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Review

3D printing in Ophthalmology: From medical implants to personalised medicine

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ABSTRACT

3D printing was invented thirty years ago. However, its application in healthcare became prominent only in recent years to provide solutions for drug delivery and clinical challenges, and is constantly evolving. This cost-efficient technique utilises biocompatible materials and is used to develop model implants to provide a greater understanding of human anatomy and diseases, and can be used for organ transplants, surgical planning and for the manufacturing of advanced drug delivery systems. In addition, 3D printed medical devices and implants can be customised for each patient to provide a more tailored treatment approach. The advantages and applications of 3D printing can be used to treat patients with different eye conditions, with advances in 3D bioprinting offering novel therapy applications in ophthalmology. The purpose of this review paper is to provide an in-depth understanding of the applications and advantages of 3D printing in treating different ocular conditions in the cornea, glaucoma, retina, lids and orbits.

1. Introduction

The first three-dimensional (3D) printer was invented in the 1980s by Charles W. Hull using the stereolithography (SLA) technique. 3D printing (3DP) was then described as a process of layering materials on top of each other to create certain objects. Hence, 3DP is also part of the additive manufacturing (AM) technologies (Schubert et al., 2014). The stereolithography printing technique was introduced to biomedical applications a few decades ago, which inspired new printing techniques to emerge and had been constantly improved upon to suit different unmet clinical needs. This new range of techniques is identified based on its layering methods and the specific materials that could be used during the printing process (Fan et al., 2020). The cost of AM is very expensive when it comes to large scale production (Fan et al., 2020). However, the 3DP technology is highly cost-effective in smaller scale production.

Since the 3DP technology was introduced to the healthcare industry for implantable modelling, it has improved our understanding of various disease mechanisms and human anatomy (Aimar et al., 2019). The introduction of 3D bioprinting using bioinks by combining both biological materials and cells, was marked as an evolutionary step of 3DP for biomedical applications. Most importantly, it has opened new doors to develop novel therapeutic approaches. 3D bioprinting is the deposition of compatible biomaterial but also involves the incorporation of cells or reaction with cells after the fabrication is completed (Derakhshanfar et al., 2018). The applications of 3D bioprinting in the medical world include but are not limited to organ transplantation (Ji and Guvendiren, 2017; Charbe et al., 2017), surgical planning (Zein et al., 2013; Qiu et al., 2018), medical education (Giannopoulos et al., 2016), and drug delivery (Goyanes et al., 2016; Konta et al., 2017).

Bioinks used for 3DP are mostly composed of cells and occasionally matrix constituents required to produce tissue-like constructs (Whitford and Hoying, 2016). However, a single bioink cannot result in a functioning tissue-like structure (Hospodiuk et al., 2017). Novel multicomponent bioinks can combine the favourable characteristics of the individual biomaterials to provide a solution (Zhang and Khademhosseini, 2017). Multicomponent bioinks are characterised by one or more types of biomaterials, cells and the addition of different materials or biomolecules. There are several categories of multicomponent

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bioinks that can be used to build different tissue structures (Table 1). The different categories are bioinks composed of natural materials, natural and synthetic materials, synthetic materials, and hydrogels and particles (Ashammakhi et al., 2019).

One important feature of AM is to provide greater flexibility for specific-patient customisation (Fan et al., 2020). This advantage is reflected in the process of creating a 3DP medical device. It starts by the image acquisition of the patient's target organ via a computerised tomography (CT) or magnetic resonance imaging (MRI) scan. These images are then processed to segment the target tissue and to generate a 3D model in a computer-aided design (CAD) software (Fig. 1). The 3D model is then optimised for the preparation of the final printing in a 3D printer (Aimar et al., 2019). Printing parameters are especially important, including printing speed, printing nozzle size, material, and the temperature that could affect the cell viability, the materials used, the active pharmaceutical ingredient (API), and the printability of the designs (Derakhshanfar et al., 2018). The careful selection of each printing parameter that goes into the printing process can affect the quality and biocompatibility of the end products. Therefore, the benefit of creating a treatment plan tailored to each patient by using AM is particularly preferred in the production of ocular, dental, and orthopaedic devices.

The potential applications of 3DP can significantly change the current and future prospects of treating patients with various eye disorders. The invention of 3DP cornea can help solve the severe shortage of donor corneas (Zhang et al., 2019). In addition, the AM technology can provide a better anatomical match since it possesses the ability to customise a design according to each patient's needs. Many ophthalmic implants have been manufactured using the traditional methods, such as high-speed multi-axis computer numerical control (CNC) machining and laser beam machining (LBM) types of subtractive manufacturing techniques via casting and forging (Davis et al., 2022). They usually result in inflexible mechanical properties and unfitted anatomy for each patient. The AM technology is able to craft a product with refined physical characteristics preferred by users (Fan et al., 2020). It also allows us to choose biocompatible materials and to easily change the printing techniques to meet the various requirements of clinicians and patients.

There are some features that 3DP implants possess that traditional fabrication lacks. For instance, 3DP tracheobronchial stent reserves self-expandable ability to help patients with a collapsed bronchus to breathe efficiently (Zopf et al., 2014). The AM technology can also accurately reassemble the anatomical defects in patients with fetal craniofacial anomalies (VanKoevering et al., 2015). In ophthalmology, 3DP can be beneficial by replacing the medical treatment by an efficient 3DP drug delivery system. The flexibility and customisation of the AM technology can also produce patient-specific glaucoma and cataract implants with carefully selected biomaterials.

Although this approach is still facing many challenges when choosing biocompatible materials and their printability under different 3DP techniques, the future of 3DP can benefit many patients who suffer from complications after ophthalmic surgeries and from the side effects of medical treatments. This review paper discusses the applications of the advanced AM technology in different fields of ophthalmology and provides an insight of the advantages that 3DP can offer. This comprehensive review of 3DP in eye care is also written in order to inspire many others who seek to utilise the AM technology in their fields of interest.

Table 1
Types of bioinks and biomaterials for the manufacturing of implants.

