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The Journey of Biomaterial Discovery to Collaboration in Tissue Engineering and 3D Printing

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A B S T R A C T

For generations, there has been a development in biocompatible materials used for various medical purposes. Metals, Ceramics, Polymers, and Composites are well-known biomaterials in application. The most popular applications of these materials are prosthetics used for correction and enhancement of several structures of the human body, orthotics for replacements of bones and joints in arms and legs, dental implants, and last cosmetic implants. Biomaterials have always been a vast field of research, and since the introduction of 3D printing in medical sciences, the scope of development has broadened even further. The existing technologies of 3D printing using silicones, ceramics, metals, and other biocompatible materials have proven as a boon and a breakthrough in aspects of treatments, correction of body structures, and enhancement capabilities while being aesthetically lifelike. The purpose of biomaterials as bioinks in developing implants, braces, and bone replacements has opened gates to new possibilities of ailments that can become available for humans. The most stimulating area for development appears to be the 3D printing of organs using bioinks developed by tissue engineering supported with silicon structures. The idea behind this would be to procure a sample of tissue from the patient in need of transplantation and recreate the same through tissue culture, processing it further to create a bioink for printing the organ, creating a mold for the organ for printing in using 3D image processing techniques such as CAD, and finally printing the organ using the bioink in the mold. For modeling the organ to be bioactive and functional, there must be a series of post-processing measures performed. This technology could prove to be a breakthrough in the field of medical sciences and reduce the strain on the organ donor market, as well as reduce the complications such as surgery complications, the high rejection rate of the body, transportation of organs, deficiency of donors, associated with traditional transplantation methods (Jin et al., 2021).

Keywords: Biomaterials, 3D printing, organ implants, Tissue engineering

History of Biomaterials

The foundation of Biomaterials has been laid out in the years between 1920 and 1980. However, the discoveries of how biomaterials can be embedded, implanted, and assisted in the body date back to the era before World War II when an explorer's remains (called the "Kennewick man") were found. A spear point was embedded in his hip, which had fused with the bones and healed in. That evidence was one of the first introductions of foreign materials interacting with the human body and realizing the concept of Biocompatibility. Another such application has been seen in suturing. As mentioned in the early Greek literature, suturing was performed using gold and other metallic wires. In the late 90s, Dental implants became one of the significant inventions involving biomaterials. During the period of 1800s, the interpretations of the heart being a pumping device started taking root thereby encouraging various scientists, thinkers, and experimentalists to develop artificial pumps. Since then, there have been attempts to create an artificial heart and certain developments have been made in the same way. The period before the 1950s had a poor understanding of biocompatibility and hence the implants would lead to failures. The beginning of understanding the factors of biocompatibility and sterilization broke ground in 1829 with noble metals. Thus began the journey of zinc, copper, nickel, and alloys being used for screws, bone replacements, joints, etc. Although, the history of plastics and polymers dates as recently as the mid-90s.

The era post World War II can be considered a multi-collaboration era of surgeons, researchers, and engineers. With ease in government regulations, there were a lot of experimentations to further introduce biomaterials with enhanced biocompatibility, which led to significant recoveries in treatment, aesthetically pleasing implants, and better correction of structures in the human body. During the period 1906-2001, Sir Harold Ridley discovered Intra Ocular Lens. He observed in many pilots, that shards of broken plastic in the eye would automatically heal without leaving any trace of it. He found the material to be poly (methyl methacrylate). He became a pioneer of implants in an organ as delicate and complex as the eye, along with introducing polymers plastic as a biomaterial (Ratner, 2013).

These early inventions are the structural foundations of the biomaterial industry today. It also opened paths for collaboration in healthcare and engineering. The advancement further led parallel to biochemistry, medicine, and pharmaceutics.

Recent Advancements in Biomaterials

There are various characteristics to be fulfilled when considering a material to be biocompatible. The material should not cause any harm to the surrounding of its insertion, it should not be inflammatory or toxic, it should replicate the physical properties of the structure being replaced and many more.

As studies and research started getting conclusive, the materials then began to be identified according to their function and reactivity with the body. They identify as Bioinert – does not interact with tissues and retain their structure when implanted, Bioactive – functions according to the surrounding, and Biodegradable – fuse with the body and assist in the regeneration of tissues. The biomaterials such as metals, ceramics, and composites used until recently are bioinert and so they do not react with the human body. They function in supporting and correcting the structures of the human body. This led to a curiosity in the development of biomaterials that are physiologically interactive and could replace the functionality of the existing systems of the human body.

