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3D PRINTING IN OPHTHALMOLOGY

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ABSTRACT
The technique of 3D Printing was invented thirty years ago, but its use in healthcare has become more prevalent in recent years. It offers a cost-effective way to create model implants that aid in the understanding of human anatomy and diseases, and can be used for organ transplants, surgical planning, and advanced drug delivery systems. This technology can also be customized for individual patients to provide tailored treatment options. In ophthalmology, 3D bioPrinting offers new therapeutic opportunities for various eye conditions. This review paper examines the many benefits and applications of 3D printing in treating ocular conditions such as cornea, glaucoma, retina, lids, and orbits. The vast market for 3D Printing makes it worth exploring, particularly its role in ocular drug delivery systems. This review will cover the problems with traditional delivery methods, the different types of 3D bioPrinting, and its applications in ocular drug delivery, the challenges associated with it, patents, and market trends.

KEYWORDS: Model Implant, Organ Transplant, Surgical Planning, Ophthalmology, BioPrinting etc.

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. 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. The cost of AM is very expensive when it comes to large scale production. However, the 3DP technology is highly cost-effective in small scale production.

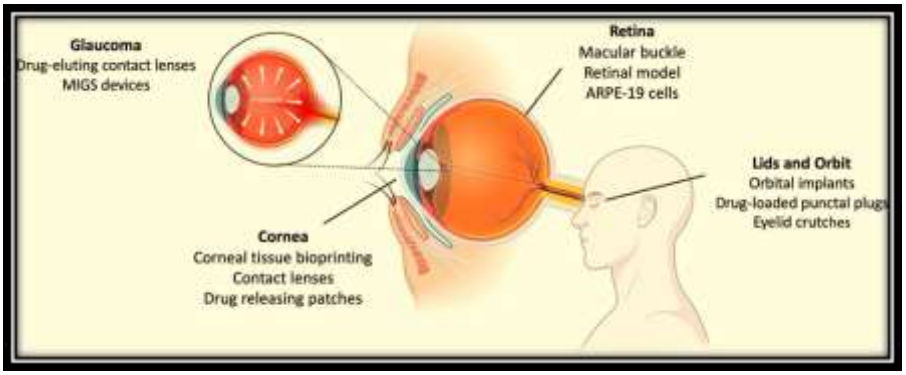

Fig. 1: - anatomy of the eye and the associated 3d printed therapies.

The use of 3D Printing technology is on the rise in the medical field, including in the creation of pharmaceuticals. 3D Printing allows for the production of complex and personalized surgical guides and devices, such as customized implants for spine surgery, surgical guides for craniofacial and prosthetic hands for children as shown in figure no. 1.

The effectiveness of 3D printing in pharmaceuticals depends on the material used. Most studies on 3D printed tablets have used material extrusion-type 3D printers, which come in two techniques: -

I. Fused Deposition Modeling (FDM)

It requires heating to melt drug-loaded polymers as ink.

II. Semi-Solid Material Extrusion (SSME)

It uses high pressure to extrude drug-loaded hydrogels and pastes as ink, using air pressure or a screw.

Researchers have explored using 3DP to create personalized medicines, such as tablets with specific dosages for patients. 3DP unique manufacturing process allows for the creation of complex objects, including tablets with varying dosages. This is particularly useful for drugs with a narrow therapeutic dosage window, like theophylline and warfarin, which require strict dosage control.

2. Types of Bioinks

When it comes to 3DP of tissue-like constructs, Bioinks are the main component they are made up of cells and other matrix constituents that are needed for the process. However, a single bioink is not enough to produce a functioning tissue-like structure.[1] This is why multicomponent bioinks have been developed to combine the favorable characteristics of different biomaterials.[2] These bioinks can contain one or more types of biomaterials, cells, and other materials or biomolecules. There are different categories of multicomponent bioinks that can be used to build different tissue structures as shown in table no.1. These include bioinks made up of natural materials, natural and synthetic materials, synthetic materials, hydrogels and particle as shown in figure no. 2.

Table No. 1: Types of Bioinks and Biomaterials for the manufacturing of Implants.

