Discover Materials

Review

Advancements in 3D printing techniques for biomedical applications: a comprehensive review of materials consideration, post processing, applications, and challenges

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Abstract
Three-dimensional (3D) printing has become a potent production tool in the field of biomedical engineering over the past 20 years. Through layer-by-layer deposition of materials, proteins, and even living cells, it offers considerable advantages in the creation of sophisticated and individualized biomedical products with accuracy, efficiency, cost effectiveness, and reproducibility. Despite the tremendous advances made in 3D printing, more work needs to be done to improve the quality of biomedical goods created with this technology. To assure the creation of remarkable and ground-breaking goods that address patients' demands, numerous challenges in 3D printing processes, materials, and applications must be addressed. It is necessary to incorporate developments in physics, materials science, engineering, biological sciences, and medicine to meet these problems. This article reviews a variety of 3D printing-related issues in the biomedical industry, including processes, post-processing techniques, applications, and related difficulties. It analyzes the difficulties 3D printing in biomedical engineering faces and makes suggestions for potential future advancements. It is obvious that 3D printing is becoming more and more important in this field and has the ability to provide a wide variety of useful biological items. This review seeks to identify future directions for research and development while also advancing understanding of the existing state of 3D printing and the effect of post-processing in biomedical engineering.

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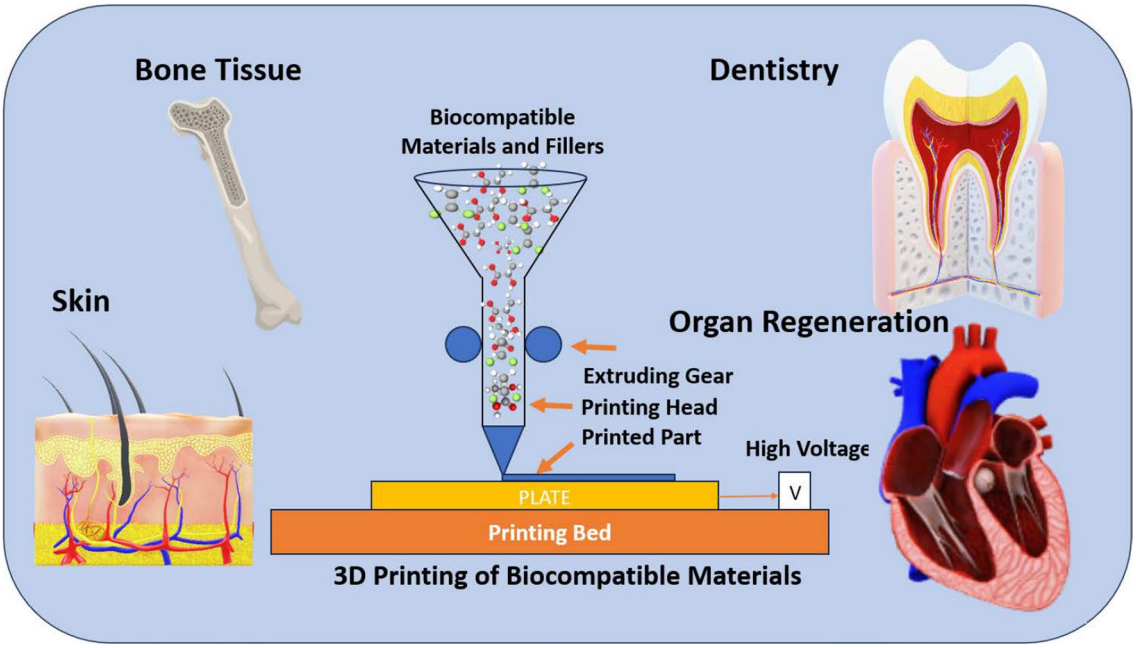
Graphical Abstract



Keywords 3D printing · Biomedical applications · Material considerations · Challenges