The use of polymers introduced the category of bioactive and biodegradable materials for implants and assisted in the growth of regenerative tissues. The ease of use due to flexibility was one of the many advantages observed. The use of polymer began with denture applications. Further, along the line, the use of artificial grafts in cardiovascular surgery was introduced.

PMMA (polymethyl methacrylate), was one of the first polymers to have displayed biocompatibility. The ability to fuse with the bones and tissue structures, and dissolve in the body by hydrolysis thereby assisting the growth of regenerative tissues at the site of damage was remarkable. One of the popular applications of PMMA was displayed in the fusion of metal in total hip joint replacement. PMMA acted as a binding agent between the metal and the pelvis.

The skeletal structure of the body is almost entirely made up of soft tissues. Polymers have been the closest of all to share similar physical properties. It was found to create an environment suitable for the regeneration of tissues. There are various polymers used in replacing damaged skeletal structures such as filaments, valves, and vessels.

The latest experimentation being conducted is on hybrid biomaterials. To combine bioinert materials with polymers to replicate the exact structure and function of the systems further closely in the human body.

The next area where biomaterials have been breaking ground is tissue engineering, which focuses on creating a bridge for the blending of biological and non-biological elements and reproducing artificial living tissues. There are two approaches for tissue and organ culture. Both procedures require extensive use of natural polymers to combine vital and non-vital elements, preservation of organs, and reconstruction of lesions. The process of regenerating tissues is carried out *in vitro* (outside the body). The extracellular matrices (ECM) are extracted from the tissue of the host and reassembled as a natural polymer to introduce non-vital elements in the same. This new structure becomes biologically active to carry out the functions of the damaged tissues. Tissue engineering has played a vital role in the creation of various ailments from organ culture to treatment of lesions up to the replacement of damaged tissues in the body. It is also involved in various cosmetic surgeries and enhancements (Suh, 1998; Kumar, 2018).

Tissue Engineering

Tissue Engineering is focused on the redevelopment, regeneration, and replacement of injured or damaged tissues. It is either replacing a tissue with artificial scaffolds that mimic the functionalities of the tissue or creating an environment for the regeneration of natural tissues. The tissue engineering approach consists of cells, cells and scaffolds, and scaffolds only depend on the requirement of the procedure, The structures built are a product of the patient's own cell sample, a person with a similar genetic makeup, or a nonhuman species. Scaffolds also started being created using synthetic polymers. The properties to be taken care of were the compatibility with the transplant site, physiological characteristics, and functionality of the scaffold.

Tissue Engineering is one of the most important breakthroughs in the field of regenerative medicine. There have been several discoveries that helped advance the healthcare and medicine sectors. The two most widely known, accepted, and used applications are drug development and organ fabrication.

Tissue engineering in drug screening has become quite popular as it mimics the multiorgan response. The live cells interact with the environment and prompt responses almost identically to the human tissues. One of the prime examples is liver cells. They are printed and layered in between epithelial cells. The interactions with different cells created a comparison of a healthy and diseased liver suggesting the drug screening of the liver.

There have been discoveries of flat and hollow organ structures. Bioprinting of these structures has made it feasible for creating flat organs such as skin, and cartilage tissue to be transplanted using the sample from the patient's own cells. Hollow structures such as blood vessels, and trachea using synthetic polymers have also begun to be widely used. These discoveries introduced the concept of 3D printing complex organ structures using tissue engineering which could replace the need for human organ transplants (Shafiee & Atala, 2017; Ikada, 2006).

3D printing and Tissue Engineering

The process of tissue engineering is supported by a scaffold. It is an external support that acts as a catalyst for the regeneration of cells and tissues. 3D printing is a sought-after approach for the development of these scaffolds. There are two types of scaffolds constructed for tissue engineering using the 3D printing technique. They are acellular and cell-laden scaffolds. The difference holds in the application part of it. Acellular scaffolds contain biological products for the development of cells whereas cell-laden scaffolds are used in mimicry of tissue function.