Types of Bioinks	Biomaterials
Bioink composed of natural biomaterials	• Alginate with gelatin/fibrin • Silk fibroin with gelatin • Agarose with collagen • Chitosan with gelatin • Cellulose with alginate • Hyaluronan with cellulose
Bioink composed of natural and synthetic biomaterials	• Gelatin combined with Methacryloyl (GelMa)
Bioink composed of synthetic biomaterials	• Poly(ethylene glycol) diacrylate (PEGDA) • Poly(ethylene glycol) methacrylate (PEGMA) • PEGDA with alginate
Bioink composed of hydrogels and particles	• PLGA-PEG with cell-laden carboxymethyl cellulose (CMC) • Silicates (Lithium sodium magnesium silicate) with GelMa • Hydroxyapatite (HAp) with GelMa/ Gelatin • Tricalcium phosphate (TCP) with alginate • Bioactive glass (BaG) with silk fibroin • Carbon nanomaterials with PLGA/ GelMA

2. Cornea and external eye disease

The cornea is the transparent, outermost layer of the eye that is responsible for transmitting and refracting light. Corneal blindness due to bacterial infections affects millions of people worldwide. The corneal limbus contains the epithelial stem cells that are self-renewing (Sun and Lavker, 2004). The patients with severely damaged limbal tissues usually need corneal transplantation to regain the self-renewing epithelium. The traditional transplantation can also help with the replacement of the damaged corneal stroma that is usually accompanied when the limbus is injured. However, the transplanted corneas cannot self-renew sustainably and there is a shortage of corneal donors. There is thus an increasing clinical need for a better alternative to corneal donors.

2.1. Corneal tissue bioprinting

It is feasible to use biomaterials combined with human proteins to create 3D bioprints for corneal tissues (Table 2). The reconstruction of corneal tissues usually requires careful selection of biocompatible materials to be used in *in vitro* settings. The 3D bioprinting of a stromal structure containing human adipose tissue derived stem cells (hASCs) was able to replicate the characteristics of native corneal stroma with high cell survival rates (Sorkio et al., 2018). Human embryonic stem cell-derived limbal epithelial stem cells used in a separate bioprinting also resembled the structure and biological functions of the corneal epithelium. The interaction of the 3DP stroma containing hASCs with a porcine cornea also showed its preliminary biocompatibility to integrate with the host tissue. The laser-assisted bioprinting (LaBP) technology is a powerful printing technique that can generate high-resolution medical devices with the flexibility to virtually correspond with any type of stem cells. Most importantly, the bioprints using these stem cells in LaBP do not affect their biological characteristics and functional properties.

It is important that these artificial corneas maintain the symmetric curved shape and the distinct arrangement of collagen lamellae that the native cornea possesses. In the study by Li *et al.*, the plastic contact lens mould was used to form the curved surface of the cornea where corneal epithelial cells were introduced (Li et al., 2003). In 2018, Isaacson *et al.* developed 3D bioprinted corneas using pneumatic 3D extrusion bioprinting (Fig. 2) (Isaacson et al., 2018). Topographic data from adult human cornea were used to construct the 3D models. In this study, they tested different combinations of low viscosity bioinks, such as collagen and alginate. The results showed that models printed with collagen-1 bioink and incorporated with alginate, had enhanced mechanical stability. After cell incorporation, high viability of corneal keratocytes was also observed after printing and it remained high after seven days. Hence, the conservation of high viability keratocytes indicates that composite bioinks of collagen and alginate can be used for 3DP corneas.

As aforementioned, the cornea has a distinct organisation of collagen fibrils that provides a transparent layer required for refraction and vision. This lattice pattern of collagen in the corneal stroma affects the transparency (Meek and Knupp, 2015). Despite novel techniques to replicate corneal structures, including magnetism or electrospinning,

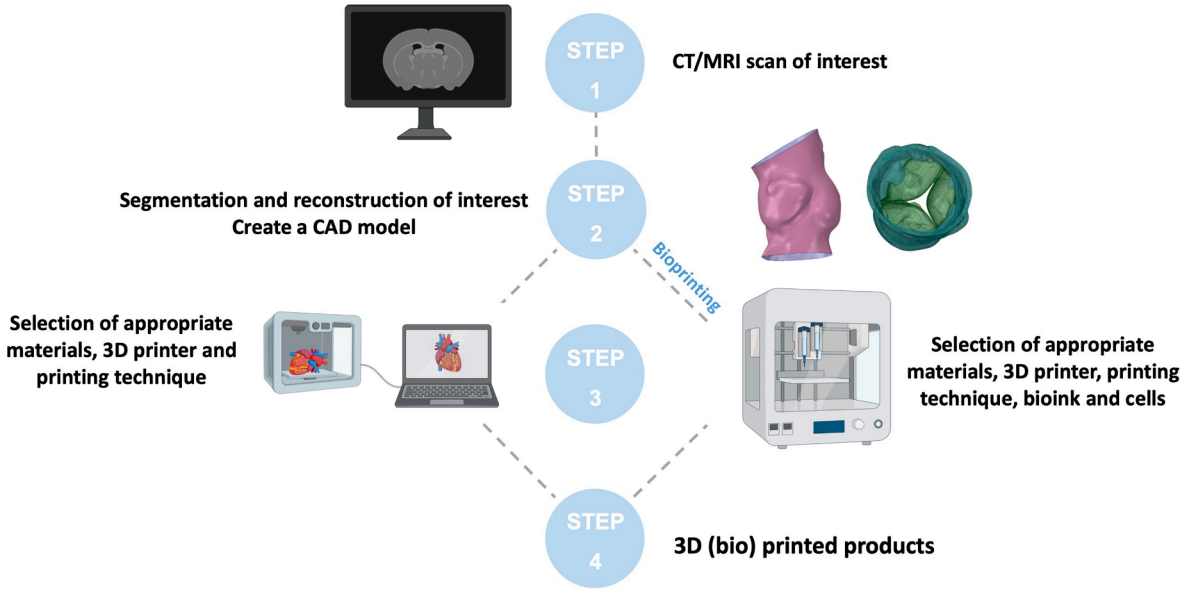

Fig. 1. 3D printing and bioprinting process.

Table 2
Studies of 3D bioprinting in ophthalmology.

