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Review of 3D Printing Applications in Biomedical Engineering: A Comprehensive Analysis

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Abstract

Three-dimensional printing (3DP), also known as additive manufacturing, has significantly impacted the biomedical field by enabling the creation of complex, patient-specific medical devices, implants, and tissues. The need for advanced medical solutions due to an aging population and increased reliance on electronic gadgets has driven research into 3DP application. This review focuses on the various biomedical applications of 3DP, including drug synthesis, medical device fabrication, bioprinting, and surgical planning. The review discusses key techniques such as bioprinting, which combines cells, growth factors, and biomaterials to create tissue-like structures, and the use of 3DP for patient-specific prostheses and orthoses. Additionally, the role of 3DP in tissue engineering, organ printing, and the development of bioactive and biodegradable scaffolds is explored. The findings highlight the versatility of 3DP in creating patient-specific medical devices, enhancing surgical outcomes, and advancing tissue engineering and regenerative medicine. Different 3DP techniques discussed also shows promise in producing robust and biocompatible implants, while challenges remain in the widespread application of bio printed organs and tissues. 3DP has the potential to revolutionize the biomedical field by providing customized, efficient, and effective solutions for various medical challenges.

Keywords: Three-dimensional printing; Bioprinting; Biomedical applications; Tissue engineering; Patient-specific implants; Regenerative medicine; Additive manufacturing

1 Introduction

Due to the growing human population and advanced technologies, society is changing and becoming heavily dependent on electronic gadgets. It led to increased medical teaching, accidents, viral diseases, old age, and many other complications for the human body, creating a demand for research in various healthcare segments. However, lesions and abnormalities that necessitate tissue or organ transplantation, for example, continue to be of critical clinical concern, and issues persist with utilising existing techniques, including the biocompatibility of implants and the development of new materials for implants. As a result, the medical industry would always search for engineers and scientists to develop solutions to those challenges. Also, as time progresses, the mechanical engineering field evolves and provides various advancements for the biomedical industry. Three-dimensional printing (3DP) is one of them. By merging the customized/patient-specific production of human bionic tissue or organs, three-dimensional printing technology (3DPT) is intended to overcome the restrictions that are invariably experienced when utilising traditional fabrication methods.

3DP, called additive manufacturing (AM), utilises a layered manufacturing concept, which involves the overlay of materials layer by layer. This method may be utilised to fabricate components with complicated shapes rapidly by precisely adding material. The fabricated components are designed using Computer Aided Design (CAD) or obtained from 3D scanning. The 3DP sector has recently grown manifold due to lower fabrication costs and greater print precision and speed that allow enormous breakthroughs in the fabrication of equipment, implants, and printing of cells. 3DP is also expected to influence, particularly in medical and customized electronics. For example, developing tailored implants [1], regenerative scaffolds [2], and drug delivery devices [3] can address a broad spectrum of unmet clinical requirements. Furthermore, 3D-printed models of a patient's unique anatomy obtained through advanced medical imaging technology can enhance surgical planning implant design and provide unmatched medical training. Another exciting breakthrough is the 3DP of live cells [4], which might lead to the construction of biological structures that can repair or augment missing tissues or organs due to illnesses, injuries, or congenital impairments.

Current advances in 3DPT for medical applications lead them to be divided into four sectors: (i) research to fabricate organ models for different purposes (ii) research to fabricate permanent non-bioactive implants [1]; (iii) advances in fabricating local bioactive and biodegradable scaffolds; (iv) advances to print tissues and organs with full life functionalities. Surgical uses of 3DP therapies have a history starting in the mid-1990s with anatomical modelling for bony reconstructive surgery planning. Due to the mounting need for customization, the world calls for 3D printers, materials, and software. The 3DP sector grows at 20 percent per year, and it is the fastest progress in the medical segment.

Objectives

1. To provide the latest applications of 3DP in the biomedical field.
2. Compare different 3DP techniques used for biomedical applications.
3. To discuss the technological advancement and limitations of 3DP in biomedical field.