There are various approaches to printing scaffolds. Inkjet printing uses strategically placed biological organelles for a layer-by-layer development of the structure desired. The ink must be heated first and then droplets flow with high precision of quantity and time. In extrusion-based bioprinting there is no heating involved and hence the biological components can be included directly in the ink material. This offers a wider range of biomaterials that can be used, and complex structures can be created. The most common materials used for these scaffolds are a wide range of ceramics, composites, and polymers.

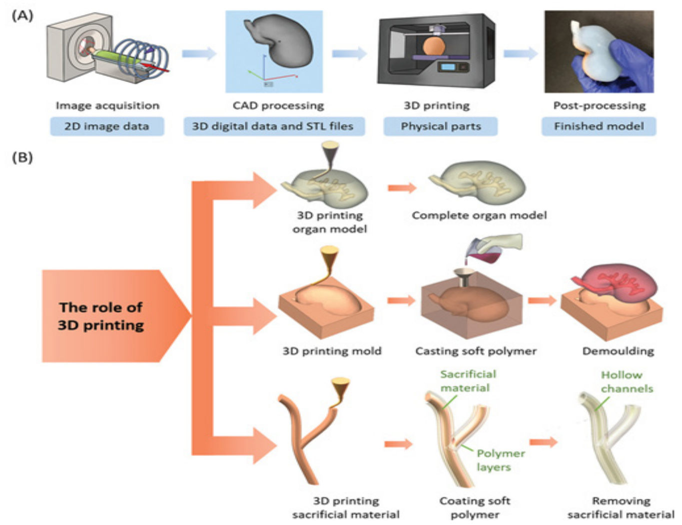

Image 1: Role of 3D printing

A. The basic steps of the 3D printing of an organ model.
B. The types of structures that can be printed are the organ directly, through a mold and creating hollow structures using sacrificial materials.

Used from (Jin et al., 2021).
https://onlinelibrary.wiley.com/cms/asset/2f56ab66-f298-45b2-8d2a-563df488ecf6/advs2797-fig-0003-m.png

Laser-assisted 3D printing is yet another modernized approach to creating structures without being in contact with the bioink. It works with the assistance of a ribbon which is supported by a titanium layer to act as a transporter of energy to the ribbon on which the bioink and cells rest. The bioink and cells rise due to the temperature and form a layer above the ribbon. The process is repeatedly used to create the 3D structure layer by layer (Yi et al., 2017).

Lastly, stereolithography (SLA) is a bioprinting technique based on the concept of photopolymerization. UV light is directed over a pattern on the hardened platform on which bioink is suspended. The hardened platform is moved below for further layering of the structure above it, thus creating a desired 3D organ or tissue.

Modern 3D printing technology further enhances the process by offering multiple printing heads and therefore the development of even complex structures such as vascular grafts, bone structures, organ regenerative scaffolds, blood vessels, and tissues. Further, small organs such as ovaries, skin, and bone cartilage have been successfully printed to date (Jammalamadaka & Tappa, 2018; Wragg et al., 2019a; Song et al., 2021).

Bioink

Bioink is the most important element in 3D bioprinting. The bioink must consist of mechanical, biological, and rheological properties of the tissue/organ to be printed. Due to the water solubility under physiological conditions, natural polymers are ideal for creating scaffolds. The most common natural polymers used are collagen, alginate, hyaluronic acid, and gelatin. They form 90% of the polymer used in bioprinting. The remaining 10% is occupied by synthetic polymers due to higher heat resistance and rigidity to maintain structural balance. This compound mixture helps in enhancing the biocompatibility and regeneration performance of the scaffold. It is seen that using a gel-based formula for creating bioinks is a suitable approach for extrusion 3D bioprinting (Montero et al., 2019; Song et al., 2021; Javaid & Haleem, 2021).

Notable Discoveries in 3D Organ Printing

There has been a significant development in the 3D printing of organs with a few notable milestones. There are several flat and hollow organs that have been proven feasible and are used in transplantation. The discoveries of those organs opened doors to the possibility of creating and developing more complex organ structures.

The most commonly used and one of the first organs to be printed is the Skin. The applications of artificial skin have been widely popular in the treatment of burns and traumas, reconstruction purposes, and cosmetic surgeries as well. 3D-printed artificial skin has proven to be quite a successful event in the history of printing organs. The skin is printed layer by layer after the reconstruction of images using a CAD model.