Tissues	Studies	3D printing techniques
Cornea	• Corneal tissue bioprinting	• Laser-assisted bioprinting/ pneumatic 3D extrusion bioprinting
	• Contact lenses	• Digital light printing
	• Drug releasing patches	• Hydrogel-based bioink
Glaucoma	• Drug-eluting implants, e.g. contact lenses	• Fusion deposition modelling and hot melt extrusion
	• Minimally invasive glaucoma surgery (MIGS) devices	• Projection micro stereolithography
Retina	• Macular buckle	• CAD software 3D printing
	• Retinal model	• Inkjet bioprint
Orbit	• Orbital implants	• Computer-simulated rapid prototyping (RP) models
Lids	• Adjustable eyelid crutches	• 3D printing
	• Drug-loaded punctal plugs	• Digital light processing (DLP) 3D printing

the results show low transparency. 3DP technology can be used to create shear-induced fibres. Since collagen fibres are different from collagen fibrils and can even affect corneal keratocytes, thin collagen fibrils derived from decellularised corneal tissues can be used (Muthusubramaniam et al., 2012; Kim et al., 2019). Kim *et al.* investigated the effects of applying shear stress in a controlled manner while using atelocollagen fibrils instead of collagen fibres (Kim et al., 2019). By applying varying shear stresses, the authors observed different shear-induced collagen fibrils and cellular behaviours. More specifically, shear stress can be induced by changing the viscosity of the bioink, the flow rate, and the inner diameter of the nozzle. In addition, shear stress can also influence cellular processes, such as apoptosis, during the printing process. The study induced shear stress by using three different nozzle diameters on differentiated keratocytes. Cellular morphologies were observed 28 days after printing. The results showed that the groups with the highest shear pressure, namely 25G and 30G, demonstrated higher expression levels of keratocytes. However, the 30G group also demonstrated some corneal wounding. Samples of the 25G group were cultured *in vitro* and *in vivo* for 28 days. Aligned cells, activated keratocytes, and increased amount of secreted type-I collagen were observed in the 25G group. Therefore, shear stress through 3DP, can be applied to correctly orientate collagen fibrils to mimic the structure of the native human cornea (Kim et al., 2019).

Contact lenses were invented for the purposes of optical correction in the 1800 s (Key, 2007). The advent of hydrogel soft lenses was a significant development in the development of contact lenses. The evolution of contact lenses progressed while the manufacturers were seeking biocompatible materials that were oxygen permeable and that had robust mechanical properties. The manufacturing process for contact

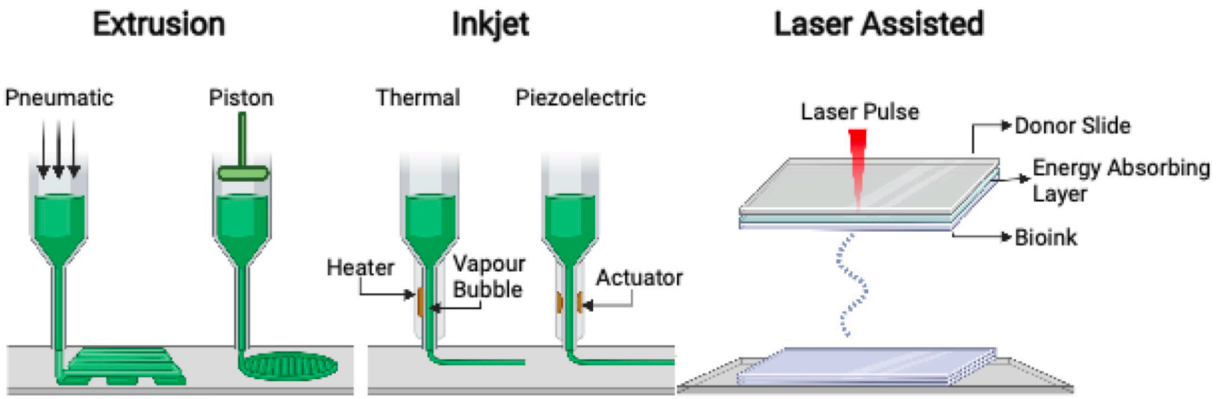

Fig. 2. Forms of 3D bioprinting used in ophthalmic applications.

lenses is still challenging with many steps involved and limited flexibility for design. 3DP can be utilised to produce many different types of contact lenses, including the smart contact lenses that can detect and control eye diseases. Digital light printing (DLP) is usually preferred for light-curing-based polymerisation 3DP because it can print at a much higher resolution, compared to the performance of the fused deposition modelling (FDM) (Bandari et al., 2021). Asiga DentaClear Resin, a widely used resin for the dental industry, can be used to produce corrective contact lenses via the DLP printing (Alam et al., 2021). The DLP 3D-printed contact lenses added with nanopatterns via the direct laser interference patterning (DLIP) can generate smart contact lenses. These smart contact lenses can help clinicians to monitor the changes in patients' eye health. The 3DP contact lenses with a thin polyvinyl chloride (PVC) plastic film can achieve light transmission to about 90%, although it would be interesting to see the comparison of their mechanical, physical, and chemical characteristics between the novel 3DP contact lenses and the traditional contact lenses. AM also grants the freedom of generating customised contact lenses tailored to patients' eye structures and conditions.

2.2. Drug delivery

3D printed drug patches with hydrogel-based formulations can also help release the drug efficiently in the eye, such as the conjunctiva, without causing any visual impairment or uncomfortable blinking (Table 2). Tagami *et al.* proposed lyophilised ophthalmic patches capable of producing novel dosages, that could be customised to patients in hospitals (Tagami et al., 2022). The drug releasing patches contained the antibiotic drug levofloxacin. The 3DP drug releasing patch was printed using a hydrogel-based bioink containing hydroxypropyl methylcellulose (HPMC), mannitol, xylitol, and the drug. The preparation of the formulation underwent a freeze-dried process. Different concentrations of HPMC, mannitol, and xylitol were also tested and compared. The composition of biomaterials determined the viscosity property of the bioink, which in turn could affect the printability of the patches.

The physical properties, water uptake, antimicrobial activity of the drug, and the drug release ability were also measured for these lyophilised ophthalmic patches. The amounts of mannitol and xylitol used in the composition greatly affected the viscosity of the bioink. Among the two alcohol sugars, xylitol was also highly water soluble, therefore, xylitol-based formulations possessed a rapid water absorption capability. In addition, these patches combined with levofloxacin were able to effectively fight against the presence of bacteria in the *in vitro* assays. Most importantly, the patches can carry different active pharmaceutical ingredients, and can be tailored to release various dosages according to the patients' needs. These eye patches can also be designed to deliver other drug formulations, including eye drops for patients undergoing cataract surgery (Grob et al., 2014) and mini-tablets for treating the inferior conjunctival fornix (Moosa et al., 20142014). The chemical and physical characteristics of the materials used in the drug release patch can help construct an ophthalmic patch customised to each patient. The biocompatible drug-releasing patch can help eliminate the need for repetitive administration of eye drops in patients after glaucoma and cataract surgeries.

3. Glaucoma

Glaucoma is the leading cause of irreversible blindness worldwide, currently affecting 76 million people and its prevalence is estimated to increase to 112 million by 2040 (Tham et al., 2014). Glaucoma is an eye condition where the optic nerve is damaged by the pressure of the fluid inside the eye, and treatment involves reducing the intraocular pressure (IOP) using medications, laser or surgery (Sanghani et al., 2021; Fernando et al., 2018). The prevention of further progression of glaucoma aims to reduce the IOP level by decreasing production or increasing the drainage of aqueous humour out of the eye.