1 Additive manufacturing (3D printing) techniques used in biomedical applications

Additive manufacturing methods are classification based on the physical state of the primary material involved, which can be solid, liquid, or powder. Various techniques are employed depending on the specific type of material being utilized. Each method has its own advantages and limitations. 3D printing provides advantages like accurate and customized manufacturing, minimized waste, cost-effectiveness, and quicker production, making it a compelling option for medical applications. One of the most significant benefits is the ability to create customized and personalized devices tailored to individual patient needs [1, 2]. This level of customization ensures better fit, comfort, and functionality, leading to improved patient outcomes. Additionally, 3D printing enables rapid prototyping and production, allowing devices to be quickly designed, tested, and brought to market [2]. This speed is crucial in time-sensitive situations and facilitates faster responses to medical needs. Cost-effectiveness is another major advantage of 3D printing [3]. By eliminating the need for expensive molds and minimizing material waste, the technology reduces production costs, particularly for small batches and specialized devices. Moreover, 3D printing allows for the creation of complex geometries and intricate designs that are difficult or impossible to achieve with traditional manufacturing methods, enhancing the functionality of medical devices such as implants and tissue scaffolds [4]. On-demand manufacturing is another benefit, enabling medical devices to be produced on-site as needed. This reduces reliance on supply chains and allows for quicker responses in emergencies or in remote locations. Finally, 3D printing fosters innovation in medical device design by encouraging rapid experimentation and iteration. This flexibility allows for the development of novel solutions, advancing healthcare and improving patient outcomes.

According to ASTM F2792-12a, the standard terminology for additive manufacturing technologies, 3D printing methods can be broadly categorized into the following seven categories:

1.1 Vat photopolymerization

This technique involves curing photopolymer resin layer-by-layer using a light source. Stereolithography (SLA) and Digital Light Processing (DLP) are common examples. These methods are known for their high resolution and accuracy, making them suitable for intricate medical devices and tissue scaffolds.

Stereolithography (SLA) is an additive manufacturing technology where a liquid photopolymer resin is used as the main component. A build platform is lowered into a vat of resin, and the resin is layer by layer solidified according to the design. The object is often post-cured to ensure its strength and stability. The thickness of each layer during the SLA fabrication process is crucial for achieving the best resolution. While confined to polymeric materials, the SLA exhibits the capability to attain smaller wall thickness and strut diameters compared to alternative techniques currently accessible [5–7]. The SLA procedure is schematically illustrated in Fig. 1a. The solidification of liquid resins is achieved by either thermal or light-activated polymerization processes, which, through temperature and irradiation settings, respectively, can be carefully controlled and optimized. This method finds extensive use in the production of porous scaffolds and intricate structures using biopolymers, catering to applications in the regeneration of both hard and soft tissues. Recognized for its capability to achieve high printing resolution, reaching values as fine as 20 µm, this technique is acknowledged as one of the most precise 3D printing methods. In this process, curing is initiated through the degradation of photo-initiators upon exposure to a light source. Thermoset resins utilized in the Stereolithography (SLA) technique typically display limited degradability under light exposure. To address this, a combination of biodegradable polymers, including diethyl fumarate (DEF), poly(propylene) fumarate (PPF), poly(trimethylene carbonate) (PTMC), and poly(D,L-lactic acid) (PDLLA), has been employed for fabricating biodegradable tissue scaffolds [8]. However, SLA is not suitable for the concurrent printing of living cells due to the insolubility of photo-initiators in water, rendering cells highly toxic. Moreover, the UV light used in the curing process traumatizes cells. Consequently, cells are introduced into the scaffolds after their development. This technique ensures the achievement of high printing resolution and enables the fabrication of precise items for various applications such as dental reconstruction [9], delivery devices like microneedles for insulin skin delivery [10], implantable drug delivery systems for osteosarcoma chemotherapy [11], scaffolds for bone tissue engineering [12], and microfluidics chips [13]. A detailed review of the key characteristics of VAT polymerization technologies can be found in recent literature [14]. Additionally, if biomolecules or cells are employed in the construction of a biomedical product, UV radiation used in the SLA method may cause damage to such materials. Due to the diameter restriction of the employed laser beam, the vertical resolution (i.e., the thinnest layer thickness) of SLA is capped at roughly 250 µm [15].

