form at times (Wu *et al.*, 2016). Another area to work is to eliminate the purely usage of biological material in liquid form and to develop a novel deposition method that could

Table II List of practices with bioprinters

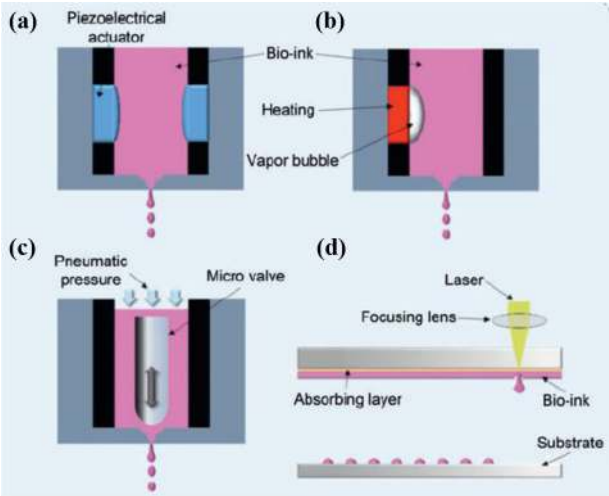
S. No.	Type of bioprinter	Purpose	Material used	Remarks	Ref.
1	Inkjet based	Micro-environments engineering for printing spatially direct adult stem cells toward muscle- and bone-like subpopulations	Fibrin-coated glass slides	This approach can be useful for understanding cell behaviors to immobilized biological patterns and could have potential applications for regenerative medicine	Phillippi *et al.* (2008)
2		Construction of complex heterogeneous tissue constructs with multiple cell types	Human amniotic fluid-derived stem cells, canine smooth muscle cells and bovine aortic endothelial cells	Each printed cell types maintained their viability and normal proliferation rates, phenotypic expression and physiological functions within the heterogeneous constructs. The bio-printed constructs were able to survive and mature into functional tissues with adequate vascularization in vivo	Xu *et al.* (2013)
3		To study droplet formation process during drop-on-demand of living cell	Fibroblasts cells and alginate hydrogel	As the cell concentration of bio-ink increased, the droplet size and velocity decrease, the formation of satellite droplets was suppressed, and the breakup time was increased	Xu *et al.* (2014)
4		3D fabrication of origami structures with designed images	Gel precursor solution,gel reactant and HeLa cells	Highly complex gel structures were successfully fabricated both with and without living cells	Arai *et al.* (2011)
5		Designed seeding of individual living cells	Bovine endothelial Cells	Living cells were safely ejected by inkjet printing onto culture disks and were adhered and proliferated	Nakamura *et al.* (2005)
6		Printing of micro-vessels	Solution of alginate, BSA and HEPES	Following triggered dissolution of the alginate, endothelial cells migrated to scaffold periphery, spread and formed a confluent monolayer	Hewes *et al.* (2017)
7		Printing of paraffin wax for cell patterning applications	Rat RN22 Schwann cells and dermal fibroblasts	Human dermal fibroblasts and RN22 Schwann cells were proliferate within the fabricated patterns. Wax constructs were able to be removed from the substrate at any stage after cell seeding	Tse *et al.* (2016)
8	Extrusion based	Alginate-based tubular constructs using multi-nozzle extrusion-based technique	Sodium alginate powder, phosphate-buffered saline solution and xanthan gum	Limitation of this method was induced shrinkage during the cross-linking process	Tan and Yeong (2014)
9		Shear-thinning gelatin methacryloyl bio-inks	Gelatin, methacrylic anhydride, GelMA, fetal bovine serum, penicillin–streptomycin and 2-hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone	The bio-printed constructs were not only permitted cell survival but also enhanced cell proliferation as well as spreading at lower concentrations of the GelMA physical	Liu *et al.* (2017)
10		To investigate thermal degradation	PLGA with a lactic acid/glycolic acid	Severe thermal degradation was observed in the scaffold group prepared by the syringe type dispensing module	Lee *et al.* (2016)
11		Cartilage bioprinting	Pronase, collagenase, chondroitinase, dithiothreitol, iodocetamide, calcium chloride, D-mannitol, formaldehyde and L-ascorbic acid	Extruding the alginate sulfate/nano-cellulose bio-ink and chondrocytes significantly compromised cell proliferation, when using small diameter nozzles and valves	Müller *et al.* (2017)
12		Printing of alginate based tubular constructs using multi nozzle extrusion	Sodium alginate powder, PBS solution, Xanthan gum and calcium chloride	The process allowed printing taller structures	Tan and Yeong (2015)

(*continued*)

Table II

S. No.	Type of bioprinter	Purpose	Material used	Remarks	Ref.
13		Two step printing of photo-cross-linkable hyaluronan-gelatin hydrogels	HepG2 C3A, Int-407, and NIH 3T3 cells, methacrylated ethanolamide derivative of gelatin and methacrylated hyaluronic acid	Cells encapsulated within this printed construct were viable in culture and gradually remodeled the synthetic extracellular matrix environment to a naturally secreted extracellular matrix	Skardal *et al.* (2010)
14	Laser based	Printing of tissue with high cell density and micro scale organization	Rabbit carcinoma cell line B16 and human umbilical vein endothelial cell line Eahy926	Laser assisted cell printer can deposit cells with a micro scale resolution, at a speed of 5kHz and with computer assisted geometric control	Guillotin *et al.* (2010)
15		Alginate gelation induced cell death prepared with laser bioprinters	Solution of sodium alginate solution and NIH 3T3 mouse fibroblast cells	Two-minute gelation was observed to increase the cell viability after 24h incubation, mainly due to the protective cushion effect of forming gel membrane during droplet landing. The cell viability decreased after 24h incubation because of the forming thick gel membrane that reduces nutrient and oxygen diffusion from culture medium	Gudapati *et al.* (2014)
16		Printing of cells into 3D scaffolds	poly(ethylene glycol) diacrylate and ovine endothelial cells	The combination of laser induced forward transfer and two-photon polymerization provided a route for the realization of 3D multi-cellular tissue constructs	Oysianikov *et al.* (2010)
17		Dispensing pico to nano-litre of a natural hydrogel	Hydrogel of alginate and ethylene-diaminetetraacetic acid blood plasma	The existence of a counter jet had been proven, verifying the predicted bubble. Laser pulse energy and printed droplet volume had a nearly linear relationship at a constant viscosity and layer thickness in the energy regime	Gruene *et al.* (2010)
18		Creating on demand patterns of human osteoprogenitor cells and nano-hydroxyapatite	nano-hydroxyapatite bio-ink and MG63 cell	While physicochemical properties of nano-hydroxyapatite were not altered by the printing process, cell adhesion, spreading, proliferation and differentiation capacity over time	Catros *et al.* (2011)
19		In-situ printing of mesenchymal stromal cells	Mesenchymal stromal cells, collagen and nano-hydroxyapatite	Their approach allowed using different ribbons with distinct cell types and bio inks on the same platform	Keriguel *et al.* (2017)
20		Laser assisted ultrafast hydrogel photo-cross-linking method	GelMA hydrogel and NIH 3T3 fibroblast Cells	Hydrogel with a diameter of 8mm was cross-linked using laser bioprinting within 10sec with over 90% cell viability	Wang *et al.* (2016)