Sr. No.	Types of Bioinks	Biomaterials
1.	• 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
2.	• Bioink composed of natural and synthetic biomaterials	• Gelatincombined with methacryloyl (GelMa)
3.	• Bioink composed of synthetic biomaterials	• Poly (ethylene glycol) diacrylate (PEGDA) • Poly (ethylene glycol) methacrylate (PEGMA) • PEGDA with alginate
4.	• Bioink composed of hydrogels and particles	• PLGA-PEG With cell-laden Carboxymethyl Cellulose (CMC) • Silicateb (lithium sodium magnesium silicate) with GelMa • Hydroxyapatite (HAP) with GelMa/ gelatin • Tricalcium phosphate (TCO) with alginate • Bioactive Glass (BaG) with silk fibroin • Carbon Nanomaterial with PLAGA/GelMa

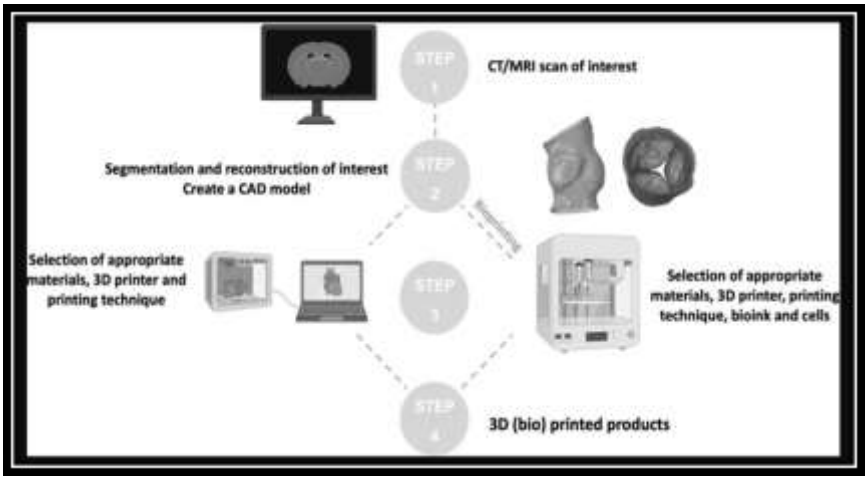

Fig. 2: 3D printing and bio- printing process.

2.1 Biomaterials

Bioinks for ophthalmic applications must meet three main requirements: -

- Biocompatibility
- Printability
- Mechanical Properties.

To create a highly biocompatible environment for cells, Decellularized Extracellular Matrix (DECM) and hydrogels that are nature-derived or semi-synthesized are commonly used. (Table No.1)

2.1.1 Decellularized Extracellular Matrix (DECM)

The Extracellular Matrix (ECM) is essential for cell nutrition, protection, and tissue function. It consists of collagen, elastin, microfibrillar proteins, adhesive glycoproteins, and proteoglycans that provide support and vital cues for cell adhesion, engraftment, and functions. The DECM was developed to mimic an optimized microenvironment for specific tissue engineering. For example, cornea- and retina-specific DECMs were developed for ocular tissue regeneration.[3] In corneal engineering, DECMs maintain keratocyte morphology and transparency by preventing the transdifferentiation of corneal fibroblasts. Prepared a cornea-specific DECM bioink for bioprinting by Decellularizing the ECM from the bovine corneal stroma and lyophilizing the cornea-derived DECM (Co-DECM) samples. When printing, the Co-DECM powder was solubilized in acidic solutions and adjusted to form a printable gel. The removal of cells reduces the immune rejection response in tissue grafting. Additionally, the Co-DECM bioink has comparable levels of collagen and glycosaminoglycans as the natural cornea. The thin collagen fibrils in the bio-ink have a larger amount of proteoglycans, which allows it to maintain the transparency property of the native cornea. The Co-DECM bioink did not show toxicity in animal experiments and demonstrated good therapeutic potential in corneal disease.[4]

2.1.2 Hydrogels

Hydrogels are networks of crosslinked polymers that can absorb and retain large quantities of water. They can be engineered to support cellular growth, migration, and tissue formation. Hydrogels have strong biomimetic advantages in clinical translational applications due to their hydrophilic nature, good biocompatibility and biodegradability, controllable responsiveness to external stimuli, and tunable physical and chemical properties such as adhesion or low mechanical properties. Both naturally derived and synthetically derived hydrogels are widely used in bioprinting.

- **Naturally Derived Hydrogels**

Ex. Alginate, Chitosan, Gelatin, Hyaluronic Acid, and Fibrin etc.

- **Synthetically Derived Hydrogels**

Ex. PLA, PGA, PU, PLGA and PCL etc.

3. Cornea and External Eye Disease

When this tissue is damaged, patients may require corneal transplants to restore the self-renewing epithelium. Traditional transplantation methods can also be used to replace damaged corneal stroma that's often caused by limbus injuries. However, it's not a sustainable solution as transplanted corneas cannot self-renew and there's a shortage of corneal donors. Therefore, there's a growing need for better alternatives to corneal donors in clinical settings.