The development of skin, however, was conducted directly on the wound of the patient. This technology termed "3D bioprinting" is now the latest used in the 3D printing of organs and is a step further in the dream to print every organ structure. The fabrication of skin directly on the site of the wound provides customized treatment for every person depending on the type and severity of the wound. The portion of skin to be replaced is examined and a CAD model for the preparation of the transplant is created. A bioink using stem cell samples of patients with some customization is prepared. The skin is then printed with the help of the CAD model and bioink. There are certain post-processing tests conducted to increase the compatibility and functionality of the skin before it is implanted in the patient (Javaid & Haleem, 2021).

Another organ that happens to be the focus of development is the kidney. A tremendously high requirement for the organ and a subsequent low number of donors have raised the need for the development of alternatives to transplantation. The cycle of patients with kidney disorders is as follows: long-term medications; dialysis; transplantation, or death. Printing a functioning kidney is still a long way to go, however, there has been development of organoids. These organoids are currently being used to replicate certain functions of the kidney if not whole. They are being implanted as a treatment for certain nephron damage and injuries. The main challenge is that the artificial organoid cannot differentiate in certain structures and lacks vital vasculature (Wragg et al., 2019b).

A notable event in the field of 3D printing is considered to be the printing of a miniature, anatomically accurate human heart. A group of scientists in Israel were successful in creating a human heart inside a support bath. They extracted a cell sample and created personalized hydrogel, cardiomyocytes, and endothelial cells. These were then processed to create bioinks. The image of a 3D heart was created by reconstructing using multiple CT scans with several slices for accurate structure. The bioinks and 3D image then led to the printing of the heart inside a support bath which is a glass box filled with a transparent aqueous solution (Noor et al., 2019).

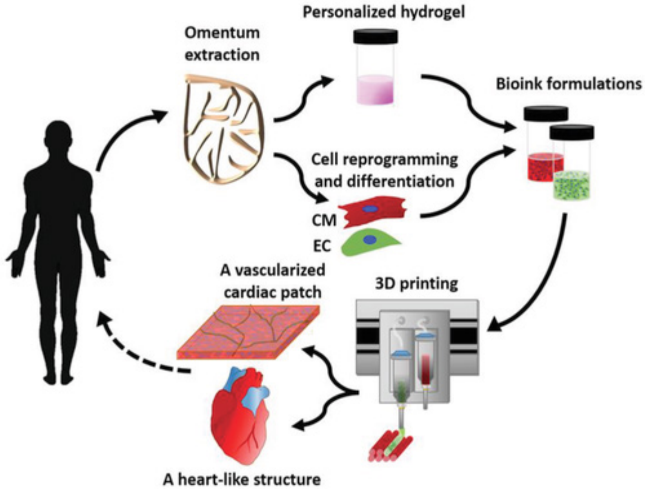

Image 2: 3D printing of a heart structure.
The figure displays the complete process of printing a heart structure. The materials used and the steps of the procedure are explained.
Used from (Noor et al., 2019).
https://onlinelibrary.wiley.com/cms/asset/598066e0-4191-47aa-8a76-7277125d0e2f/advs1070-fig-0001-m.png

The most recent and transformative innovation is the printing of a functioning lung. United Therapeutic in collaboration with 3D Systems cooperation were able to demonstrate a working artificial lung scaffold model created using 3D bioprinting at the LIFE ITSELF Conference in June 2022. They developed a lung scaffold with an anatomically accurate network of alveoli and pulmonary capillaries. The lung scaffold model has shown functionality in an animal model where it is able to perform gas exchange. Since the scaffold will be created using the patient's own stem cells, there would be no need for immunosuppressants. There is hope for these lungs to be undergoing human trials in the next 5 years (United Therapeutics, 2022).

These developments and discoveries have paved the way to create a world where organs could be printed and transplanted without having a need for a donor. These inventions could be considered milestones in the timeline of the 3D printing of organs.

Challenges in 3D Printing

With every emerging technology, there are a set of challenges to be faced. For 3D printing, the challenges can be categorized into processing and management sections.

The process of 3D printing is extensive and delicate. Each step must be taken with extreme caution. With the number of components involved, the positioning of these components, binding abilities, and maintaining the structure *in vivo* (inside the body) are the main drawbacks that can be observed. Further, with the existing imaging and reconstruction techniques the precision and dimensions of the structures are difficult to obtain. The lifespan of the materials chosen is also a factor of question. Finally, the printing techniques used, the nozzle, the distribution of material, and the thickness of the layer are elements to be taken care of.