Figure 2 Jetting-based bioprinters



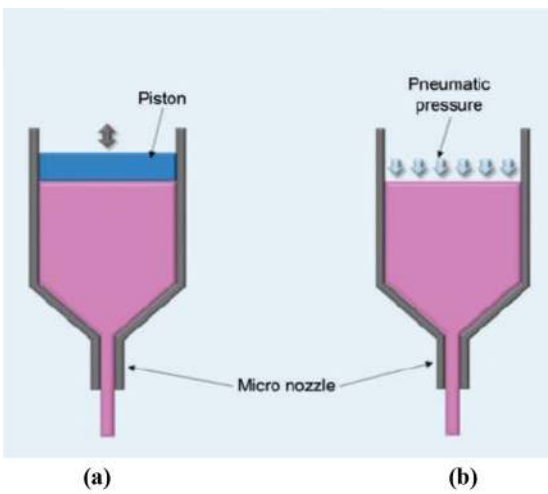
Notes: (a) Piezo-electrical actuator; (b) thermal; (c) pneumatic pressure; (d) laser energy. Reproduced with permission from reference
Source: Seol *et al.* (2014)

allow other category of materials involving powders, ceramics, and thereby combinations. In the future, printing of jetting printing of ophthalmological parts (like: artificial lenses, conjunctiva, sclera, corneas, glaucoma valves and implants) would be highly customized and *in situ*-based wherein such parts could be printed in the human body during surgical treatments. The jetting-based bioprinters should be available with ergonomically refined features designed for the surgeons (Lupeanu *et al.*, 2010).

2.1.2 Extrusion-based bioprinting

Extrusion-based bioprinting systems (Figure 3) work with a continuous, long filament of a bio-material made with cells

Figure 3 Extrusion-based bioprinting



Notes: (a) Piston; (b) pneumatic pressure. Reproduced with permission from reference
Source: Bernhard *et al.* (2016)

mixed with in hydrogel and develop the organs structures through a micro-nozzle. This printer is also referred as micro-extrusion bioprinters and pressure-assisted bioprinters. The extrusion bioprinters have been used to fabricate multiple tissue types, including aortic valves (Duan and Wang, 2013), branched vascular trees (Li *et al.*, 2016), *in vitro* pharmokinetic (Norotte *et al.*, 2009) and tumor models (Cui and Boland, 2009). The most common methods to extrude biological materials for bioprinters are pneumatic (Norotte *et al.*, 2009) or mechanical piston or screw (Fedorovich *et al.*, 2009) dispensing systems. Piston-driven deposition generally provides more direct control over the flow of bi-oink through the nozzle as material flow may get delayed due to compression of gas in pneumatic systems. Cell-laden hydrogel can be dispensed by using pneumatic pressure or a syringe pump, and the amount dispensed can be controlled by adjusting the level of pressure or simply piston displacement (Malda *et al.*, 2013; Landers *et al.*, 2002). Once the organ or structure is printed, it is solidified or fixed either physically or chemically. One of the biggest advantageous of extrusion-based bioprinters is that they allow a wider selection of biomaterials and even dense biomaterial can be easily printed through micro-nozzle.

Extrusion-based bioprinting was to deposit different cell types loaded in a wide range of biocompatible hydrogels (Lee *et al.*, 2010). Hepatocytes and adipose-derived stromal cells were used together with gelatin/chitosan hydrogels to engineer artificial liver tissue constructs through extrusion type bioprinters. A group of researchers developed a multi-nozzle low-temperature deposition system with four different micro nozzles (such as: precision deposition nozzle, pneumatic micro valve, piezoelectric nozzle and solenoid valve), Yan *et al.*, 2005. Moreover, other researchers fabricated multilayered cell hydrogel composites by using an extrusion-based technique (Khalil and Sun, 2009). Rheology study of cell viability was performed to investigate cell damage as a result of mechanical stress during printing (Khalil *et al.*, 2005). Cell viability after extrusion bioprinting was lower than inkjet bioprinting as the survival rate of the cells was 40-86 per cent, which was further tend to decrease by increasing extrusion pressure and increasing nozzle gauge (Nair *et al.*, 2007).