Table No. 2: Studies of 3D Bioprinting in Ophthalmology.

Sr. No.	Tissues	Studies	3D Printing Techniqes
1.	Cornea	• Corneal tissue bioprinting • Contact lenses • Drug releasing patches	• Laser –assisted bioprinting /pneumatic 3D extrusion Bioprintig • Digital light printing • Hydrogel-based bioink
2.	Glaucoma	• Drug- eluting implant, e.g. contact lenes • Minimally Invasive Glaucoma Surgery (MIGS) Devices	• Fusion deposion modelling and hot melt extrusion • Projection micro stereolithography
3.	Retina	• Macular buckle • Retinal model	• CAD Software 3DP • Inkjet bioprinting

3.1 Corneal Tissue Bioprinting

Creating 3D Bioprints for corneal tissues is possible by using bioinks combined with human proteins, as demonstrated in Table No. 2. The selection of biocompatible materials for in vitro settings is crucial for reconstructing corneal tissues. Recent studies have shown that 3D bioprinting of a stromal structure containing Human Adipose Tissue-Derived Stem Cells (hASCs) can replicate the characteristics of native corneal stroma with high cell survival rates. Similarly, bioprinting using human embryonic stem cell-derived limbal epithelial stem cells has shown promising results in replicating the structure and biological functions of the corneal epithelium. The preliminary biocompatibility of the 3DP stroma containing hASCs with a porcine cornea has also been demonstrated. Laser-assisted Bioprinting (LaBP) technology is a powerful printing technique that can generate high-resolution medical devices with the

flexibility to correspond with any type of stem cells, without affecting their biological characteristics and functional properties.

3.2 Contact Lenses

Additive Manufacturing offers new possibilities for the fabrication of contact lenses, which have been used for optical correction since the 1800s. Hydrogel soft lenses were a significant development in the evolution of contact lenses, as manufacturers sought biocompatible materials with oxygen-permeable and robust mechanical properties. However, the manufacturing process for contact lenses remains challenging, with limited design flexibility. 3DP can produce various types of contact lenses, including smart contact lenses that can detect and control eye diseases. Digital Light Printing (DLP) is preferred for light-curing-based polymerization 3DP, as it can print at a higher resolution than Fused Deposition Modeling (FDM).[5] Asiga DentaClear Resin, widely used in the dental industry, can produce corrective contact lenses via DLP Printing. DLP can add nanopatterns to 3DP contact lenses, generating smart contact lenses that clinicians can use to monitor changes in patients' eye health as shown in figure No.3. 3DP contact lenses with a thin PVC plastic film can achieve up to 90% light transmission, although a comparison of their mechanical, physical, and chemical characteristics with traditional contact lenses would be interesting. AM offers the freedom to generate customized contact lenses tailored to patients' eye structures and conditions. Creating 3D Bioprints for corneal tissues is possible by using.

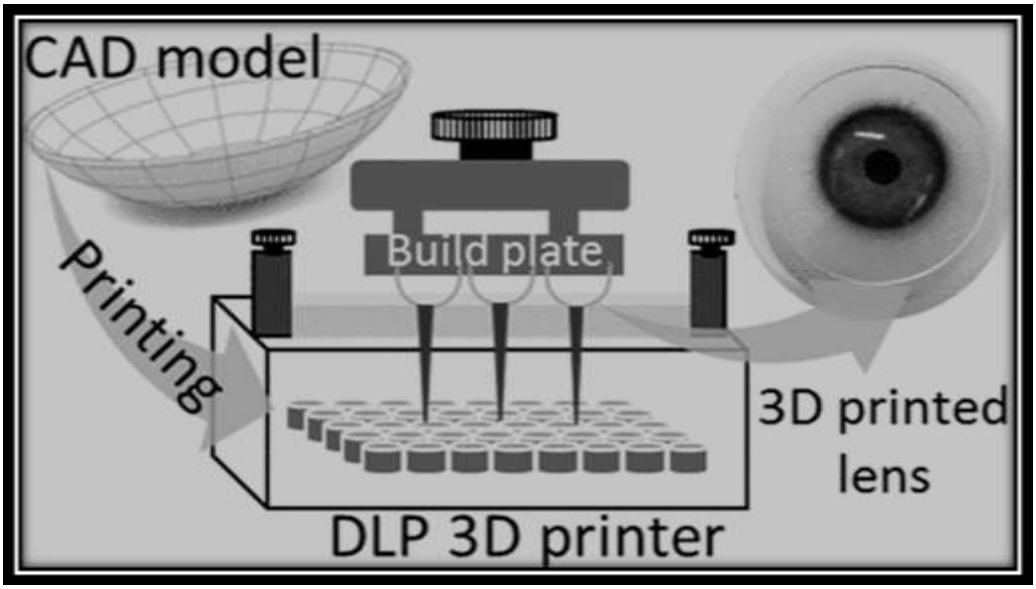

Fig. 3: - 3D printing contact lenses.