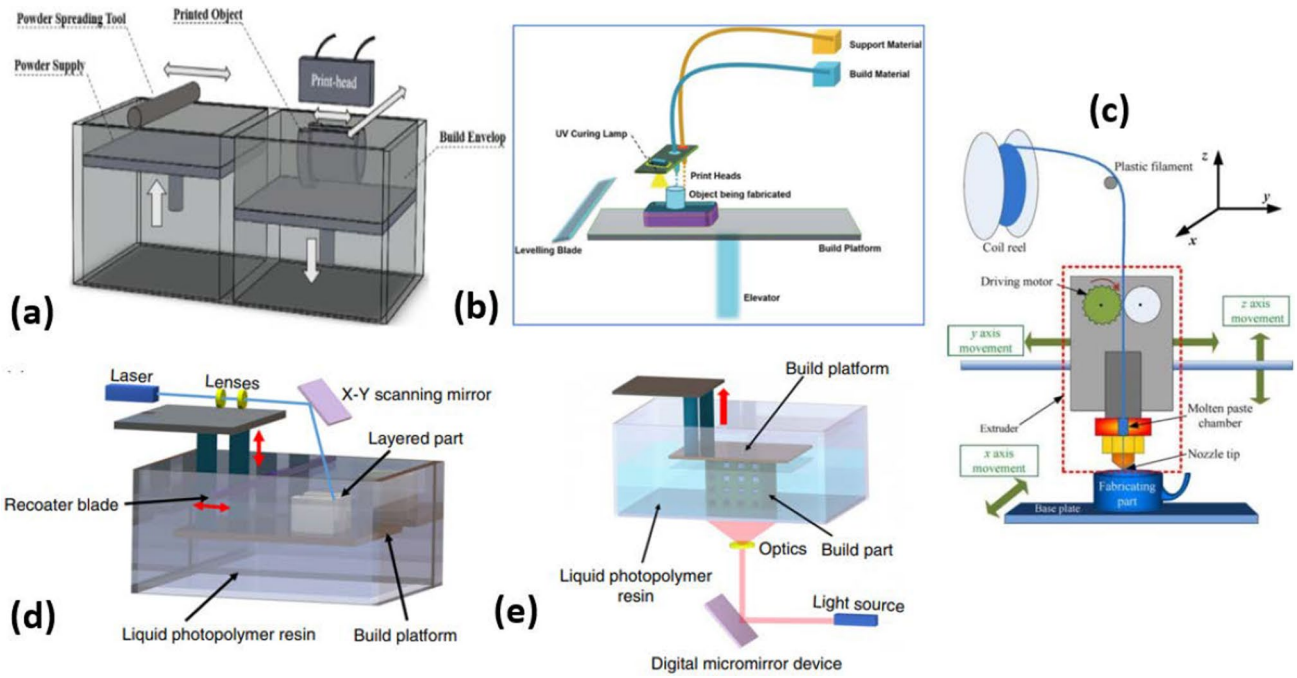


Fig. 1 Schematic illustration of various types of 3D printer **a** SLA [16], **b** DLP, **c** FDM [17], **d** BJ, and **e** MJ [18]

Stereolithography (SLA) is an additive manufacturing technology that utilizes a liquid photopolymer resin as its primary component. The process involves lowering a build platform into a vat of resin, where the material is solidified layer by layer according to the specified design. Post-curing is often performed to enhance the strength and stability of the final object. The thickness of each layer is a critical factor in achieving optimal resolution during the SLA fabrication process. Illustrated schematically in Fig. 1a, the solidification of liquid resins can be achieved through either thermal or light-activated polymerization processes, carefully controlled and optimized through temperature and irradiation settings [19].

This technique is widely employed in producing porous scaffolds and intricate structures using biopolymers, catering to applications in the regeneration of both hard and soft tissues. Acknowledged for its ability to achieve high printing resolution, reaching values as fine as 20 µm, SLA stands out as one of the most precise 3D printing methods. Curing is initiated through the degradation of photo-initiators upon exposure to a light source. While thermoset resins in SLA typically exhibit limited degradability under light exposure, a combination of biodegradable polymers, including diethyl fumarate (DEF), poly(propylene) fumarate (PPF), poly(trimethylene carbonate) (PTMC), and poly(D,L-lactic acid) (PDLLA), addresses this limitation for fabricating biodegradable tissue scaffolds. However, SLA is not suitable for concurrent printing of living cells due to the insolubility of photo-initiators in water, rendering cells highly toxic. Furthermore, the UV light used in the curing process can traumatize cells, leading to their incorporation into the scaffolds after development.