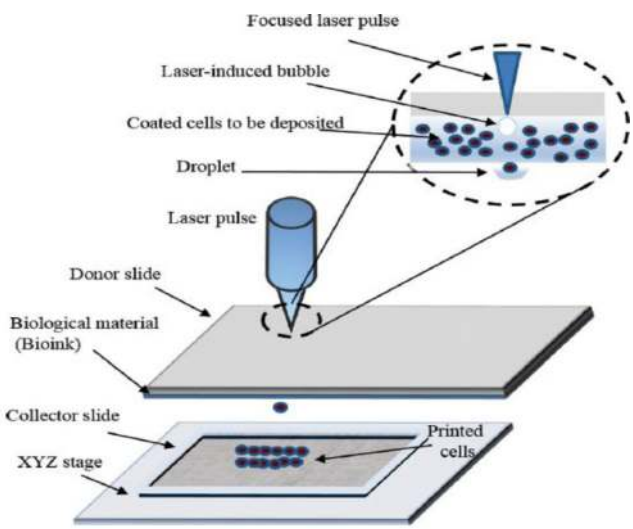
Generally, hydrogel could not degrade the surrounding gel matrix which caused the resulting structures to remain poorly proliferating and in non-differentiating state (Ozbolat and Hospodiuk, 2016), that affects the serviceability of the medical devices as well as their applications. These printers can work with numerous types of materials, as listed by Gudapati *et al.* (2014), for wide range of medical applications. However, very few have reported the utilization of this technology for treating ophthalmological problems as well as making devices and implants for the same. The reasons for this could be different, but with regard to the current advancements in extrusion bioprinting technologies, the research and innovations are still lagging in-terms for accuracy and feasibility of fabrication nanostructures that can enable this technology for fabrication of retina and eye wears, such as contact lens. Additionally, pneumatically driven extrusion printers often need sterilization of the worn air that comes from the compressor which causes the deterioration of the biological structures. On the other hand, in case of mechanically driven system, the sterilization is unimportant ahead can be easily autoclaved (Gudapati *et al.*, 2014). Viscosity of the bio-inks is the

second major issue with these printers as systems do not generate precise and controlled extrusion with partially solid or completely solid bio-ink. Third, the poor surface roughness of the resulting structure is also a barrier which seems to be impossible to overcome without post treatments. For instance, printing of a contact lens with extrusion printer will result into rough surface which would be unpleasant for a user to wear and may cause inflammation. Along with, the roughness profiles in this case will affect the transfer of light to the eye. Although many post processing technologies are available with plastic extrusion printers, the scope for bio-printed products is still questionable. By keeping in mind the versatility of extrusion based bioprinters with various bio-ink types, their capability of diffusion and perfusion and rapidity, efforts should be made to overcome the above-mentioned limitations and to establish this flexible manufacturing tool for ophthalmology applications.

2.1.3 Laser-based bioprinting

Laser-assisted bioprinting (Figure 4) uses a laser as the energy source to deposit biomaterials onto a substrate. As given in schematic diagram, it consists of three parts (pulsed laser source, ribbon coated with liquid biological materials that use to deposit over a metal film, and receiving substrate), Smith *et al.* (2004). This technology makes the use of ultra-violet laser as energy sources to print hydrogels, cells, proteins and ceramic materials (Jana and Lerman, 2015). The resolution with which the organs/structures can print generally varies from pico- to micro-scale features and the quality of the final print is influenced by many input characteristics such as thickness of the biological materials on the film, rheological properties, energy of laser, wettability of substrate and printing speed. Many researchers have demonstrated the feasibility of this technology to print cells, human dermal fibroblasts, mouse C2C12 myoblasts, bovine pulmonary artery endothelial cells (BPAECs), breast cancer (MCF-7) cells and rat neural stem cells (Guillemot *et al.*, 2010). In 2013, Graftskin skin substitutes were created through this technology, acted as a limestone incident in the field of laser-assisted bioprinting.

Figure 4 Schematic of laser-based bioprinting



Note: Reproduced with permission from reference
Source: Dababneh and Ozbolat (2014)

Fibroblasts and keratinocytes were used as sources to fabricate the skin constructs and were subsequently transplanted into the skin folds of mice. This experiment turned out successful as after eleven days the graft adhered well to the tissue around the skin wound (Barron *et al.*, 2004). In comparison of other bioprinting technologies, it has unique merits, including a nozzle-free, non-contact process, printing cells with high activity and high resolution and control of ink droplets in delivery (Michael *et al.*, 2013). The nozzle-free mechanism of printing enables the use of high viscosity bio-ink, which is not feasible with other bioprinters. Moreover, lasers offer ease of printing the smallest features of an organ (Phillippi *et al.*, 2008). Barron *et al.* (2004), demonstrated the ability to print mammalian cells onto a hydrogel substrate as either stacks or individual cells via laser bioprinting. The results of their study showed that with laser printers, it was possible to deposit cells and build 50-100-lm-thick cellular stacks. *In vivo* laser bioprinting was used to place nanohydroxyapatite in a 3-mm diameter and 600-μm deep hole of a mouse calvaria 3D defect model (Nishiyama *et al.*, 2007). Laser bioprinting has been used to produce medical tool (such as: customized, non-cellular, bioresorbable tracheal splint) that was implanted into a young patient with localized tracheobronchomalacia (Patrascioiu *et al.*, 2014).

This technology also has number of limitations and is waiting for progressive innovations. The heat generated from laser energy may damage cells and affect the ability of cells to communicate and aggregate. Also, gravitational and random setting of cells in the precursor solution, prolonged fabrication time, limitations in printing in the third dimension and the need for photo cross linkable biomaterials are other limitations in laser-based bioprinting (Zopf *et al.*, 2013). Among the three types of bioprinting technologies, laser-based technologies are most popular in the area of ophthalmology. Laser-assisted printing, the most expensive method, allows printing of concentrated fluids whilst maintaining cell viability, but is relatively slow and cell placement accuracy can be an issue. This is a nozzle free method that enables the practitioners to use high viscosity inks, unlike other techniques (Gudapati *et al.*, 2014).

Also, this technology facilitates the structures produced with high end precision, even for the tiny devices, thus making it a strong candidate amongst the other technologies for ophthalmology applications. The research community is consistently working on the various limitations exist in laser-based bioprinting such as laser energy damage the cells, their ability to communicate and aggregate in final construct (Lorber *et al.*, 2016). However, very less efforts are documented as on today to overcome the challenges in the construction of functional integration of the various cell types and sustainment of long-term survival of the laser prints. High cost associated with laser printer should be specifically targeted to enable patients to take advantage of this technology. This could be only possible through the transfer of the technology rights between the 3D printer manufacturers and their users at ground level. By doing so, it will become reality in the near future to restore vision for visual rehabilitation and to provide a better quality of life for visually impaired patients.