Biomaterials combined with human proteins, as demonstrated in Table No. 2. The selection of biocompatible materials for in vitro settings is crucial for reconstructing corneal tissues.

3.3 Drug Releasing Patches

The use of 3DP technology has proven to be a practical and innovative way to produce complex and unique objects for various industries, including medicine. The US – FDA have approved the use of 3DP tablets, leading to further exploration into 3DP drug formulations and dosage forms in the pharmaceutical field. Our study focuses on the creation of ophthalmologic patches for controlled drug release, using a semi-solid material extrusion-type 3D printer. These patch-shaped objects were produced using hydrogel-based printer inks made of hypromellose (HPMC), sugar alcohols (mannitol, xylitol), and drugs. The printer ink and patch viscosity were dependent on the concentration of HPMC and sugar alcohols. We then characterized the physical properties, surface structure, water uptake, antimicrobial activity, and drug release profile of the lyophilized patches as shown in figure no.4. These lyophilized ophthalmologic patches were made with different dosages and patterns, serving as models for personalized treatment in hospitals. We were also able to create ophthalmologic patches containing multiple drugs using commercially available eye drop formulations. Our findings suggest that 3DP technology is an effective method for producing novel dosage forms, allowing for the customization of patient-tailored dosages in a clinical setting. Then, the physical properties, surface structure, water uptake, antimicrobial activity, and drug release profile of lyophilized patches were characterized. Lyophilized ophthalmologic patches with different dosages and patterns were fabricated as models of personalized treatments prepared in hospitals.

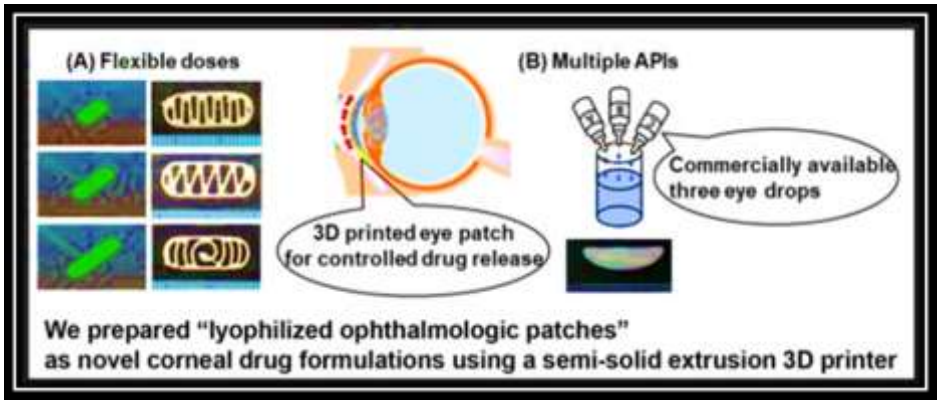

Fig. 4: lyophilized ophthalmologic patches as novel corneal drug formulation using a semi- solid extrusion 3D printer.

4. Glaucoma

The Glaucoma is the leading cause of irreversible blindness worldwide. It currently affects 76 million people and is estimated to affect 112 million by.[6] Glaucoma occurs when the optic nerve is damaged by the pressure of fluid inside the eye. Treatment involves reducing the Intraocular Pressure (IOP) using medications, laser, or surgery. Preventing further progression of glaucoma aims to reduce the IOP level by decreasing production or increasing the drainage of aqueous humor out of the eye.