2 Material and methods

3DP has biomedical, manufacturing, architecture, medicine, automotive, aerospace, design, arts and food industry applications. However, the focus of this assessment article is on biomedical applications only. The critical biomedical applications of 3DP are synthesizing specific drugs, fabricating medical devices and implants, and helping doctors decide on proper patient treatment procedures [5]. Out of its many advantages, one of the important ones is the rapid prototyping of a physical model from a CAD file. The Medical 3DP applications are used by different professionals, such as clinicians, engineers, biologists, and laboratory technicians [4].

The process involves selecting the target anatomical area of the patient, utilizing Computer Tomography (CT)/Magnetic resonance imaging (MRI) scans to develop the 3D geometry, file optimization so that it suits physical printing, selection of the appropriate 3D printer/technology and the material. The surgeons plan the operative procedure based on the information obtained from the physical 3D model of patient anatomy. 3D-printed surgical guides/tools help the surgeons during intra-operative procedures. It reduces the time in the operating room, and the patient treatment time also gets reduced. The 3D printed models have an advantage in terms of durability, and they can also be printed in different materials and colour-coded for a better understanding [6 7]. Due to this technology, the costlier casting, forging, and mould-making methods can be avoided.

A. Bioprinting

The process of combining cells, growth factors, bio-inks, and/or biomaterials to create biomedical components that mimic the properties of natural tissues, create functioning biofilms, and help remove pollutants is known as three-dimensional bioprinting. The three standard printing methods used for bioprinting are inkjet, laser-assisted, and extrusion bioprinting. Inkjet bioprinters primarily used for tissue engineering applications are of thermal and piezoelectric type. Bio inks, the main constituent of bioprinting, consist of hydrogels. Hydrogel's choice is due to its printability, biocompatibility, crosslinking ability, and high swelling capacity. Hydrogels can have any natural or synthetic source [8]. Figure 1 shows different applications of 3D printed bioprinting.

Surgeons rely on their earlier training, experience gained during earlier surgery, and image data obtained from techniques such as CT, MRI, and others. In some cases, the complex anatomical nature of the surgical site demands more information to plan the surgery. Examples are aneurysms and congenital heart defects. In such cases, the 3D-printed organ models become helpful for better preoperative plan-

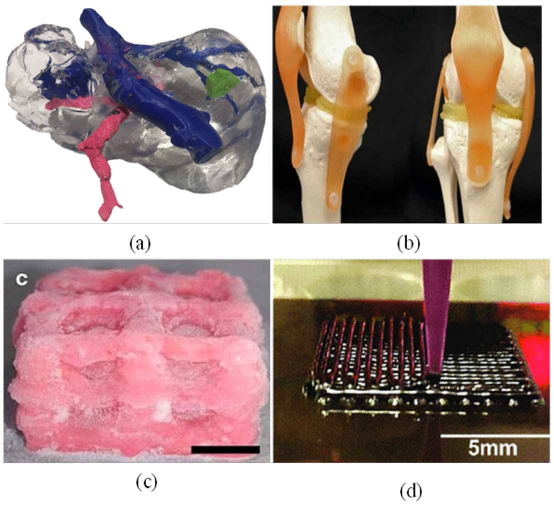


Fig 1. 3D printed organ models (a) organ model for preoperative planning for 3D printed liver,Reproduced under Creative Commons CC0 License [9]; (b) The 3D printed menisci in the knee model: a cartilage mimicking material, Reproduced with permission from Reference number 10. Copyright 2017 American Chemical Society [10]; (c) Soft tissue scaffold, Reproduced under Creative Commons Attribution 4.0 International License [11]; and (d) biodegradable scaffold, Reused under Creative Commons Attribution 3.0 Unported Licence [12]

ning. These models can be fabricated from the information obtained from CT or MRI images. Training new surgeons with these organ models can increase the success rate of the surgeries and drastically reduce the time required to perform the surgery. The surgeon gets a better understanding of the organ and its surrounding region. The tactile feature of the organ, surgical guidance, and other features greatly help the surgeon [13].