3. Bioprinting in the future of ophthalmology

Bioprinting techniques, which involve 3D printing of biological substances, have tremendous potential within ophthalmology. More than 30 per cent of the world population has some form of visual impairment, which includes conditions such as refractive errors and cataracts (Lupeanu *et al.*, 2010). The eye is a complex organ, but provides easy access for surgery and implantation. Hence, it is relatively feasible to meet the complex demands of treatments in ophthalmology with the aid of bioprinting. Several parameters have to be considered when using bioprinting techniques for ophthalmology. The constructs printed are required to be biocompatible to promote cell attachment, possess adequate mechanical properties to withstand the mechanical forces within the eye (Li *et al.*, 2016), and be of appropriate size to be used within the eye. Bioprinting can involve printing with or without cells. The use of cells usually necessitates encapsulation within a hydrogel (Bertassoni *et al.*, 2014). As per a recent study, only five clinical trials have been made on the implications of bioprinting technologies in ophthalmology (Witowski *et al.*, 2018). However, with such small steps, these advanced technologies have started to contribute to several breakthroughs in ophthalmology. This review further discusses bioprinting for lenses and prosthetics, cell printing, eye dieses, drug delivery and developments such as the bionic eye.

3.1 Lens and prosthetic

Customized optical devices are highly expensive and impractical to produce due to the involved manufacturing precision and very fine finishing requirements. Recently, 3D printing technology has come up to enable the fabrication of high-resolution transparent plastics with comparatively similar optical properties. With 3D printed technologies, it is now possible to rapidly design and fabricate optical elements for significantly less cost than conventional manufacturing, more increasing accessibility as well as minimized end-to-end prototyping time (West and Hubbell, 1999). Moreover, the use of AM in the development of flexible optical lenses for smart-phones has been reported as well. Host of ground-level 3D printing systems are now being used for fundamental, and economical photopolymer printing technology behind printed optics has been demonstrated (Willis *et al.*, 2012).

According to Huang and Zhang (2014) with precision AM technologies, it is now possible to produce the advanced models of a patient's eye anatomy that would allow surgeons to practice before an intervention, increasing precision and success. The research in this area is not sufficient to support these claims. Furthermore, the 3D hollow eye model which was fabricated about 10 years back with AM machine to test novel healing complications in retinal diseases treatments had failed to find its successors. Due to the limited availability of workable materials with AM in ophthalmology, the research practices still have abundant of scope for the development of ocular tissues (such as conjunctiva, sclera and corneas). The printing of artificial lenses, glaucoma valves and other medical implants developed in customized processes will be a reality in the future. Ayyildiz (2018) described the use of 3D printing technology to create customized spectacles for patients with facial deformities. The applications of bioprinting in ophthalmology are promising. A number of patents (refer Table III) highlighting the application of 3D printing technologies in ophthalmic are available.

The patents are mainly focused on 3D bioprinting in ophthalmology, mainly for the development of ophthalmic lenses. Manchester Metropolitan University (UK) patented a method of manufacturing an artificial eye for fitting as a whole or partial replacement of a patient's original eye. According to this patent, the whole task will be accomplished by clubbing various steps such as imaging an iris on a substrate by 3D printing, providing support to the frontal region of an artificial eye, positioning the substrate and support in a mold and encapsulating the substrate within a mold material. It is believed that printing of artificial lenses, glaucoma valves and other medical implants with customization and on-demand supply will be possible in the coming years. Further, numerous next generations ophthalmological products are likely to be benefited with this technology (Marasco and Foote, 2017).

3.2 Cell printing

TE aims to address numerous problems relevant to damages and defects that occur either naturally or due to un-natural circumstances. In this area of engineering, now surgeons are taking help from duo to available technologies and biomaterials to restore or replace the faulty tissues/organs with strategic assignment of suitable cells exhibiting normal functional potency (Salvador and de Menéndez, 2016). Ample numbers of literature reports are available in developing the complicated cellular structures based on 3D printing by adopting various printing techniques such as laser-assisted printing (Lee *et al.*, 2009), inkjet printing (Michael *et al.*, 2013), and micro-extrusion printing (Gao *et al.*, 2015; Gaetani *et al.*, 2015; Kolesky *et al.*, 2014). Gibney *et al.* (2017) developed a new method for producing thin collagen films suitable for the culturing of corneal mesenchymal stem cells, using 3D printing techniques to produce functional corneal substitutes.