4.1 Polymeric Drug – Eluting Implants

A 3DP that uses extrusion has been utilized to manufacture sustained drug-release implants made of Poly-ε-Caprolactone (PCL). These implants can help with issues of reduced patient compliance due to the frequent administration required by TDDS like tablets, capsules, and solutions. Lidocaine was the model drug selected for this study. Polymeric implants with no barrier shell and polycaprolactone core-shell implants were printed with various drug loadings, without adding solvents or other excipients. Scanning Electron Microscopy (SEM) analysis confirmed the structural integrity of the printed formulations. Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), and Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR) were used to detect any potential chemical interactions or modifications. Raman spectroscopy was also used to study material distribution in the prints. The drug release rate of the differently printed formulations was evaluated using a USP4 flow-through cell apparatus. All printed implants showed sustained lidocaine release, proving the effectiveness of the PCL barrier. The Korsmeyer-Peppas model was suggested as the best fit for drug release profiles for all the produced implants. This study demonstrates that hot-melt extrusion-based 3D Printing is a reliable and promising technology for the production of personalized drug-eluting implants as shown in figure no. 4.

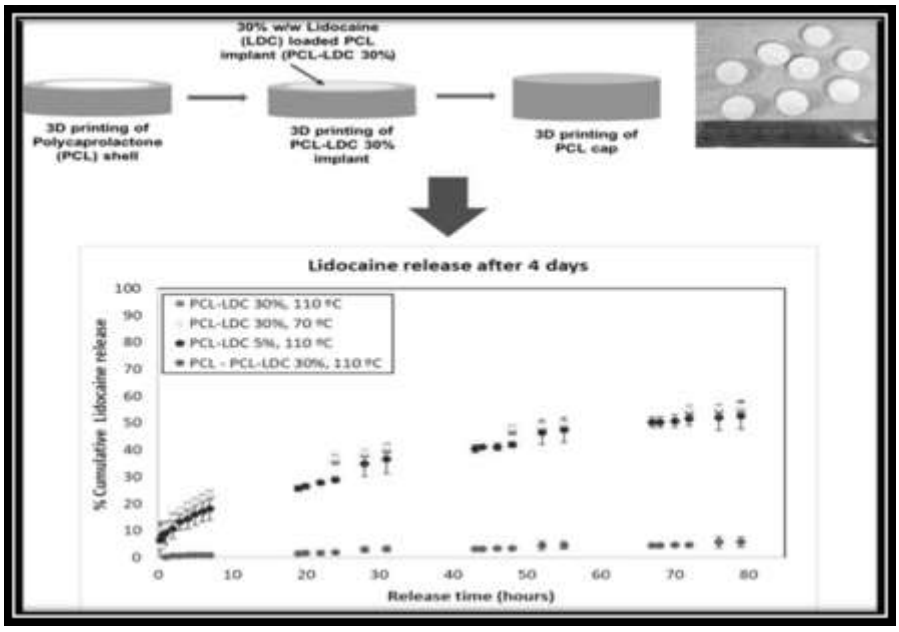

Fig. 4: 3DP polymeric drug-eluting implants.

4.2 Minimally Invasive Glaucoma Surgery (MIGS) Devices

Glaucoma surgery is a procedure done to reduce the risk of vision loss by lowering Intraocular Pressure (IOP). In recent times, devices like Xen, iStent, and Cypass have been developed for Minimally Invasive Glaucoma Surgery (MIGS) to lower IOP. However, there is a need for a better understanding of IOP and flow resistance after glaucoma surgery for future device design. To study the effect of flow resistance on IOP following glaucoma surgery, we created a 3DP engineering eye model.

Another 3DP technique used for developing therapeutic devices for glaucoma is called Projection Micro Stereolithography (PuSL), which combines the benefits of both DLP and SLA technologies. Each device drains aqueous humor through a different pathway and is chosen based on the specific patient's conditions. However, they all have the same limitation of short-term efficacy due to fibrotic encapsulation. 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 personalized instrument for surgeons to improve the surgical procedure.

3DP technology allows for 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. The design allows for an ergonomic handgrip, flexible steering control, and high efficiency when holding tissues. Such instruments can help surgeons to carry out the surgery comfortably without limiting their wrist motions. The systems manufactured by AM also allow customization for different patients and surgeons by modifying the gripper handle.[7] Furthermore, 3DP surgical instruments can be easily adapted to other fields of minimally invasive surgery. Glaucoma management requires close monitoring of the drainage of aqueous humor in the eye so that clinicians can manage the IOP level.

5. Retina

Retinal Pigment Epithelium (RPE) is a crucial component of the Blood-Retinal Barrier (BRB) that plays a multifunctional role. Damage to this epithelium can lead to a range of diseases related to retinal degeneration. Unfortunately, there is no cure for these diseases, and human clinically implantable RPE is still under development. To address these issues, we developed a porcine Bruch's membrane-derived bioink (BM-ECM) and the Bruch's Membrane-Mimetic Substrate (BMS) that can facilitate natural RPE functions.[8] The BMS could be helpful in RPE-based research and for further applications as it provides an ECM environment that can facilitate natural RPE functions as shown in figure no.5.