3.1. Drug-eluting implants

A common treatment for glaucoma requires daily administration of anti-glaucoma eye drops to decrease the IOP. Drug-eluting implants represent an alternative treatment introduced for glaucoma patients who experience non-adherence to anti-glaucoma medications (Table 2). There are promising ocular implants embedded with efficient drug delivery systems for the treatment of glaucoma. The drug-eluting implants should be biocompatible and tolerated for use in patients. Current conventional drug implants on the market have limitations in terms of a short period of drug release and active pharmaceutical ingredient loading. These implantable devices can deliver drugs to the whole body through the blood system, which will lead to systemic side effects. On the other hand, 3DP possesses a flexible capacity to customise ocular devices with high precision (Mohamdeen et al., 2021 Dec 20). The contact lenses designed by Mohamdeen *et al.* delivered the β-blocker timolol maleate for seven days at a sustainable rate. These implantable contact lenses were made with the combination of fusion deposition modelling and hot-melt extrusion (HME) technologies (Fig. 2). The combination of ethylene vinyl acetate (EVA)/poly(lactic acid) (PLA)/timolol maleate (TML) at a ratio of 84:15:1 (wt:wt:wt) showed a great physical blending with desirable thermal durability. The authors also pointed out the optimal printing parameters, namely low print speed and small nozzle diameter, in order to achieve high resolution and a smooth surface (Mohamdeen et al., 2021 Dec 20). However, the sustainability of drug release by this drug-eluting implant needs further improvement due to the slow diffusion of the polymer mixture.

3.2. Minimally invasive glaucoma surgery (MIGS) devices

Another 3DP technique that has been used in developing therapeutic devices for glaucoma is called projection micro stereolithography (PuSL), which combines the benefits of both DLP and SLA technologies (Table 2). Many MIGS devices have been developed in the last decade to increase drainage of aqueous humour from the eyes of glaucoma patients. Currently, there are commercially available devices, such as iStent, Hydrus and XEN, and each of these devices drains aqueous humour through a different pathway (Pillunat et al., 2017). These minimally invasive implants are chosen based on the specific patients' conditions. However, they all share the same limitation of short-term efficacy due to fibrotic encapsulation (Siewert et al., 2017).

There are also challenges during the surgical procedure for minimally invasive devices due to the requirement of high precision. AM can be used to design a personalised instrument for surgeons to improve the surgical procedure. 3DP technology allows great flexibility to produce a complicated surgical instrument while ensuring its functionality. A 3DP cable-driven steerable instrument for minimally invasive surgery can be easily assembled and handled with one hand (Culmone et al., 2021). The design enables ergonomic handgrip, flexible steering control, and high efficiency when holding tissues. The characteristics of the instrument can help surgeons to comfortably carry out the surgery without limiting their wrist motions. The systems manufactured by AM allow customisation for different patients and surgeons by modifying the gripper handle. In addition, 3DP surgical instruments can be easily adapted to other fields of minimally invasive surgery.

Glaucoma management requires close monitoring of the drainage of aqueous humour in the eye so that clinicians can manage the IOP level. Physicians can take the advantage of 3D modelling of the anterior chamber to assess the mechanism of aqueous humour drainage and to understand the physiology tailored to each glaucoma patient. A 3D printed anterior chamber can help achieve the simulation of the aqueous humour outflow (Wang et al., 2016). The validation of this device shows the velocity, pressure, and distribution of the fluid outflow. It can further help clinicians to understand the IOP changes in glaucoma patients to

prevent the progression of visual field loss and to design the most appropriate treatment plan.

4. Retina

The retina is a complex tissue made of different cellular layers, that detects and converts light signals into electrical signals, which are then transmitted to the brain. Photoreceptors, known as rods and cones, are responsible for the phototransduction. The retinal pigment epithelium (RPE) is a monolayer found between the retina and the choroid. The RPE provides growth factors and plays an important role in nutrient transport and phagocytosis of the photoreceptors (Chiba, 2014). Any damage to the retinal layers can lead to diseases, such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP). These diseases are caused by photoreceptor deterioration that leads to RPE atrophy. Therefore, retinal regeneration approaches can be used to treat the affected eye. It is critical to maintain the retinal cell and layer organisation to achieve normal function. Scaffold approaches were originally used as a solution; however, they did not resemble the functions of the human retina. 3DP can be used to generate the complexity of the retina that is crucial for its function.

The 3DP technology can be used to create customised devices that are tailored to fit patients' needs. With the help of CT technology, the patient's eye geometry can be captured (Chiba, 2014) and are then used to create a 3D model using a CAD software (Fig. 1). The 3D model can be used to determine the characteristics of the patient-tailored medical device. Pappas *et al.* have demonstrated the use of CT images and 3DP for developing a customised macular buckle in a patient with severe myopia (Pappas et al., 2020) (Table 2). The macular buckle is designed based on the patient's eye by using biocompatible materials. The unique design will make it easier for ophthalmic surgeons to deploy the macular buckle and to avoid further manipulations before, during and after implantation.

Shi *et al.* also reported the creation of functioning RPE and retinal photoreceptors (Y79) using 3DP. Human retinal pigment epithelia (ARPE-19) cells were precisely bioprinted on an ultrathin membrane that represents the Bruch's membrane. The Bruch's membrane is a thin tissue layer between the retina and the choroid, where RPE cells attach themselves. Successful formation of an intact monolayer was observed after the proliferation of ARPE-19 cells. Hence, the ARPE-19 seeded on the ultrathin membrane represented the Bruch's membrane and RPE. Photoreceptor (Y79) bioink was printed on the monolayer. The bioprinted retinas were then placed in culture and no cell viability was compromised. Using scanning electron microscopy (SEM), the bioink was shown to be porous, which forms a suitable environment for the proliferation of photoreceptors (Shi et al., 2017).

Furthermore, Masaeli *et al.* reported the development of a functional retinal model using an inkjet bioprinting approach. They first developed a Bruch's membrane using gelatin methacryloyl (GelMA) thin layer, to mimic the microenvironment of the retina. RPE cells were then bioprinted onto the Bruch's membrane. They demonstrated that the RPE cells proteins were similar to that of the RPE layer *in vivo*. Moreover, isolated and differentiated photoreceptors from pig eyes were deposited onto the RPE monolayer and hence mimicking the different cellular layers of the retina. Three days after bioprinting, the presence of correctly positioned photoreceptors was confirmed. Masaeli *et al.* also reported for the first time that both bioprinted RPE and photoreceptors expressed essential transcription factors, validating that functional retinal bioprinted constructs could be achieved for clinical applications (Masaeli et al., 2020).