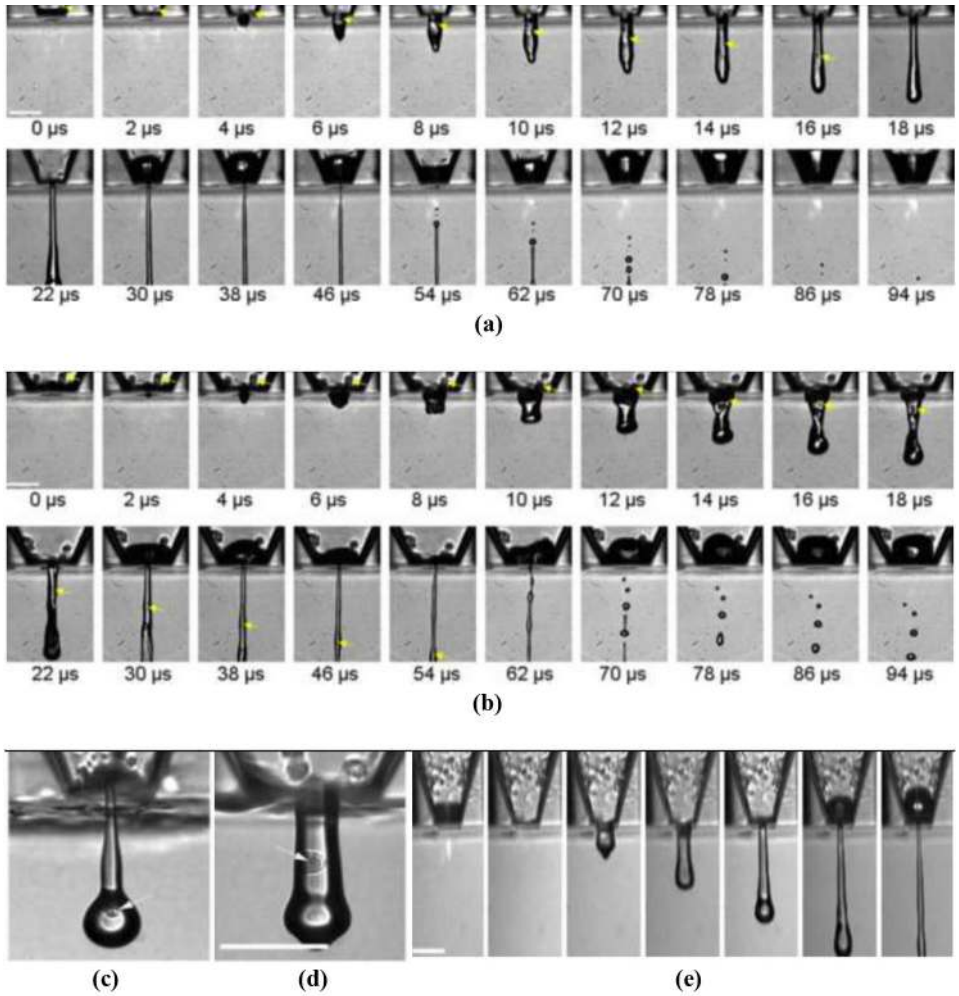
Nowadays, researchers are taking advantageous of neural cells to fabricate artificial neural tissues for studying repair of diseases or to investigate the properties of artificial networks (Murphy and Atala, 2014). The invention of highly advanced cell patterning techniques (like: soft-lithography, ink-jet printer, bio-plotters, etc.) made the placement of neural cells convenient, within a micro-sized chamber (Tooker *et al.*, 2005) or to form a specific shape (Sanjana and Fuller, 2004). 3D printing has potential to specify cell positioning to improve ganglion cells placement in conjunction with a radial electrospun scaffold designed to regulate axon guidance. Researchers at University of Cambridge (Orcutt, 2014) used a commercial ink-jet printer to form layered structures, made by two different cells, by using input materials from retinas of rats. The results of their preliminary examination highlighted that the ink-jet printing process did not compromise the health and ability of the cells to grow in culture. This is the first time in the history of 3D printing when adult animal's cells have been used to print nervous system. Certain other types of embryonic neuronal cells have been already deposited, successfully, through ink-jet printer and now plan to print cells including light-sensitive neurons and retinal pigment epithelial cells are in pipelines. The research group is confident to develop this technology further for fabricating new tissues that can grow outside and then implant in patient's damaged retinal during

Table III Patents on ophthalmic lens printing

Patent no.	Description	Publication date	Organization
WO2015014381A1	The one or more compositions are present in an ophthalmic lens to constitute voxels in which 3D manufacture require at least any of the compositions consists of one or more pre-polymers or polymers	Feb 5, 2015	–
WO2015014380A1	During the construction of the 3D ophthalmic lens, it is highly administered with high management level of homogeneity	Feb 5, 2015	–
WO2014195654A1	An optical function is involved in developing ophthalmic lens. It contains the step of additively manufacturing and an intermediate optical element	Dec 11, 2014	–
WO2014195653A1	The processes involved in manufacturing ophthalmic lens have at least one optical function which has the characterization that comprises of a step of additively manufacturing technique	Dec 11, 2014	Essilor International SA (France)
FR3008196A1	The process involved in manufacturing ophthalmic lens have at least one optical function which has the characterization that comprises of a step of additively manufacturing technique with starting optical system of the lens with minimal optical function	2015-01-09	–
WO2014049284A1	The invention related to ophthalmic lens manufacturing process consists of a step of marking to perform technical permanent marks on these ophthalmic lenses	Apr 3, 2014	–
WO2013098511A1	This method comprises two separate transparent elements, such as a base and a cap whose surface has a curved portion along at least one radius of curvature and having a fitting portion fitted into a fitting portion of complementary shape provided on the base	2013-07-04	–
US20160167323 A1	During the construction of the 3D ophthalmic lens, it is highly administered with high management level of homogeneity	06/16/2016	–
CN102854639A	Researchers have reported on designing the manufacturing process for photosensitive resin eyeglasses. Optometry prescription data is directly taken as input and convert into rapid prototyping equipment in a factory or eyeglass store	2013-01-02	Jiangsu Wanxin Optical Co. Ltd. (China)
DE102012011311A1	The invention is related to an intraocular lens that has a front side at which light occurs and a back side at which the light emerges. The lens is manufactured by an injection molding process, rapid prototyping or laser sintering	2013-12-12	Becker Hartwig (Germany)
CN104091506A	The invention reveals a novel 3D simulation eye. According to the novel 3D simulation eye, the 3D printing technology is adopted	2014-10-08	Liu Qinghuai (China)
GB2504665A	A method of manufacturing an artificial eye is presented. A digital image of an iris may be acquired and transferred to a substrate either by 3D printing or a transfer material, such as a dye sublimation film	2012-07-11	Manchester Metropolitan University (UK)
GB2487055A	An artificial eye is presented using a manufacturing method. Iris image is designed using CAD model and the substrate may be formed as an inherent part of the transfer step by a 3D printer using silica powder and then bound using cyanoacrylate	2015-08-20	Fripp Design Ltd. (UK)