This versatile technique ensures high printing resolution and facilitates the fabrication of precise items for various applications such as dental reconstruction, delivery devices like microneedles for insulin skin delivery, implantable drug delivery systems for osteosarcoma chemotherapy, scaffolds for bone tissue engineering, and microfluidic chips [20]. A comprehensive review of the key characteristics of VAT polymerization technologies is available in recent literature. Additionally, if biomolecules or cells are utilized in the construction of a biomedical product, the UV radiation used in the SLA method may cause damage to such materials. The diameter restriction of the laser beam imposes a limit on the vertical resolution (i.e., the thinnest layer thickness) of SLA, capped at approximately 250 µm. In DLP process liquid photo-resins selectively cure layer by layer using a laser from light-emitting diodes with a range of wavelengths, as illustrated in Fig. 1b. It also incorporates a digital micromirror device (DMD) to cure the photo-resin from the bottom of the vat, reducing oxygen inhibition. It achieves a lateral resolution of 10–50 µm. The vertical resolution primarily depends on the curing depth, which is controlled by the exposure dose [21]. The biomedical field has witnessed various applications of DLP, including the construction of medical implants and the fabrication of tissue engineering scaffolds [22–25].

1.2 Material jetting

In this process, droplets of build material are selectively deposited and cured. Techniques like PolyJet and MultiJet Modeling (MJM) fall under this category. Material jetting is advantageous for producing multi-material and multi-color parts, which can be beneficial for complex anatomical models. Material jetting (MJ) technology is an additive manufacturing technique that employs the selective curing of liquid photopolymer to create functional components, as shown in Fig. 1e. The utilization of MJ technology has gained widespread acceptance across various industries due to its ability to produce parts with exceptional dimensional accuracy and minimal surface roughness, offering significant advantages in terms of quality and precision [26]. This technology enables the utilization of thin layer thicknesses, resulting in the production of high-quality parts with reduced visible stair-step effects and improved printing of thin wall features [27]. The layer thickness can be as minimal as 16 µm [17]. MJ has been used in biomedical applications such as printing hand prostheses [28], surgical training models [20], and multi-color bone models [29]. It has the highest dimensional accuracy among PolyJet, SLA, and MJ printing for maxilla and mandible implant guides [30]. It has also been used to print mouthpiece fixation instruments used in head and neck radiotherapy [31]. MJ-printed samples exhibited the highest 3D dimensional accuracy at the entry point and apex among MJ, DLP, and SLA.

1.3 Binder jetting

This method uses a liquid binding agent to join powder particles. It is less commonly used in medical applications but offers potential for creating custom implants and porous structures. Binder Jetting (BJ) is a high-production process

that involves printing, powder deposition, dynamic interaction, and post-processing methods. Various researchers have reviewed binder jetting for biomedical applications [32, 33]. Prior research has generally used simple geometries [34], although differences in process factors can affect various feature types differently [25, 35]. Layer thickness, printing saturation, drying time, spreading speed, powder size, and powder size distribution are a few examples of variables that might affect the precision of measurements and final qualities of the created product [36, 37].

1.4 Powder bed fusion

This category includes Selective Laser Sintering (SLS) and Electron Beam Melting (EBM). These methods use thermal energy to fuse powder particles, resulting in strong and durable parts. Powder bed fusion is widely used for producing orthopedic implants and prosthetics.

1.5 Material extrusion

Fused Deposition Modeling (FDM) is the most well-known example, where a thermoplastic filament is extruded layer-by-layer. This method is popular due to its affordability and ease of use. It is often used for prototyping and producing surgical guides. In this method, a heated nozzle is continuously fed a filament made from the suggested manufacturing material. The filaments melt into a semi-liquid state at the nozzle and are then extruded onto the build platform one layer at a time. Figure 1c shows how these layers combine and solidify to form the finished product [38]. By changing printing parameters including layer thickness, printing orientation, raster width, raster angle, and air gap, one can alter the quality of the printed components. Due to its efficiency, usability, and low waste, fused deposition modeling (FDM) is a key 3D printing technique in the field of biomedicine [39, 40]. However, the mechanical characteristics of fully printed polymeric parts limit their use in load-bearing tissue engineering scaffolds to some extent. Binder Jet printing is an additive manufacturing method where a liquid binding agent is dispensed onto the powder, creating a two-dimensional pattern on each layer as shown in Fig. 1d [41]. These layers are then stacked to construct a tangible object.