The brain is one of the delicate parts of the human body. So, the safest surgical procedure is required to minimize tissue damage [14]. The virtual simulation obtained from MRI or CT data and the 3D printed model provides an edge for preoperative planning. The 3D models are also helpful for preoperative planning of differ cardiac related issues [15].

A permanent bioinert implant is a type of medical device that is implanted into the body and is not intended to be removed. Examples are Maxillofacial, craniofacial, dental, load bearing, spine fusion, sternocostal, and cardiovascular stents used as permanent implants. The porosity, grain structure, and surface are the essential parameters of permanent implants comprising titanium alloys, tantalum, cobalt-chromium (Co-Cr) alloys, and gold [16]. The advantage of 3D-printed implants is that they can be formed specifically for a patient. It increases the probability of a successful implant.

The fabrication of tissues and organs is one of the prime applications of bioprinting. There are two basic methods to fabricate organs. In the first method, which is indirect cell assembly, a 3D scaffold is first formed, and then the cell seeding process occurs. The second method, direct cell assembly, creates a composite structure using cells and materials [4]. The main requirements of scaffold materials are good biodegradability and biocompatibility. The tissue material and scaffold reaction enhance the tissue regeneration, and the hydrogels speed up this process [17]. The scaffold should create an interconnected network with porosity required for cell growth, metabolic waste, and transport of nutrients. The mechanical properties, structural features, and other properties of scaffolds should match the tissues required to be implanted [18]. The scaffolds can be classified according to the technique used to form them in indirect cells. These are (a) inkjet-based, (b) extrusion-based, (c) laser-assisted, and (d) microvalve-based. Microvalve-based printing is a type of drop-on-demand bioprinting. It has high throughput compared to inkjet bioprinting [19]. When cells are directly seeded into 3D-printed scaffolds, it causes a low inoculation rate and increases cell distribution. To resolve the problem, the cell mixture was encapsulated into scaffolds composed of another gel type. It provides better shape and strength for scaffolds. Researchers encapsulated cells directly into the hydrogels for better printing cells/gel results [20]. Using bioprinting, Xue et al. manufactured scaffolds using human dental pulp cells with alginate/gelatin gel. It controlled the cell density and adherence of highly viable cells with the 3D network [2]. Researchers are developing these techniques to help in minimally invasive surgery. The enhancement of the mechanical properties of the scaffold is also an essential parameter of concern.

The utilization of engineering and medical principles for tissue regeneration is known as tissue engineering. The living cells were produced in vitro environments on specific biomaterials. Then, these were placed in the damaged area, the artificial 3D tissues and organs were produced, and the injured tissues were replaced. Scaffold materials were used in tissue engineering to move cells to specific locations. The newly formed tissues get structural support from them. 3DP provides controlled pore parameters required for a scaffold. The stem cells were also used for the regeneration of the tissues. As a host cell, they renovate themselves. Their growth provides one or more cells in the tissue. The cell renewal process provides a repairing action during an injury or illness. This technique is helpful in deadly diseases like cancer [21].