ocular surgery. Another group of researchers examined the effect of thermal based ink-jet printing on survival and growth of retinal ganglion cells *in-vitro*, printed in variable buffers, ejection energies and cell densities (Kador *et al.*, 2016). However, it has been reported in many studies that heating in thermal inkjet print heads has negligible effects on the viability of several cell types involving cell lines, hamster ovary cells, muscle and stem cells (Xu *et al.*, 2005, 2006). Investigations has been made to check whether ink-jet printers can be used to print cells of the adult rat central nervous system, retinal ganglion cells and glia, and the survival and growth of cells (Lorber *et al.*, 2013). It has been found that ganglion cells and glia was successfully printed with piezo-electric printer (Figure 5). However, the piezo-electric process reduced the cell population in the areas where cells experienced higher shear stresses. Further researches are focused to move the success achieved toward forming a functional retina translated into a complex 3D cellular structure. Moreover, retinal cells are required to behave in concert with one another to relay visible information from eye to brain. There are chances in case of certain diseases, when specific cells need replacement (such as cells in glaucoma or cells in pigmentosa), may result into primary cell loss (Fariss *et al.*, 2000). Printed macula could be surgically implanted into the eye and in advanced retinoblastoma the whole eyeball (including retina) may require to be changed. To bear latter issue, 3D model (non-cellular) of human eye has recently printed (Xie *et al.*, 2014) (Figure 6). Here, ink-jet printer can be an excellent route to

Figure 5 A schematic diagram of retinal and glial cells printed by inkjet printing



Notes: (a) Retinal cell printing; (b) glial cell printing; (c) close up of retinal cells in a jet; (d) close up of glial cells in a jet; (e) retinal cell settlement in nozzle during jetting. Reproduced with permission from reference

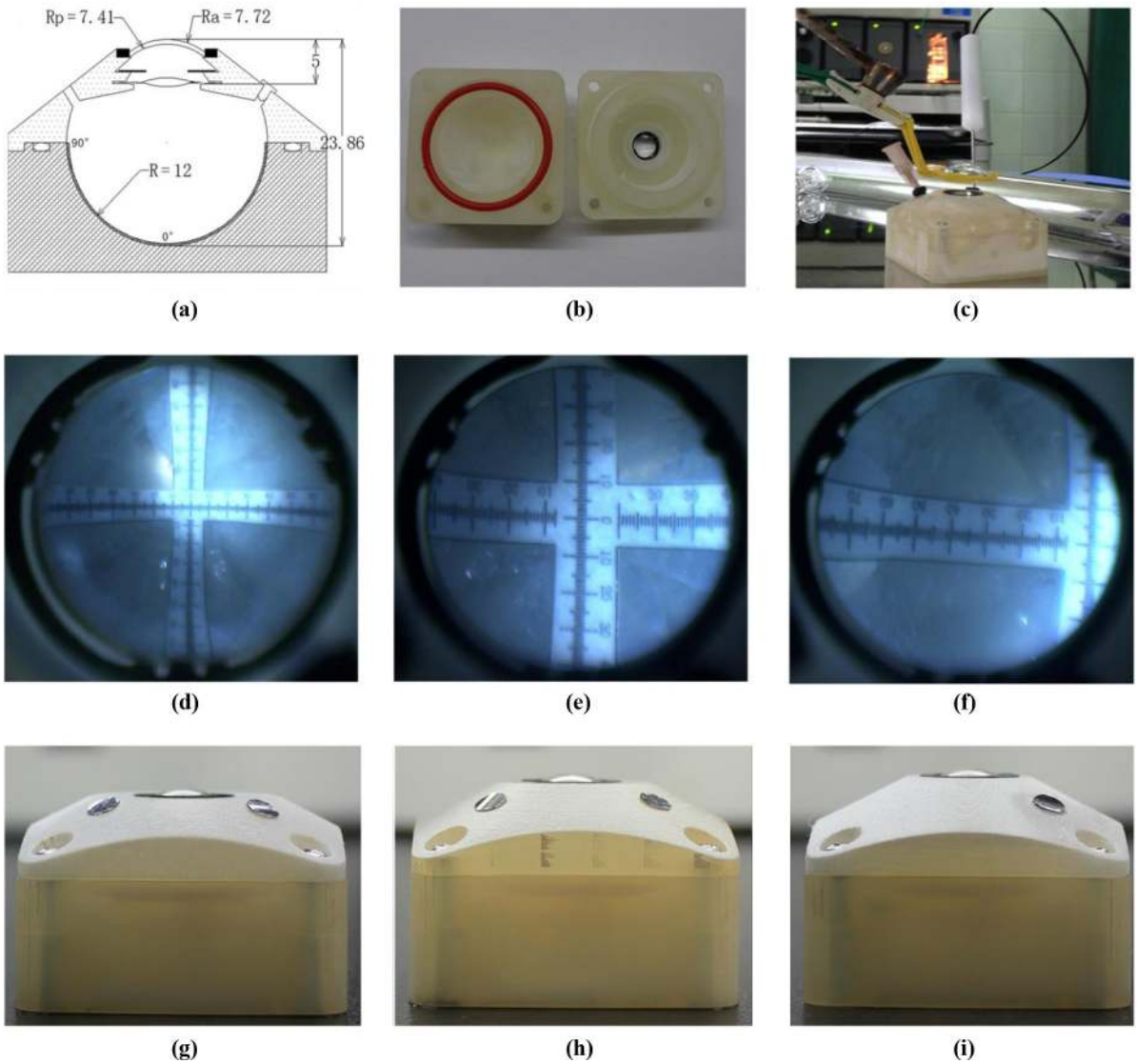
build such new tissue to restore vision to people suffering from common blindness problems because of degeneration.

3.3 Eye disease

Medical printing technologies and 3D bio-printing techniques have marked importance in ophthalmology. Age-related macular degeneration (AMD), diabetic retinopathy (DR), myopic choroidal neovascularization (mCNV) and retinal vein occlusion (RVO) taken together are leading causes of blindness worldwide. AMD is a complex and multifactorial disorder and the prevalence of the disorder is increasing with increased longevity around the world.