The concept of bioprinting was established in 2004 at the first international bioprinting conference [35, 42, 43]. Creating 3D objects with living cells is the main objective of bioprinting, which calls for a sterile printing environment and specific tools. Hydrogels (such as alginate, gelatin, and collagen) and decellularized extracellular matrix (dECM) are frequently used biomaterials in bioprinting. Research is also being done on direct printing of living cells or cell aggregates [35, 44, 45]. Notably, 3D bioprinting has achieved substantial progress in a number of areas, including tissue engineering, tailored medication delivery, personalized drug production, wound healing, and skin regeneration. Inkjet-based bioprinting stands out among the various strategies as the most popular method for creating customized medicines.

In the field of 3D bioprinting, several techniques have been developed to fabricate complex tissue constructs for biomedical applications. Extrusion-based bioprinting involves the layer-by-layer deposition of bioink through a nozzle, allowing for the creation of large-scale structures with high cell density. However, the shear stress exerted on cells during extrusion can affect their viability [46, 47]. Jetting-based bioprinting, or inkjet bioprinting, ejects droplets of bioink from a print head to form patterns with high precision, minimizing cell damage compared to extrusion methods but restricted by bioink viscosity [48]. Vat photopolymerization-based bioprinting uses light to cure layers of photo-sensitive bioink in a vat, offering high resolution and intricate detail but posing challenges to cell viability due to heat and reactive species generation [49]. Each technique requires careful optimization of parameters to balance structural fidelity with cell survival. Ensuring high cell viability throughout the bioprinting process is critical for the successful fabrication of functional tissue constructs, driving ongoing research into bioink formulations, printing conditions, and post-printing cell behavior assessments.

1.6 Sheet lamination

In this process, sheets of material are bonded together using adhesive or ultrasonic welding. Laminated Object Manufacturing (LOM) is an example. While less common in medical applications, it can be used for creating large-scale anatomical models. Sheet lamination is the least utilized 3D printing technique, accounting for only 0.59% of applications, and is primarily used to fabricate medical devices like maxillofacial prostheses. This method can employ a variety of

materials, including polymers, metals, ceramics, and composites. In sheet lamination, pre-defined shaped sheets are bonded together to form a 3D object, with the final quality depending on the sheet thickness. Various bonding mechanisms are used in this process, including gluing/adhesive bonding, thermal bonding, clamping, and ultrasonic welding. Adhesive bonding uses adhesive-backed sheets, thermal bonding involves heating the material above its melting point, clamping uses mechanical forces to hold sheets together, and ultrasonic welding employs ultrasonic waves and pressure for bonding [50, 51].

The bonding process can follow two sequences: "bond then form" or "form then bond." In the "bond then form" approach, sheets are first aligned and bonded using a heated roller and then cut into the desired shape using a laser or mechanical cutter. This method offers advantages such as low material shrinkage, high fabrication speed, multi-material fabrication, and lower costs. However, it also has limitations, including inhomogeneous mechanical and thermal properties due to glue, poor dimensional accuracy, and difficulty in creating small internal structures. The "form then bond" approach involves cutting the sheets into the desired shape first and then bonding them. This method allows for intricate features and channels, prevents cutting into previous layers, and eliminates material removal steps but requires an alignment system for precise bonding [51].

1.7 Directed energy deposition

This technique uses focused thermal energy to fuse materials as they are deposited. Laser Engineering Net Shaping (LENS) and Electron Beam Additive Manufacturing (EBAM) are examples. This method is suitable for repairing and adding features to existing parts, including medical implants. Directed Energy Deposition (DED) is an advanced 3D printing technique used for the fabrication and repair of high-performance components, particularly in the aerospace, automotive, and biomedical industries [52]. DED involves the deposition of material through a nozzle, which is simultaneously melted by a focused energy source such as a laser, electron beam, or plasma arc. This process enables the precise addition of material to existing parts or the creation of new components layer by layer. The DED process starts with the delivery of feedstock material, which can be in the form of powder or wire, to the deposition head. The focused energy source melts the material as it is deposited, allowing for a high degree of control over the resulting microstructure and properties of the build. The process is capable of handling a wide range of materials, including metals, ceramics, and metal-matrix composites, making it highly versatile for various applications [53, 54].