5. Lids and orbit

Orbital fractures occur when the bones surrounding the orbit buckle or break due to blunt force trauma. Despite novel treatment methods and techniques, the restoration of the orbital wall is challenging as any implant mispositioning can lead to enophthalmos or complications in visual acuity. The intricate concave and convex 3D structure of the orbit remains a challenge for craniofacial surgeons. In addition, patients have orbits of different sizes and shapes. Given that the slightest change in orbital volume can lead to enophthalmos, which is the posterior displacement of the eye, it is critical to precisely restore intraorbital volume for a successful orbital wall reconstruction. Oh *et al.* designed titanium-Medpor mesh implants by manipulating CT images and using them in computer-simulated rapid prototyping (RP) models (Table 2) (Oh et al., 2016). In this study, 104 patients with one-sided blowout orbital fractures were included. Using the preoperative RP model that was produced, the intact side was mirrored and superimposed onto the fractured side to help produce the implants. After successful insertion of the implants into the orbital wall, postoperative CT images were taken for evaluation (Fig. 1). The volumes of both intact and injured orbits were measured pre- and postoperatively, and the results showed no significant difference in the orbital volumes. Furthermore, there were no reports of enophthalmos or any other complications in patients. Hence, novel computerised techniques like rapid prototyping modelling can provide solutions to overcome the limitations of reconstructing the orbital wall. Using the RP models, the implants can be moulded into individualised patient designs, resulting into successful and faster surgical operations (Oh et al., 2016).

Blepharoptosis is a condition that can lead to severe vision impairment. Surgery is the usual approach for treatment. However, blepharoptosis can cause advanced myopathies, such as chronic progressive external ophthalmoplegia (CPEO), that can be difficult to treat due to the recurrence even after multiple surgeries. Crutches are placed onto the patient's glasses to lift the eyelid. Even though eyelid crutches can be used as an alternative treatment, they lack malleability and patient-specific designs are expensive. Sun *et al.* used their patients who suffered from CPEO-related blepharoptosis, to develop low-cost, universal and easily adjustable 3DP eyelid crutches (Table 2). The patients had several eyelid surgeries but there was recurrence of the ptosis. Moreover, the patients had developed keratopathy and corneal thinning due to the lack of blinking and weakness of the orbicularis. In order to design 3DP crutches for patients, the marginal reflex distance, eyelid and glasses frame dimensions were measured. After five months, they reported that the patients had improvements in vision and could achieve eye closure. 3DP can thus be used to develop inexpensive and universal eyelid crutches to improve the quality of life of patients (Sun et al., 2019).

Xu *et al.* also used digital light processing (DLP) 3DP to develop dexamethasone-loaded punctal plugs (Xu et al., 2021). The punctal plugs were manufactured using polyethylene glycol diacrylate (PEGDA) and polyethylene glycol 400 (PEG 400) to create a semi-interpenetrating network (semi-IPN). The authors demonstrated that punctal plugs made with 20% w/w PEG 400 and 80% w/w PEGDA achieved sustained release of dexamethasone for up to 7 days, while punctal plugs made with 100% PEGDA showed prolonged release for over 21 days (Xu et al., 2021). DLP 3D printing thus represents a potential manufacturing platform for personalised sustained-release drug-loaded punctal plugs in the eye.

6. Regulatory considerations

Despite the favourable prospects of the 3DP applications in the medical field, the legal regulations of 3DP technology for pharmaceutical products are not complete. Although the Food and Drug Administration (FDA) approved the 3DP drug Spritam in 2015, the application guidance for 3DP was not released until 2017 (Tsui et al., 2022). The FDA also has no publication of official regulations for 3DP technology (Mohammed et al., 2021). It is an impediment for the implementation of 3DP medical devices and slows the clinical translation of the 3DP products to patients. Therefore, it is impossible to define responsibility for litigation when it comes to the safety issues of 3DP products.

However, the regulatory organisations have just initiated programs and allocated teams to begin drafting the standard regulations for 3DP (Mohammed et al., 2021). Following the initial efforts of the FDA in 2019, the European Medicines Agency (EMA), the Medicines and Healthcare Products Regulatory Agency (MHRA), Health Canada, Therapeutic Goods Administration (TGA, Australia) and other national regulatory agencies have started to discuss the legislation of the innovating 3DP applications in medicine (Tsui et al., 2022). As of 2022, the discussion is still ongoing to provide a full regulatory guidance ensuring the safety and effectiveness of 3DP medical devices. At present, the manufacturing process and quality assurance of 3DP medical products must meet the requirements of the applicable EU legislation, such as the Medical Devices Directive 93/42/EEC (Conformity assessment procedures for 3D printing and 3D printed products to be used in a medical context for COVID-19. Docsroom - European Commission. https://ec.europa.eu/docsroom/documents/40562. Published April 1, 2020).

7. Expert opinion & future directions

The invention of 3DP and its adaptation to the healthcare industry has inspired new therapies for different types of ophthalmic diseases. It has enabled us to reconstruct the stroma of the human cornea by incorporating human stem cells. As an alternative to corneal transplantation, the 3DP cornea incorporating the patient's stem cells can avoid the immune rejection that usually occurs in transplant recipients (Tsui et al., 2022). The selection of optimal biomaterials and bioinks determines the printability of 3DP implants. For example, a bioink consisting of alginate and collagen was feasible and generated viable 3DP corneas (Isaacson et al., 2018). Changing the physical properties of the bioink, such as its viscosity, induced the shear stress to mimic what the natural human cornea experiences (Kim et al., 2019) and affected the printability of the end product (Tagami et al., 2022).

Apart from corneal transplantation, the use of 3D bioprinting on retinal regeneration is also under investigation. The retina is one of the most complex human tissues in the eye and can potentially be reconstructed by 3D bioprinting. The rat retinal cells could be successfully 3D printed without compromising their cell viability and growth using inkjet printing (Lorber et al., 2014). In addition, the effect of neurite outgrowth on retinal ganglion cells contributed by the glial cells was also preserved. This established the potential of using 3D bioprinting for tissue regeneration of the human retina. Future investigations are required to establish the vascular organisation to further complete the regeneration of retinal tissues.