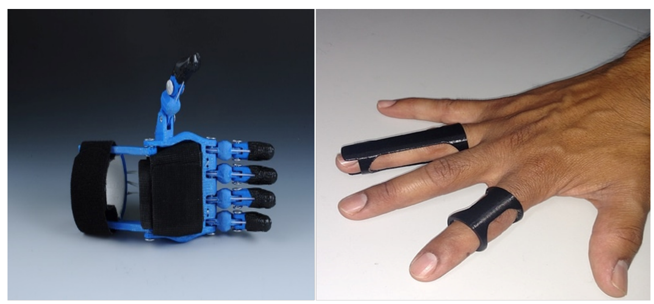
A literature survey shows that stem cells and tissue engineering techniques show promising results. Researchers have developed a cross-linkable gelatin hydrogel that permits extrusion-based AM into the porous scaffolds [22]. The Electrohydrodynamic 3D bioprinting approach is suitable for generating bacterial cellulose /polycaprolactone composite scaffolds with high biocompatibility for tissue engineering [23]. They discussed the role of this application in spinal cord injury treatment. Deo et al.[24] evaluated the criteria for designing the bioink used in fabricating complex structures. They have discussed the effect of different processing factors on the biochemical and biophysical properties of bioinks. Jaidev et al.[25] presented a surface modification approach that increases the scaffold's bioactivity for bone tissue regeneration. Jang et al.[26] studied the role and future scope of 3DPT in the background of stem cell fabrications. They identified thirteen different applications of stem cells with 3DPT. Madrid et al.[27] discussed the current state-of-the-art 3DPT for bone tissue engineering-based scaffolds, whereas Ozbolat et al.[28] have suggested the need for tumor tissue models and their placement in bioprinted tissues to study their growth. According to Parak et al., the main limitation of 3D bioprinting technology for tissue engineering is the shortage of bioinks with the required properties[29]. They described and critically compared the stated functionalization methods, focusing on their effects on bioinks. Tasmin et al.[30] have discussed examples of 3D-printed stem cell tissues such as blood vessels, cardiac tissue, adipose tissue, heart valves, cartilage, neural tissue, pancreas, and liver muscle. Wu et al.[31] reviewed the current techniques for fabricating neural tissue engineering scaffolds.

Organ transplant is one of the main requirements to save the life of patients. However, it depends on the availability of the donors, who, in most cases, cannot fulfil the urgent organ demand. The 3DPT can meet this extra demand. The 3DP technique produces tissues such as multilayer heart structure, bone structure, and others. However, when more complex tissues are produced, several difficulties also arise. The organs printed with this technology are the liver, skin, cartilage, bone tissues, and heart[32]. According to Bozkurt et al., an organ can be printed with a 3D printer, but the organ's functionality is challenging to implement[21]. Moreover, the reason is an assembly of vascular structures. Javed et al. identified eight significant AM tissue and organ printing advancements. However, bioprinting-based organs are not as efficient as normal organs for implants.

Nevertheless, different research teams are working in this direction to make it possible in the future, and these organs are very much used for preoperative planning. Sirota et al. provided a strategy to overcome the difficulties arising due to a lack of integration of electronics and biology[33]. They generated a 3D-printed bionic ear[34]. A cell-seeded hydrogel matrix is 3D printed in anatomical human ear geometry. Park and Agarwal et al. discussed the advancements and challenges of 3D-printed tissue and organ technology[35]. Mironov et al. suggested a fully integrated organ bio-fabrication line to develop organ printing technology commercially[36]. Fedorovich et al. have discussed the role of 3D organ printing in bone regeneration. The present bone size that is possible to repair with this technology is small, but larger bones can be fixed in the future. According to them, the critical factors are vascularization, architecture that supports good bone growth, and stem cell osteogenic differentiation[37]. Zhang et al. reviewed the 3DPT for organ printing with the latest advancements, challenges, and their use for toxin testing and drug delivery[3]. Fan et al. highlighted that 3D-printed anatomical models would be helpful for surgeons to understand tumor and kidney anatomy better[38].