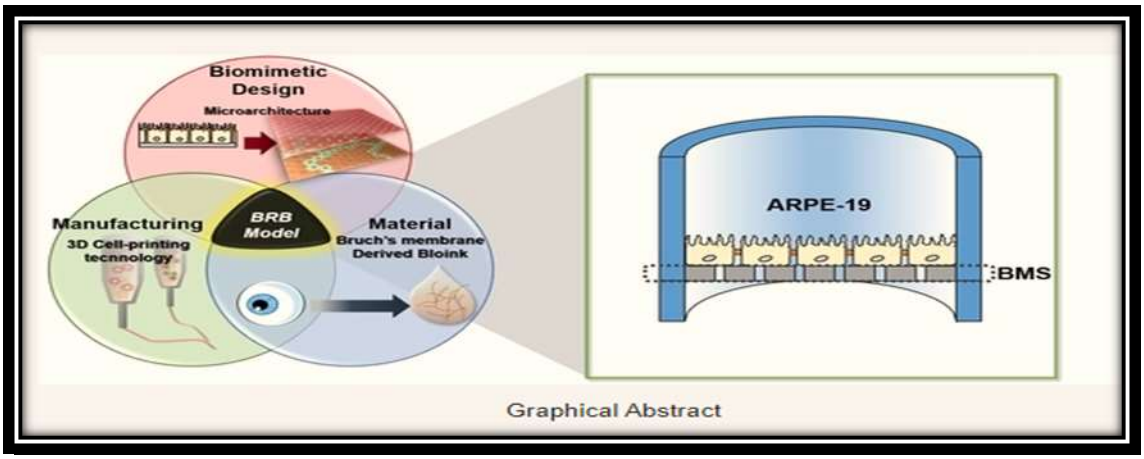

Fig. 5: Development of 3D printed Bruch's membrane-mimetic substance for the maturation of retinal pigment epithelial cells.

6. 3D Printed Tablet

In recent years, 3DP has emerged as a significant technology in the field of drug delivery and personalized medicine. This is because 3DP can manufacture dosage forms that are tailored to meet the specific needs of individual patients. This data provides an overview of the fundamental principles involved in building pharmaceutical dosage forms using different types of 3DP. It also highlights the impact of various factors such as infill percentage and pattern, raster orientation, layer thickness, and thermal processing parameters on the final product. In addition, the article describes the complex designs that can be created using 3D printing to modify the shape, density, mucoadhesion, and drug release of the printed formulations. The article summarizes numerous applications for 3DP in building drug-loaded structures, including tablets, scaffolds, implants, microneedles, capsules, films, hydrogels, mouthguards, tubes, stents, vaginal suppositories, rings, and pediatric devices. Finally, the article suggests further research that can help in the widespread adoption of 3DP in the pharmaceutical industry. 3DP technology is expected to revolutionize drug delivery systems through the customization of pharmaceutical formulations as shown in figure no.6.

Among the various routes of drug administration, the oral route is the most preferred by patients. Tablets, which are solid dosage forms obtained from powder compression, are the most commonly used oral dosage forms. They are easier to produce, handle, and store than other dosage forms. The manufacturing of tablets using 3D Printing technology provides the ability to formulate them with different geometric and drug delivery properties.