Each 3DP technique has its own advantages over the other techniques to meet the requirements for the development of ocular devices. For instance, DLP is preferred for printing contact lenses with nanopatterns. This 3DP technique could add on a layer of electronic photodetector to monitor the physiological changes in patient's eyes (Alam et al., 2021; Park et al., 2018). These 3DP contact lenses with photosensors will be helpful for patients with drug release implants to detect the regional toxicity of the released medical agents. The drug release implants are used for glaucoma and cataract patients and can be customised using 3DP technology depending on individual preferences. Hydrogel-based lyophilised eye patches equipped with the antibiotic drug were flexible in terms of releasing different dosages by adjusting the bioink compositions (Tagami et al., 2022). The customisable 3DP is also beneficial for designing drug eluting systems to treat glaucoma. The drug implants, however, are essential to retain a persistent drug releasing speed while evenly diffusing to the target area (Mohamdeen et al., 2021 Dec 20).

Ocular prostheses are necessary following enucleation and evisceration to replace the absent eye (Xu et al., 2021). The traditional manufacturing process for artificial eyes is time-consuming. In contrast, 3DP allows us to customise the design based on the anatomy of the patients' eyes and to create a mould of prosthetic eyes within a substantially shorter manufacturing time (Ruiters et al., 2016). Although 3DP currently only permits us to produce plain eyes with few cosmetic decorations, they have the potential of having add-on photodetectors to generate artificial eyes that are functional.

3DP has been widely used for preoperative planning to help in disease treatment. Its use in manufacturing surgical instruments has also efficiently improved the outcome of surgeries and the practice of surgeons. For example, 3DP has helped surgeons and clinicians to shape the orbital structure before implantation based on patient-specific cases (Oh et al., 2016; Kozakiewicz et al., 2009). This is particularly useful for patients suffering from orbital fracture who require orbital restoration and implants. In addition, the customised 3DP instruments can be produced according to the specific needs of the surgeon. Their production time has been greatly reduced compared to the conventional manufacturing methods (Xu et al., 2021). The invention of 3DP cable-driven steerable instruments can also assist surgeons to carry out minimally invasive surgery smoothly and efficiently (Culmone et al., 2021).

With the right biomaterials and appropriate printing parameters selected, 3D bioprinting can generate a biocompatible and customisable model to meet the requirements of each patient. Therefore, the development of a 3DP ocular device requires careful considerations when choosing the biocompatible materials and printing techniques. However, there are still many challenges ahead before 3DP ophthalmic products can reach clinical trials and eventually commercialisation. A current concern is the sterility of the materials and biocompatibility in patients. Most of the 3D printers can prepare sterile products, for example bioprinters. Moreover, there are manufacturers that are currently developing sterile 3D printers. Hospitals also have sterile areas that could be used in the future for the manufacturing of implantable systems.

Furthermore, the process of 3DP still requires manual segmentation for exhaustive details. In the future, artificial intelligence assisted by human supervision will be able to increase the proficiency of the segmentation output. The concurrent improvement of the computational technology, such as the CAD software, provides us with the prospect of accurate and precise printing techniques in the future.

As 3DP techniques have been developing rapidly for the past decade, the four-dimensional printing (4DP) incorporating the 4th dimension (time) is slowly emerging as a newly unconventional printing technique for medical applications. The 4DP technology allows the biomaterials to change over time physically and functionally (Willemen et al., 2022). This adds another layer of flexibility to the development of 3DP applications, especially for the progression of tissue engineering. It helps to construct realistic tissue organisations with added flexibility. The biomaterials used for 4DP can change their physical appearances by responding to the changes in temperature, pH, ion concentrations etc. Biomaterials can also result in functional changes due to the cell maturation apart from the morphological changes.

One of the 4DP applications is to use the hydrogel, that can respond to the environmental stimuli, for the construction of 4DP drug delivery systems (Willemen et al., 2022). The 4DP microneedles can change their shapes in response to dissolving, bending, and UV curing to improve cell adhesion. The changes in physical properties while responding to external stimuli can be useful in the development of 4DP drug-eluting implants. These exciting designs using 4DP technologies can further benefit the ophthalmic applications, namely the drug-eluting implants incorporating IOP-responsive biomaterials that are feasible for glaucoma treatment.

8. Conclusions

The emergence of 3DP technology allows us to produce personalised medical products that conventional manufacturing techniques cannot offer. The adaptability and flexibility of 3DP will enhance prospects of therapeutic practices, including dentistry and orthopaedics. The promising discoveries of 3DP in ophthalmology encourage the medical

research community to continuously provide advanced treatment and to gain confidence in patients. 3DP in the ophthalmic field is still not fully understood and developed, but its potential to provide revolutionary solutions for various eye diseases is indisputable. 3D bioprinting as a novel technology introduced in the medical field marks a revolutionary approach in modern medicine. The invention of bioinks in 3DP can potentially solve the shortage of corneal transplantation and promote the enhancement of tissue regeneration. Furthermore, the constantly evolving 3DP techniques tailored for ophthalmic devices and drug delivery systems guarantee the individualisation of AM manufacturing.

The challenges and obstacles in biomedical 3DP manufacturing require further investigation in the role of 3DP in the medical field. Once the ongoing establishment of legal regulation is in place for the medical production using 3DP at the point of care, the personalised 3DP medical products will help meet in the near future the current clinical needs as well as satisfy patients' needs on demand.

CRediT authorship contribution statement

Greymi Tan: Writing – original draft. **Nicole Ioannou:** Writing – original draft. **Essyrose Mathew:** Writing – review & editing. **Aristides D. Tagalakis:** Writing – review & editing. **Dimitrios A. Lamprou:** Conceptualization, Writing – review & editing. **Cynthia Yu-Wai-Man:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Schubert, C., van Langeveld, M.C., Donoso, L.A., 2014. Innovations in 3D printing: a 3D overview from optics to organs. Br. J. Ophthalmol. 98 (2), 159–161.

Fan, D., Li, Y., Wang, X., Zhu, T., Wang, Q.i., Cai, H., Li, W., Tian, Y., Liu, Z., 2020. Progressive 3D printing technology and its application in medical materials. Front Pharmacol. 11 https://doi.org/10.3389/fphar.2020.00122.

Aimar, A., Palermo, A., Innocenti, B., 2019. The role of 3D printing in medical applications: a state of the Art. J. Healthc Eng. 1–10.

Derakhshanfar, S., Mbeleck, R., Xu, K., Zhang, X., Zhong, W., Xing, M., 2018. 3D bioprinting for biomedical devices and tissue engineering: a review of recent trends and advances. Bioact. Mater. 3 (2), 144–156.

Ji, S., Guvendiren, M., 2017. Recent advances in bioink design for 3D bioprinting of tissues and organs. Front Bioeng. Biotechnol. 5, 23.

Charbe, N., McCarron, P.A., Tambuwala, M.M., 2017. Three-dimensional bio-printing: a new frontier in oncology research. World J. Clin. Oncol. 8 (1), 21–36.