One of the key advantages of DED is its ability to produce parts with complex geometries and internal features that are difficult or impossible to achieve with traditional manufacturing methods. Additionally, DED is particularly beneficial for repairing and adding features to existing components, offering significant cost savings and extending the life of expensive parts [54, 55]. The process is also highly efficient in terms of material usage, as it can deposit material only where needed, reducing waste. In the biomedical field, DED has shown promise in the fabrication of customized implants and prosthetics, where the ability to tailor material properties and geometries to individual

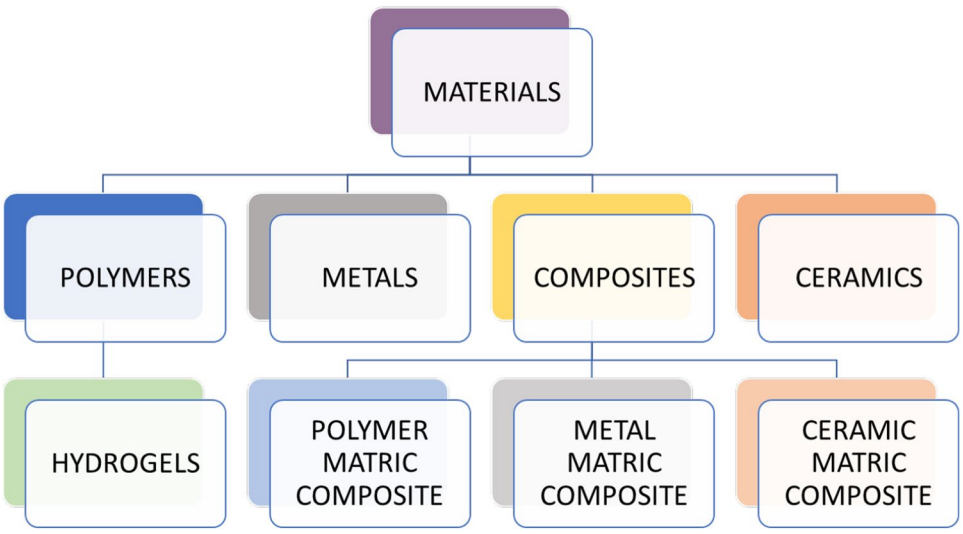


Fig. 2 Materials used in 3D printing for biomedical applications

patient needs is crucial. The process can also be used to create functionally graded materials, where the composition and properties vary gradually within a component, mimicking natural biological structures [55].

2 Materials used in additive manufacturing for biomedical applications

With the advancements in additive manufacturing techniques, an expanding range of materials including metal, ceramic, polymer, composite, and living cells can now be utilized to mimic natural or living structures with distinctive properties [56–65]. These materials are classified in Fig. 2. For instance, traditional metallic and ceramic biomaterials have been investigated and applied in the development of bioinspired scaffold-assisted microenvironments [64]. Furthermore, biomimetic polymeric materials such as nanocomposites and hydrogels have gained significant attention in the field of tissue engineering in recent years [58, 65, 66]. Compared to other materials, biocompatible and biodegradable hydrogels [67] and polymers [68] have long been used for creating 3D cell culture environments. Hydrogels offer a water-based environment that supports nutrient transportation and waste removal [65] while exhibiting numerous advantages, including structural resemblance to the natural extracellular matrix (ECM), ease of handling and processing, and tunable biochemical and biophysical properties [67].

One of major challenges in the field of additive manufacturing for biomedical engineering is the development of materials that possess both favorable printability for 3D printing and desired biomedical properties. These properties include biocompatibility, bioactivity (when needed), and mechanical characteristics suitable for specific biomedical applications. Currently, biomaterials are primarily used for 3D printing in biomedical engineering, while non-biological materials can be employed for printing physical models for surgical planning. However, there is a need to develop new materials that can provide the appropriate physical properties. Biomaterials are non-living materials used in medical devices intended to interact with biological systems. To meet the requirements of their interactions within the biological environment, biomaterials must be non-toxic, biocompatible, chemically pure, chemically stable or biodegradable, chemically inert or bioactive, possess adequate mechanical properties, be easy to fabricate and use, and be easy to sterilize. In addition to biomaterials, 3D bioprinting techniques can be used to create functional tissues or organs for drug screening or tissue engineering applications by printing living cells, spheroids, and organoids.