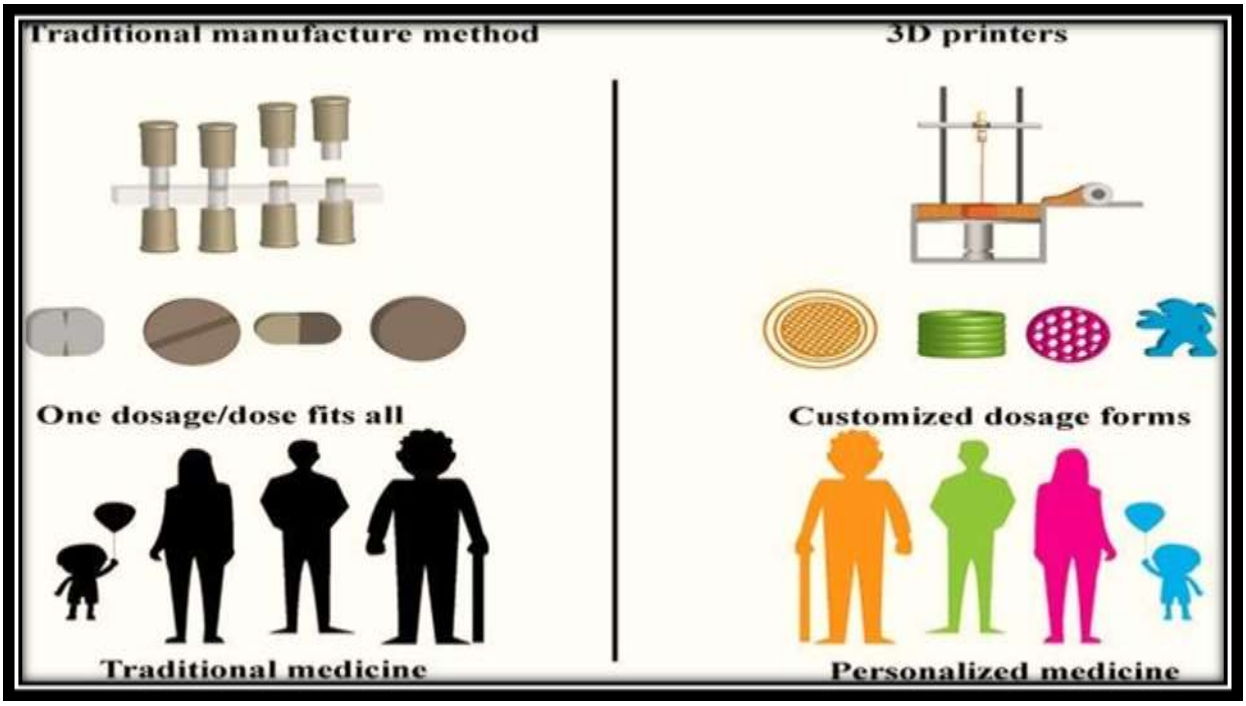

Fig.6. – 3DP in personalized medicines & traditional medicine.

7. Applications of 3DP in Ophthalmology and Eye Care

3DP is great for small-scale production with customization needs. It eliminates the need for molds, saves time and money, and allows for unlimited design possibilities at a reasonable cost as shown in figure no.7.

7.1 Orbital Implants

3DP technology is commonly used in orbital wall reconstruction surgery to create implants that fit the exact size and shape of each fracture site 3DP is also used for printing orbital implant spheres, allowing for customization of implant formats and sizes to fit varying eye socket dimensions.

7.2 Ocular Prostheses

Creating customized ocular prostheses for patients who have lost their eyes can be a lengthy, laborious, and expensive process that requires skilled craftsmanship. However, with the advent of 3DP technology, it is now possible to manufacture high-quality, tailor-made ocular prostheses that are faster and more cost-effective to produce. In fact, in 2016, a 68-year-old man was fitted with the first 3DP ocular prosthesis successfully. The fitting process involved using a cone beam CT scan to create a digital 3D model of the anophthalmic cavity, which is different from the traditional method of creating an impression mold that involves injecting impression material into the anophthalmic cavity.[9]

7.3 Surgical Planning

Pre-operative surgical planning involves the use of various techniques to prepare for a surgical intervention.[39] One of the emerging methods is the use of 3DP models of eyes in patients suffering from intraocular tumors, such as uveal melanomas. Studies show that 3DP can help clinicians in planning Stereotactic Radiosurgery (SRS), which is a treatment option for uveal melanoma, one of the most aggressive types of intraocular tumors. Accurate planning of stereotactic coordinates of radiation beams of SRS is crucial for the success of the treatment. The 3DP of models of the tumor is useful in providing additional information and better localization of the lesion inside the globe, thereby increasing the accuracy of the treatment.

7.4 Intraocular Devices

3DP technology has revolutionized the ophthalmic surgical setting. A 3D pupil expansion device called Canabrava's Ring has been manufactured for the first time, expanding the pupil by 6.5 mm and enabling cataract surgeries using standard techniques. A customized trocar system for vitreoretinal surgery has also been made using commercially available 3DP technology, with the potential for surgical instruments to be inexpensively customized and printed. 3DP has also benefited personalized items such as Intraocular Lenses

(IOLs), with the potential to offer complete customization of future IOL designs.[10]

7.5 Bioprinting and Tissue Engineering

3D Bioprinting is a technology that uses 3DP to create tissue constructs with micrometer precision. It has been used to create functional tissues such as vasculature, muscle, cartilage, and bone for tissue engineering. The ultimate goal of tissue engineering is to produce 3D artificial tissues or organs that mimic the real environment of the human body. Scaffolds, cells, and microenvironments are combined to create the necessary support for transplanted cells. Traditional manufacturing methods have limitations. 3DP is a potential solution to overcome these limitations and manufacture complex tissue-engineered scaffolds with precise control over size, shape, porosity, and interconnectivity. This technology can also be used.