Zein, N.N., Hanouneh, I.A., Bishop, P.D., Samaan, M., Eghtesad, B., Quintini, C., Miller, C., Yerian, L., Klatte, R., 2013. Three-dimensional print of a liver for preoperative planning in living donor liver transplantation. Liver Transpl. 19 (12), 1304–1310.

Qiu, K., Haghiashtiani, G., McAlpine, M.C., 2018. 3D printed organ models for surgical applications. Annu. Rev. Anal. Chem. (Palo Alto Calif). 11 (1), 287–306.

Giannopoulos, A.A., Mitsouras, D., Yoo, S.-J., Liu, P.P., Chatzizisis, Y.S., Rybicki, F.J., 2016. Applications of 3D printing in cardiovascular diseases. Nat. Rev. Cardiol. 13 (12), 701–718.

Goyanes, A., Det-Amornrat, U., Wang, J., Basit, A.W., Gaisford, S., 2016. 3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems. J. Control Release. 234, 41–48.

Konta, A.A., García-Piña, M., Serrano, D.R., 2017. Personalised 3D printed medicines: which techniques and polymers are more successful? Bioengineering (Basel). 4 (4), 79.

Whitford, W.G., Hoying, J.B., 2016. A bioink by any other name: terms, concepts and constructions related to 3D bioprinting. Future Sci. OA. 2 (3), FSO133. https://doi.org/10.4155/fsoa-2016-0044.

Hospodiuk, M., Dey, M., Sosnoski, D., Ozbolat, I.T., 2017. The bioink: a comprehensive review on bioprintable materials. Biotechnol. Adv. 35 (2), 217–239.

Zhang, Y.S., Khademhosseini, A., 2017. Advances in engineering hydrogels. Science 356 (6337). https://doi.org/10.1126/science:aaf3627.

Ashammakhi, N., Ahadian, S., Xu, C., Montazerian, H., Ko, H., Nasiri, R., Barros, N., Khademhosseini, A., 2019. Bioinks and bioprinting technologies to make heterogeneous and biomimetic tissue constructs. Mater Today Bio. 1, 100008. https://doi.org/10.1016/j.mtbio.2019.100008.

Zhang, B., Xue, Q., Li, J., Ma, L., Yao, Y., Ye, H., Cui, Z., Yang, H., 2019. 3D bioprinting for artificial cornea: Challenges and perspectives. Med. Eng. Phys. 71, 68–78.

Davis, R., Singh, A., Jackson, M.J., Coelho, R.T., Prakash, D., Charalambous, C.P., Ahmed, W., da Silva, L.R.R., Lawrence, A.A., 2022. A comprehensive review on metallic implant biomaterials and their subtractive manufacturing. Int. J. Adv. Manuf. Technol. 120 (3-4), 1473–1530.

Zopf, D.A., Flanagan, C.L., Wheeler, M., Hollister, S.J., Green, G.E., 2014. Treatment of severe porcine tracheomalacia with a 3-dimensionally printed, bioresorbable, external airway splint. JAMA Otolaryngol. Head Neck Surg. 140 (1), 66–71.

VanKoevering, K.K., Morrison, R.J., Prabhu, S.P., Torres, M.F.L., Mychaliska, G.B., Treadwell, M.C., Hollister, S.J., Green, G.E., 2015. Antenatal three-dimensional printing of aberrant facial anatomy. Pediatrics 136 (5), e1382–e1385.

Sun, T.-T., Lavker, R.M., 2004. Corneal epithelial stem cells: past, present, and future. J. Investig. Dermatol. Symp. Proc. 9 (3), 202–207.

Sorkio, A., Koch, L., Koivusalo, L., Deiwick, A., Miettinen, S., Chichkov, B., Skottman, H., 2018. Human stem cell based corneal tissue mimicking structures using laser-assisted 3D bioprinting and functional bioinks. Biomaterials 171, 57–71.

Li, F., Carlsson, D., Lohmann, C., Suuronen, E., Vascotto, S., Kobuch, K., Sheardown, H., Munger, R., Nakamura, M., Griffith, M., 2003. Cellular and nerve regeneration within a biosynthetic extracellular matrix for corneal transplantation. Proc. Natl. Acad. Sci. USA 100 (26), 15346–15351.

Isaacson, A., Swioklo, S., Connon, C.J., 2018. 3D bioprinting of a corneal stroma equivalent. Exp. Eye Res. 173, 188–193.

Meek, K.M., Knupp, C., 2015. Corneal structure and transparency. Prog. Retin. Eye Res. 49, 1–16.

Muthusubramaniam, L., Peng, L., Zaitseva, T., Paukshto, M., Martin, G.R., Desai, T.A., 2012. Collagen fibril diameter and alignment promote the quiescent keratocyte phenotype. J. Biomed. Mater. Res. A. 100A (3), 613–621.

Kim H, Park MN, Kim J, Jang J, Kim HK, Cho DW. Characterization of cornea-specific bioink: high transparency, improved in vivo safety. *J Tissue Eng.* 2019;10: 2041731418823382.

Kim, H., Jang, J., Park, J., Lee, K.-P., Lee, S., Lee, D.-M., Kim, K.H., Kim, H.K., Cho, D.-W., 2019. Shear-induced alignment of collagen fibrils using 3D cell printing for corneal stroma tissue engineering. Biofabrication. 11 (3), 035017. https://doi.org/10.1088/1758-5090/ab1a8b.

Key, J.E., 2007. Development of contact lenses and their worldwide use. Eye Contact Lens. 33 (6 Pt 2), 343–363.

Bandari, S., Nyavanandi, D., Dumpa, N., Repka, M.A., 2021. Coupling hot melt extrusion and fused deposition modeling: critical properties for successful performance. Adv. Drug Deliv. Rev. 172, 52–63.

Alam, F., Elsherif, M., AlQattan, B., Salih, A., Lee, S.M., Yetisen, A.K., Park, S., Butt, H., 2021. 3D printed contact lenses. ACS Biomater. Sci. Eng. 7 (2), 794–803.

Tagami, T., Goto, E., Kida, R., Hirose, K., Noda, T., Ozeki, T., 2022. Lyophilized ophthalmologic patches as novel corneal drug formulations using a semi-solid extrusion 3D printer. Int. J. Pharm. 617, 121448. https://doi.org/10.1016/j.ijpharm.2022.121448.

Grob, S.R., Gonzalez-Gonzalez, L.A., Daly, M.K., 2014. Management of mydriasis and pain in cataract and intraocular lens surgery: review of current medications and future directions. Clin. Ophthalmol. 8, 1281–1289.