As for the management, there is a lack of training available for research in the field. The individuals do not possess the adequate skills required for developing these structures and handling the equipment. The technique being an emerging one is of high fidelity making it difficult for availability to the masses.

Following is a summary of the challenges faced in the field of 3D printing.

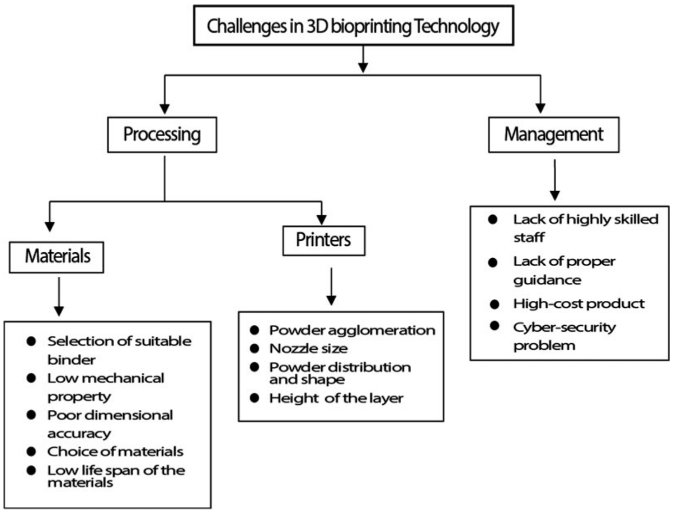

Image 3: Challenges faced in the field of 3D printing.
The various challenges faced in the field of 3D printing at different levels of processing and management are displayed in a flow chart to understand the roots of the problems.
Used from(Agarwal et al., 2020)
https://www.frontiersin.org/files/Articles/589171/fmech-06-589171-HTML/image_m/fmech-06-589171-g009.jpg

Prospects of 3D printing with Biomaterials

3D printing with biomaterials holds a lot of potential in the development of organs. With the significant breakthrough in the industry, it is possible to create fully functioning organs that can be transplanted into the human body thereby eliminating the need to rely on donors. This also helps in the reduction of rejection rate and the need for immunosuppressants as the stem cell sample used in the printing of these organs is cultivated from the patients themselves. The number of death rates due to donor unavailability will also be deducted. Financial strain due to ongoing treatments for chronic cases would also be relieved.

The use of 3D printing could lead to the development of treatments suitable for individuals according to their own profiles. The procedures performed will be precise, accurate, true to life, and aesthetically pleasing by being personalized (Agarwal et al., 2020; Badwaik, 2019).

Conclusion

Biomaterials used in 3D printing for tissue engineering are a multi-collaboration of streams. It has proven to be one of the successful crossovers in healthcare and engineering. The developments in treatment have certainly contributed to enhanced quality of life. Over the decades, the various discoveries of biomaterials have opened doors for experimentation in treatments and led to remarkable milestones. The historical pieces of evidence laid the foundation for the possibility of materials being biocompatible. The use of noble metals for sutures, glass polymer for intraocular implants, and a metal spear for hip replacement were inventions way ahead of their time.

The fields that benefited the most from these inventions were prosthetics, orthotics, ophthalmology, dental, and cosmetics. Implantation of metals and ceramics for bone replacement and polymers as binding agents laid a new path for amputation corrections and joint replacements. Printing of vascular grafts assisted in successful surgeries for heart valve blockages thereby assisting in extension of lifespan. Fabrication and implantation of the skin using 3D bioprinting opened up opportunities for the fabrication of complex organ layers. The anatomically accurate heart and functioning lungs are hopes for printing fully functional artificial organs.

This field has a lot more untapped scope for inventions, discoveries, and experiments. All of which could lead to the betterment of human life and modern medicine.

Declarations

1. Ethics approval and consent to participate: The author declares that there is no misdemeanor of information. The article is written by the author with reference to research and discoveries in the field.
2. Consent for publication: The author declares consent for publication of the article in the "Journal of advanced biomedical engineering."
3. Availability of data and materials: All data has been taken from open-access publications and no material was required.
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6. Authors' contributions: The article was written, edited, and approved by Kajal Babani.
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