B. Medical devices

A medical device is a tool, apparatus, or other article used to diagnose, prevent, monitor, treat, or alleviate a human disease. It can include components, parts, or accessories. Conventional methods like casting and injection molding were used to make medical devices. However, several difficulties arise in this process. The use of 3DP techniques provides several advantages compared to conventional methods. The devices having complicated shapes can be efficiently designed and fabricated with the help of the 3DP technique in a lesser amount of time. The making of patient-specific medical devices is another advantage of using 3DP. An example is the hearing aid designed according to the patient's specific ear size. This technique is also suitable for making patient-specific eye lenses, stethoscopes, and others[28]. Figure 2 shows the 3D-printed prostheses and orthosis devices.



a b

Fig 2. 3D printed prostheses and orthoses (a) 3D printed prosthetic hand, Reproduced under Creative Commons CC0 License[39]; (b) 3D printed orthosis for fingers, Reproduced under Creative Commons CC0 License[40]

Persons with disabilities (due to old age or an accident) require assistive devices. These are known as orthoses and prostheses. According to the World Health Organization report, more than 35 million people around the globe will require orthotics and prosthetic services soon[41]. Furthermore, the demand increases rapidly due to the ageing population and vascular-related diseases[42]. These devices improve the quality of the life of the patients. A prosthesis is a device that replaces a missing or damaged body part. A prosthesis can be limbs, feet, toes, fingers, artificial eyeballs, hearing aids, ears, noses, and others[43]. Earlier casting methods were used to manufacture prostheses, but 3DP methods are becoming popular. Manero et al. reviewed the role of 3DPT in the field of prosthetics. According to their findings, persons with a difference in limb length generally have low self-esteem, and 3DP-based prosthetics improved their confidence. The prime benefit of 3DP is rapid prototyping with desired mechanical characteristics according to a specific patient. However, some limitations are associated with the prostheses. They have more intricate textures than the original skin, are non-adjustable, and have more weight [21].

The permanent prostheses (hip, knee, dental, cranial) and temporary prostheses (pins, plates, rods, and screws for the fixation of bone fractures) generally use metallic implants like Tantalum, gold, stainless steel, titanium, shape memory, and Co-Cr alloy. One major issue with these prostheses is the proper matching of strength and elastic modulus with bone tissues. In addition, there is a stress shielding effect for poor matching characteristics and prosthetic loosening. Polyetheretherketone (PEEK) with reinforced carbon fibre is also used for artificial hip joint prostheses [44]. Birbara et al. suggested using prostheses for cardiovascular medicine to replace heart valves [45]. Weber et al. reviewed the current neural technologies to activate sensory information in prosthetic devices [46].

The function of orthoses is to modify and support the features of human musculoskeletal and structural systems. Orthoses provide the biomechanical needs of the patients. It helps maintain body alignment, restore mobility, and perform other tasks. The main advantage of 3D printed orthoses is their relatively lesser time requirement than conventional techniques. Hasibuzzaman et al. reviewed the current literature on 3DP for the orthosis of different body parts. According to them, there are different types of orthoses available today: upper limb, lower limb, spinal, and some others. Upper limb orthosis is based on the arm and wrist/hand regions. Lower limb orthosis is based on knee orthosis brace, foot, ankle-foot, and hip regions. The types of spinal orthosis are based on the spine, cervical, and thoracic regions [47]. Choo et al. performed a meta-analysis and investigated the efficacy of ankle-foot orthosis to improve gait parameters such as mobility and walking speed in patients with a stroke and gait disturbance [48]. Quaresma et al. presented a support tool to aid the therapists/physicians decide the type of orthosis suitable for a patient. They developed a platform called OrthoRehab and tested it for different conditions [49].

Results and Discussions

rovides a comprehensive overview of the various 3D printers used in biomedical applications. The table categorizes the printers according to printing manufacturing processes, materials used, medical use, print resolution, printing speed, price, and their pros and cons. The printers featured in the table include Vat Photopolymerization (VP), Material jetting (MJ), Binder Jetting (BJ), Material Extrusion (ME), Powder bed fusion (PBF), Sheet Lamination, Direct energy deposition (DED),Nano-fabrication, Kenzan method, and Magnetic levitation (ML). The costliest printer is PBF, while the cheapest is the VP. In terms of print resolution, the DED has the highest print resolution, while the VP has the lowest resolution. ME is the fastest in terms of print speed, while ML has the slowest printing speed. Most printers support a wide range of materials, and all printers except for the PBF technique support multicolor printing. The PBF, ME, and BJ technologies are among the most popular in the biomedical field.