Neovascularization in these retinal disorders is induced largely by vascular endothelial growth factor A (VEGF-A) and progresses rapidly to blindness if left untreated. VEGF-A, with a central role in both normal and pathologic vascular growth within the eye, binds to VEGF-A receptors (e.g. Flt-1) on the vascular endothelium and promotes angiogenesis in response to hypoxia and other stimuli. The current standard of care in managing AMD, DR, mCNV and RVO is VEGF antibodies administered through intra-vitreal route to block VEGF activity, which underlies the CNV. Although this therapy improves visual acuity in a substantial proportion of patients, significant number of patients experience persistent CNV leakage, fibrotic scarring and/or geographic atrophy. Most patients do not achieve substantial visual improvement and one-third of treated eyes progress to legal blindness. Thus, a novel therapeutic strategy, which improves outcomes with acceptable safety profile, is an urgent and unmet medical need. By using bioprinting technology, it is possible to design the specific ocular cells such as retinal pigment epithelium that are damaged in retinal diseases such as AMD and DR. Retina consists of several layers of specific cells arranged in a specific order that is important for overall retina function. The cells must be intricately placed in an orderly fashion to design 3D structure to repair the retinal damage. Primary open-angle glaucoma (POAG) represent a leading cause of blindness and visual impairment worldwide affecting more than 70 million

Figure 6 (a) Schematic view of the cross-section of our physical model eye; (b) two printed parts provided main structure of the physical model eye; (c) use of the physical eye model for assessing the fundus range of the viewing system; (d–f) pictures of the angle bars photographed under 128D lens, 60D lens, and 60D lens with model eye tilt; (g–i) other three eye models printed and fabricated with different anterior chamber and total axial length



people (Tham *et al.*, 2014). It leads to retinal ganglion cell (RGC) death and blindness if left untreated. Age and increased intraocular pressure (IOP) are two major risk factors for development of POAG, the most common form of the glaucoma (Caprioli and Coleman, 2008, 2010).

However, a significant number of patients with POAG continue to lose vision despite initially responding well to therapies either due to becoming refractory to those medications and/or because patients do not administer the eye drops as prescribed and continued to have disease progression. Therefore, there is a continuing need to discover and develop novel methods for replacing RGCs. Researchers from University of Cambridge (UK) have reported that two types of neural cells were printed using retinal cells. The cells include ganglion cells and glial cells which function in such a way that transmit visual information to the brain and insulate, protect, support, and feed neurons respectively. Lorber *et al.* (2013) used gel through a piezoelectric inkjet printer to grow culture to examine survival rate. The method of piezoelectric printer is not generally used for bio-printing and is mainly due to the usage of electrical pulse to expel ink drops which can break cell membranes. However, the viability of the retinal cells is not markedly affected, but there is decrease in cell number due to sedimentation inside the printer head. In addition, the printed cells showed similar regeneration properties and survival rates in the compositional medium when comparing with non-printed counterparts. Furthermore, the printed retinal cells and retinal ganglion cells were deposited as monolayer and on the printed glial cells and retinal cell type respectively (Cui *et al.*, 2010). To create a functional retina, a complex 3D cellular structure must be generated that is capable of communicating cell signals to each other to mimic the retinal function.

An alternative use of 3D printing in ophthalmology is seen via smart phone technology. Chiong (2015) have produced two such

devices to work with smartphones. Figure 7(a) is a 3D printable imaging adapter that can be attached to a smartphone and photograph the retina. Figure 7(b) shows an image of a glaucomatous disc captured with the device, which is of better quality than that captured with a standard fundus camera in Figure 7(c). The group used a similar concept to develop a second device, which is a slit lamp microscope adapter [Figure 7(d) and (e)]. This device can be attached to the smartphone camera to document images of the ocular anterior segment, allowing for the easy detection of cataract, uveitis, ocular ulcers or corneal epithelial defects. These devices are more than ten times cheaper than standard ocular imaging devices.

As per the American Transplant Foundation, cornea stands out highest position in organ transplantation in USA in which 40,000 are undergoing with corneal transplantation per year. Nearly 53 per cent of the world's populations have poor access to corneal transplantations, as per global survey published in JAMA Ophthalmology in Feb, 2016. Furthermore, the transplanted graft was rejected due to complications associated with immune system. The anatomic structures of orbit and the eye are quite complex. In such cases, the tailoring of anatomic models based on 3D printing technology is highly useful for teaching and practicing purposes and interpreting the anatomic relationships between the complex surrounding structures and lesions. This important tool has also transformed education and clinical practice. Most of the researchers are using a 3D Systems Z650 printer to develop "highly realistic" 3D orbital prints in which it provides improved visualization of the fragile eye nerves.

3.4 Drug delivery

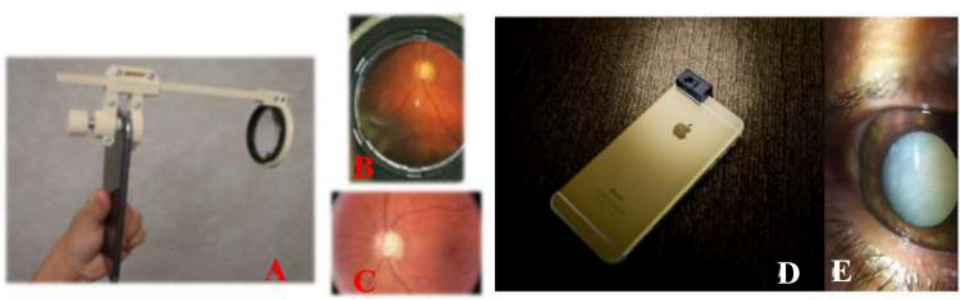
To expand the possibilities in ophthalmologist, continuous progresses are being invented particularly in the area of 3D printing so that human nervous system could be connected to electronic components, such as bionic parts, for curing blindness closer to reality. The advancement in this field will offer high-tech bionic eyes. In recent decades, nanotechnology-based drug delivery to the eye is the one of the most promising tasks to scientist in pharmaceutical industry by increasing ocular residence time and therapy enhancing ocular bioavailability and reducing drug toxicity. An ample number of nanotechnology-based carrier systems are developed and studied at large such as nanosuspensions, nanoparticles, liposomes and nano micelles. The nanocarriers/devices are sustaining drug release; improve specificity, when targeting moieties are used; and help to reduce the dosing frequency. However, we still need to develop a carrier system which could reach targeted ocular tissue, including post-non-invasive mode of drug administration, back of the eye tissues. This has become a very promising area for further research and development new drug delivery materials.