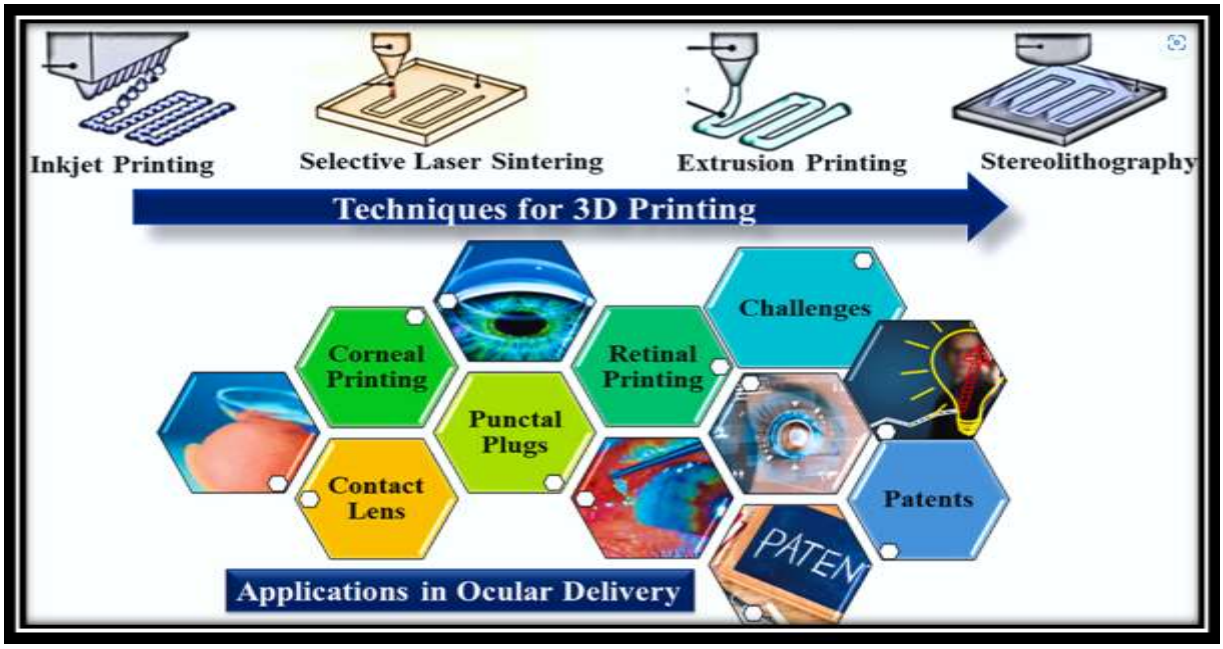

Fig. 7: the emerging role of 3d-printing in ocular drug delivery.

8. Expert Opinion & Future Directions

The healthcare industry has benefited greatly from the invention of 3DP. It has helped create new therapies for various ophthalmic diseases, including corneal reconstruction. By incorporating human stem cells, 3DP corneas have been developed as an alternative to corneal transplantation. These corneas can avoid immune rejection, which is a common issue for transplant recipients. The printability of 3DP implants depends on the selection of optimal biomaterials and bioinks. For instance, a Bioink consisting of alginate and collagen was shown to be feasible and produced viable 3DP corneas. The physical properties of the bio-ink, such as its viscosity, can be altered to mimic the natural human cornea and affect the printability of the end product.

9. CONCLUSION

The emergence of 3DP technology has enabled the production of personalized medical products that cannot be achieved through conventional manufacturing techniques. The adaptability and flexibility of 3DP are set to enhance therapeutic practices, including dentistry, orthopedics etc. The promising discoveries of 3DP in ophthalmology encourage the medical research community to continually provide advanced treatment, increasing confidence in patients. While, 3DP in the ophthalmic field is not yet fully developed, its potential is to provide revolutionary solutions to various eye diseases is undeniable. The introduction of 3D bioprinting as a novel technology in the medical field marks a revolutionary approach to modern medicine. The invention of bioinks in 3DP can potentially solve the shortage of corneal transplantation and promote tissue regeneration. Furthermore, the constantly evolving 3DP techniques tailored for ophthalmic devices and drug delivery systems guarantee the individualization of additive manufacturing.

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