3D Printing for Biomedicine is a tale of diverse technologies. This technology allows for the creation of complex, patient-specific structures with the potential to revolutionize areas like prosthetics, implants, and tissue engineering. However, navigating the diverse landscape of 3D printing technologies can be daunting. 3D printing also resolution the biomedical field and creating a balancing act among resolution and accuracy. Resolution and accuracy are paramount for intricate biomedical structures. Powder Bed Fusion (PBF) and Material Jetting reign supreme in these aspects. PBF, using lasers or electron beams, offers exceptional detail for crafting highly complex metal implants like cranial implants or prosthetics. Material Jetting, particularly with biocompatible photopolymers, boasts high resolution and smooth surface finishes, making it ideal for dental models and intricate biocompatible prototypes. However, DED, while achieving good accuracy, might require additional post-processing for a smooth finish. FDM and Binder Jetting offer moderate resolution, suitable for basic scaffolds or surgical guides. Biomedical applications often demand a balance between strength and biocompatibility (Table 1).

DED and PBF excel in strength, making them suitable for creating robust metal implants like hip replacements or custom prosthetics using materials like titanium. FDM, with biocompatible filaments, offers a balance between affordability and strength for applications like custom orthotics or surgical guides. However, the strength of FDM parts can vary depending on the material and printing parameters. Material Jetting and Vat Photopolymerization, while offering a broader range of biocompatible materials, generally have lower inherent strength, limiting their use for load-bearing implants. Speed and cost considerations are crucial for both research and clinical applications. FDM stands out for its affordability and relatively fast printing speeds, making it a popular choice for early-stage prototyping or creating cost-effective surgical guides. Binder Jetting offers similar advantages, with the added potential for using a wider range of materials, including some biocompatible options. DED and PBF, while producing high-quality parts, tend to be slower and more expensive, making them more suitable for high-value, complex implants. Material Jetting and Vat Photopolymerization fall somewhere in the middle, offering moderate speeds and costs,

Table 1. 3D Printers used in the biomedical applications

S No	Printing process	Materials used	Print Resolution	Printing speed	Printer cost ($)	Medical use	Pros	Cons
1	VP	Liquid photopolymer resin	about 1 μm	3-30 mm/sec	500	Fabricate medical devices, drug delivery structures, and dental applications.	A high degree of detail, precision, and overall quality. The process is relatively rapid.	Lack of photo-resin material, Inadequate strength and Resins can warp and bend over time.
2	MJ	Liquid photopolymer droplets	2-14 μm	30 to 60 mm/sec	2.32,000	Medical models, prototypes and casting patterns	Low wastage and material on-demand dropping technology, homogeneous thermal properties	Poor mechanical properties degrade quickly over time, Producing relatively brittle parts.
3	BJ	Metals, sand, and ceramics in granular form	35 μm	0.00776111 mm/sec	30,000	Medical models Implants	Parts can be made in a range of different colours. It uses a range of materials: metal, polymers, and ceramics, and the process is generally faster than that of other 3D printers.	It is not always suitable for structural parts. Additional post-processing can add significant time to the overall process.
4	ME	Polymeric filament	about 200 μm	60 mm/sec	1,40,000	Medical models, Implants, Tools, instruments, andparts for medicaldevices	Can produce models with good structural properties, close to a final production model.	Visible layer lines, susceptible to warping and other temperature fluctuation issues, and toxic print materials
5	PBF	Nylon, Titanium, Aluminium, Co-Cr	∼100 μm	0.000555556 mm/sec	400,000 to 800,000		No or minimum support, Powder recycling	Post-processing, Weak structural properties, Support build plate, Thermal distortion, and High power usage
6	Sheet Lamination	Adhesive-coated paper, polymer, or metal laminates	4∼200 μm	0.00776111 mm/sec	14,995	Medical models Tools, instruments, and parts for medical devices	Ability to integrate as hybrid manufacturing systems, Ease of material handling, no support structures necessary, the material can be easily recycled	Layer height cannot be changed, requires post-processing, and generates much waste compared to other AM methods.
7	DED	Titanium alloys, Stainless Steel, Aluminium alloy	500 μm	0.00305556 Kg/sec	5,00,000	Implants	Dense and robust parts, near net shape, can be used for repairing more significant parts, easy material change, and reduced material waste.	High capital cost, low build resolution, and no support structures
8	Nano-fabrication	Nanostructured surfaces, nanoparticles, materials	100 nm	50 mm/sec	1,00,000	Printing of large arrays of bifunctional beads, rapid screening for cancer cells or heart attack markers	Enabling 3D bioprinting of the hydrate biomaterials, creating a complex 3D anatomical architecture	Limitations of available biomaterials and high-cost
9	Kenzan method	Layer-by-layer dispersion of biomaterials	500 μm	3-30 mm/sec	50,000	Cell spheroids with human dermal fibroblasts, human umbilical vein endothelial cells	High cell density, reduced printing time on spheroid bioprinting	The requirement of the additional cell spheroid fabrication process - Fixed inter-needle distance
10	ML	Biocompatible magnetic nanoparticles	250 μm	0.000293981 mm/sec	30,000	For the making of prosthetic limbs, surgical devices, human organs	Rapid printing of multiple tissues, fine spatial control.	Dependent on a precise magnetic field