Moosa, R.M., Choonara, Y.E., du Toit, L.C., Kumar, P., Carmichael, T., Tomar, L.K., Tyagi, C., Pillay, V., 2014. A review of topically administered mini-tablets for drug delivery to the anterior segment of the eye. J. Pharm. Pharmacol. 66 (4), 490–506.

Tham, Y.-C., Li, X., Wong, T.Y., Quigley, H.A., Aung, T., Cheng, C.-Y., 2014. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology 121 (11), 2081–2090.

Sanghani, A., Kafetzis, K.N., Sato, Y., Elboraie, S., Fajardo-Sanchez, J., Harashima, H., Tagalakis, A.D., Yu-Wai-Man, C., 2021. Novel PEGylated lipid nanoparticles have a high encapsulation efficiency and effectively deliver MRTF-B siRNA in conjunctival fibroblasts. Pharmaceutics. 13 (3), 382.

Fernando, O., Tagalakis, A.D., Awwad, S., Brocchini, S., Khaw, P.T., Hart, S.L., Yu-Wai-Man, C., 2018. Development of targeted siRNA nanocomplexes to prevent fibrosis in experimental glaucoma filtration surgery. Mol. Ther. 26 (12), 2812–2822.

Mohamdeen, Y.M.G., Tabriz, A.G., Tighsazzadeh, M., Nandi, U., Khalaj, R., Andreadis, I., Boateng, J.S., Douroumis, D., 2021 Dec 20. Development of 3D printed drug-eluting contact lenses. J. Pharm. Pharmacol. https://doi.org/10.1093/jpp/rgab173.

Pillunat, L.E., Erb, C., Jünemann, A.G., Kimmich, F., 2017. Micro-invasive glaucoma surgery (MIGS): a review of surgical procedures using stents. Clin. Ophthalmol. 11, 1583–1600.

Siewert, S., Schmidt, W., Kaule, S., Kohse, S., Stiehm, M., Kopp, F., Stahnke, T., Guthoff, R., Grabow, N., Schmitz, K., 2017. Development of a microstent system for minimally invasive glaucoma surgery. Current Directions in Biomed. Eng. 3 (2), 779–781.

Culmone, C., Lussenburg, K., Alkemade, J., Smit, G., Sakes, A., Breedveld, P., 2021. A fully 3D-printed steerable instrument for minimally invasive surgery. Materials (Basel). 14 (24), 7910.

Wang, W., Qian, X., Song, H., Zhang, M., Liu, Z., 2016. Fluid and structure coupling analysis of the interaction between aqueous humor and iris. Biomed. Eng. Online. 15 (Suppl 2), 133.

Chiba, C., 2014. The retinal pigment epithelium: an important player of retinal disorders and regeneration. Exp Eye Res. 123, 107–114.

Pappas, G., Vidakis, N., Petousis, M., Maniadi, A., 2020. Individualized ophthalmic exoplants by means of reverse engineering and 3D printing technologies for treating high myopia complications with macular buckles. Biomimetics (Basel). 5 (4), 54.
Shi, P., Edgar, T.Y.S., Yeong, W.Y., Laude, A., 2017. Hybrid three-dimensional (3D) bioprinting of retina equivalent for ocular research. Int. J. Bioprint. 3 (2), 008.
Masaeli, E., Forster, V., Picaud, S., Karamali, F., Nasr-Esfahani, M.H., Marquette, C., 2020. Tissue engineering of retina through high resolution 3-dimensional inkjet bioprinting. Biofabrication. 12 (2), 025006. https://doi.org/10.1088/1758-5090/ab4a20.
Oh, T.S., Jeong, W.S., Chang, T.J., Koh, K.S., Choi, J.W., 2016. Customized orbital wall reconstruction using three-dimensionally printed rapid prototype model in patients with orbital wall fracture. J. Craniofac. Surg. 27 (8), 2020–2024.
Sun, M.G., Rojdamrongratana, D., Rosenblatt, M.I., Aakalu, V.K., Yu, C.Q., 2019. 3D printing for low cost, rapid prototyping of eyelid crutches. Orbit. 38 (4), 342–346.
Xu, X., Awwad, S., Diaz-Gomez, L., Alvarez-Lorenzo, C., Brocchini, S., Gaisford, S., Goyanes, A., Basit, A.W., 2021. 3D printed punctal plugs for controlled ocular drug delivery. Pharmaceutics. 13 (9), 1421.
Tsui, J.K.S., Bell, S., Cruz, L.d., Dick, A.D., Sagoo, M.S., 2022. Applications of three-dimensional printing in ophthalmology. Surv. Ophthalmol. 67 (4), 1287–1310.
Mohammed, A.A., Algahtani, M.S., Ahmad, M.Z., Ahmad, J., Kotta, S., 2021. 3D Printing in medicine: technology overview and drug delivery applications. Annals of 3D Printed Med. 4, 100037. https://doi.org/10.1016/j.stlm.2021.100037.
Conformity assessment procedures for 3D printing and 3D printed products to be used in a medical context for COVID-19. *Docsroom - European Commission.* https://ec.europa.eu/docsroom/documents/40562. Published April 1, 2020.
Lorber, B., Hsiao, W.-K., Hutchings, I.M., Martin, K.R., 2014. Adult rat retinal ganglion cells and glia can be printed by piezoelectric inkjet printing. Biofabrication. 6 (1), 015001. https://doi.org/10.1088/1758-5082/6/1/015001.
Park, S.H., Su, R., Jeong, J., Guo, S.-Z., Qiu, K., Joung, D., Meng, F., McAlpine, M.C., 2018. 3D printed polymer photodetectors. Adv. Mater. 30 (40), 1803980. https://doi.org/10.1002/adma.v30.4010.1002/adma.201803980.
Ruiters, S., Sun, Y.i., de Jong, S., Politis, C., Mombaerts, I., 2016. Computer-aided design and three-dimensional printing in the manufacturing of an ocular prosthesis. Br. J. Ophthalmol. 100 (7), 879–881.
Kozakiewicz, M., Elgalal, M., Loba, P., Komuński, P., Arkuszewski, P., Broniarczyk-Loba, A., Stefańczyk, L., 2009. Clinical application of 3D pre-bent titanium implants for orbital floor fractures. J. Craniomaxillofac. Surg. 37 (4), 229–234.
Willemen, N.G.A., Morsink, M.A.J., Veerman, D., da Silva, C.F., Cardoso, J.C., Souto, E. B., Severino, P., 2022. From oral formulations to drug-eluting implants: using 3D and 4D printing to develop drug delivery systems and personalized medicine. Bio-des. Manuf. 5 (1), 85–106.