In ocular drug delivery, a very few promising results were reported with these branched polymeric systems (Abdelkader and Alany, 2012). The controlled delivery of drug protein-loaded biomaterials must be necessary to cure many eye diseases. In particular, drug combinations in particular to the patient must be unique and is loaded onto a single 3D-printed drug delivery device. Liposomes drug delivery method is adopted by NTU (Singapore) for the development of sustained release formulation of ocular drugs and to deliver them into various anatomical regions in the eye. Till now, the researchers succeeded with prostaglandins, antimicrobials and anti-inflammatory drugs are for sustained release from liposomes to front and back of the eye.

3.5 Bionic eye

Bionic eye, often termed as visual prosthesis, is an experimentally produced visual system and devices that are intended to bring back the functional sight in population that is suffering from partial/complete blindness. It has been reported that nearly 124 and 40 million world population is affected by low vision and blindness, respectively. Compared to prosthetic eye, a bionic eye, is different. The prosthetic eyes substitute the appearance and physical structure of a specific eye that is separated due to disfigurement, pain, diseases or trauma. On the other hand, bionic eye implants device within the existing eye structures or in brain. There are recent developments in several bionic eye implants, but single commercially existing bionic eye system approved by FDA is available in USA, and it can meet blindness problems mainly due to specific eye diseases (http://edition.cnn.com/2013/02/19/health/fda-bionic-eye/). The researchers at Bionics Institute have developed 3D printing using evok3d and 3D Systems ProJet 1200 3D printers that could restore vision (https://3dprint.com/24398/3d-

Figure 7 (A) 3D printed retinal imaging adapter on a smartphone; (B) an image of a glaucomatous disc captured with the smartphone retinal imaging adapter; (C) an image of the same glaucomatous disc captured with a standard fundus camera; (D) 3D printed smartphone slit lamp microscope, (E) an image of a patient with a white cataract captured on a smartphone with the 3D printed slit lamp microscope



Note: Reproduced with permission from reference
Source: Chiong (2015)

printed-bionic-eye/). However, additional research must be carried out to meet several challenges related to integrating optic nerve, retinal ganglion cells, and visual cortex to the bionic eye. It may be possible that the bionic eye can reach the consumer market by 2020. An Italian company, MHOX, is working on an actual bionic eye which can combine electrical components with 3D printing tissue to build a working eye to link the base implanted inside the eye socket with optic nerve, and to the brain (https://3dprint.com/52616/mhox-3d-printed-eyes/).

4. Summary and future trends

The application of bioprinting technologies in ophthalmological studies is a new field of research in comparison of other biomedical applications. Ophthalmologists are already progressed long way and developed many sophistical and sensitive ophthalmic devices, such as contact lens, artificial eyes, eye-glasses, retina conjunctiva, sclera, corneas, glaucoma valves and integrated electronic enabled eye wear. But still none of the reported study came up with a full-proof concept helping the bioprinting technologies. This might be due to the un-suitability of the existing bioprinters for developing the ophthalmic devices with desirable characteristics. Commercial bioprinting systems are facing many challenges in-terms of unavailability of workable biomaterials, un-suitable processing condition, dimensional and mechanical constraints, speed and cost. The speeds at which new breakthroughs are happening in the area of bioprinting-assisted-ophthalmology, the development of fully functional artificial eye is now just a matter of time. Further, bioprinting technologies should be explored to develop vascularized scale-up tissues and organs, transition of these from bench to bedside by discovering *in situ* techniques that can mimic anatomical components of natural eye with enhanced functionality.

For this, at first, the compatibility between printing conditions and workable materials should be established under tight scrutiny so that the printed devices can survive for life-long. Second, ophthalmic industries and their academic partners should work on the improvement of accuracy and feasibility of fabrication nanostructures that can enable the users to take benefits of bioprinting technology for developing nanostructures such as retina and contact lens. Finally, the existing technology rights should be shared between the inventors and commercial ophthalmological manufacturers to make the devices and products available to visually impaired patients at minimum cost. In the recent advancement in the designing of cellular three-dimensional structures provides added credit in creating three-dimensional printed retina. Furthermore, adult rat retinal ganglion cells, certain mammalian retinal cells, and glia are printed with specific phenotypic features and without viability loss. These research findings must be extended to translate other retinal cell types and human tissue.

Apart from the wide spread acceptance of the various bioprinting technologies in biomedical and TE domain, these systems still have numerous challenges yet to resolve as listed by Ozbolat *et al.* (2017). Further, the barriers during the designing of complex 3D printed tissue by incorporating spatial, cell density, survivability of long-term cell and integration of the various cell types functionally must be addressed. Further, this technology may be combined with complex electrospun surfaces in the design of future retinal models or therapies (Lim *et al.*, 2010; Hosseini *et al.*, 2017). Research potential to design an implantable 3D printed retina necessitates engineering development, regulatory effort and capital investment. The radiological images of the patients' eye are used by doctors to generate implants which have the similar dimensions as the original one. Health-care professionals and scientists uses additive printing technology to set down patients own cells and compatible materials in a predestined manner on a specific substrate to design patient-specific implants with a lower rate of rejection. 3D bio-printing is also accounted for its usage in natural anatomical variations which subsist among humans.

Overall, it can be concluded from the research endeavors in 3D printing in ophthalmology that this technology has the potential to improve the treatments of vision impaired patient by helping the doctors in performing risky surgery. The only need for this is to explore the innovative trends in customization of the medical devices which are highly desirable in-terms of market demand. Ultimately, the printed ophthalmological devices can heal the poor vision and other ocular diseases.

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Corresponding author

Sunpreet Singh can be contacted at: snprt.singh@gmail.com