ideal for creating biocompatible prototypes, dental models, or intricate scaffolds. One ongoing challenge in 3D printing for biomedicine is the limited availability of biocompatible materials across all technologies. While PBF and DED excel in strength with established biocompatible metals like titanium, their options are narrower. FDM offers a growing range of biocompatible filaments, but their strength might not always meet specific implant requirements. Material Jetting and Vat Photopolymerization are making strides with biocompatible photopolymers, but these options are still evolving.

Challenges faced by 3PD in biomedical applications include regulatory hurdles, cost and accessibility, biocompatibility and long-term safety, scalability and standardization, and ethical considerations. Future perspectives include future advancements in materials, integration with AI and machine learning, point-of-care 3DP, bioprinting of complex organs and tissues, and regulatory reforms and harmonization. Addressing these challenges and capitalizing on these future perspectives will be crucial for realizing the full potential of 3DP in revolutionizing healthcare and improving patient outcomes.

4 Conclusion

3D printing (3DP) is revolutionizing healthcare by providing customizable solutions for diverse medical needs. It enables the creation of personalized heart valves, stem cell-based bioink for disc repair, living blood vessels, sensory artificial skin, and anatomically matched bone implants. Medications can be printed with specific shapes, sizes, and release rates. Personalized prosthetics and orthotics offer unmatched comfort and functionality. Materials like polished polymers, purified metals, and tested hydrogels ensure safety and biocompatibility. Multi-material printing and advanced biocompatible materials enhance functionality. This transformative technology improves patient outcomes, creates novel treatments, and increases accessibility while impacting industrial companies, production processes, and society. 3D technology signifies a healthcare revolution, bringing hope for a personalized and healthier future.

The choice of 3D printing technology for a biomedical application hinges on a careful consideration of factors like desired resolution, accuracy, strength, biocompatibility, printing speed, and cost. PBF stands out for high-strength, complex metal implants. DED offers similar benefits with the potential for broader material applications. FDM provides a cost-effective option for biocompatible prototypes and surgical guides. Material Jetting and Vat Photopolymerization excel in creating intricate, biocompatible models and scaffolds, with ongoing advancements in biocompatible materials. As technology continues to evolve, the future of 3D printing in biomedicine promises even more sophisticated techniques, wider material compatibility, and a broader impact on patient care.

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