3 Introduction

The 3D printing process, commonly known as additive manufacturing, involves a layer-by-layer manufacturing process of producing three-dimensional objects from a digital file. The technology involves layer-by-layer deposition of material to build a physical object [69, 70]. This technology has revolutionized manufacturing by enabling rapid prototyping, customization, and on-demand production [71]. Therefore, in the last three decades, 3D printing has experienced a surging popularity in the industry, evolving from its early applications in rapid prototyping for product design models to encompassing diverse commercial-scale manufacturing processes. In recent years, 3D printing has also gained significant attention in the biomedical field, particularly for tissue engineering, implants, and prosthetics [72–77]. The ability to create patient-specific and complex geometries has the potential to improve treatment outcomes and patient quality of life [28]. 3D printing has become increasingly important in biomedical applications due to its ability to create complex geometries and patient-specific designs that cannot be achieved with traditional manufacturing methods [69, 78].

Some of the key importance of 3D printing in biomedical applications are customization, cost-effectiveness, rapid prototyping, and improved treatment outcomes [21, 72]. By facilitating on-demand production of medical devices and minimizing the necessity for costly tooling, 3D printing holds the promise of cost reduction. Rapid prototyping is facilitated by 3D printing, hastening the development of novel medical devices and decreasing the time-to-market. This technology has also enabled the creation of personalized medical devices such as implants, prosthetics, and surgical tools that are tailored to an individual's unique anatomy, improving their comfort and functionality. In the past two decades, the field of biomedical engineering has increasingly used 3D printing to create a variety of complex, customized biomedical products for various clinical uses.

The field of biomedical devices encompasses a diverse array of implants that are instrumental in modern healthcare. In particular, implants are designed to seamlessly integrate with the human body, serving to restore, support,

or enhance various physiological functions [77]. Among these, orthopedic implants, such as joint replacements, bone plates, and screws, play a crucial role in providing structural support, alleviating pain, and restoring joint mobility. In the cardiovascular domain, implants like stents, pacemakers, and artificial heart valves contribute significantly to medical interventions [79]. Dental implants, characterized by titanium posts and prosthetic components, aim to enhance oral function and aesthetics [80]. Neurological implants, including neurostimulators and deep brain stimulation devices, address conditions like Parkinson's disease by modulating neural activity [81]. Soft tissue implants, exemplified by breast implants, showcase advancements in materials for both reconstructive and cosmetic purposes [82]. Each type of implant involves meticulous engineering, considering factors such as biocompatibility, mechanical properties, and long-term performance. Exploring the specifics of these biomedical devices is essential for a comprehensive understanding of their pivotal role in medical advancements and improved patient care.

The utilization of 3D printing enables the production of implants and other medical tools tailored specifically to each patient's unique morphology and physiology [83]. By reducing the need for extensive surgical procedures, this technology has the potential to enhance clinical outcomes while lowering healthcare expenses [84]. Additionally, 3D printing facilitates the creation of intricate shapes that would be challenging or even impossible to achieve using conventional manufacturing methods. This capability is particularly advantageous for developing implants and medical devices that require complex geometries to fulfill their intended functions [85].

An example of a practical application of 3D printing is found in the field of dental implants [86]. Traditional techniques for manufacturing dental implants involve various manual processes such as casting, milling, and polishing. These processes are time-consuming, labor-intensive and can lead to errors and inconsistencies in the final product. In contrast, 3D printing allows for the precise and accurate design and production of dental implants [86]. Dental professionals can employ computer-aided design (CAD) software to create a virtual model of the patient's mouth and design a customized implant that fits the patient's jaw's specific anatomy [87]. This level of customization is particularly crucial for dental implants as they require precise geometries to match the contours of the patient's jaw and provide a stable foundation for prosthetic teeth. By utilizing 3D printing, dental professionals can reduce production time and costs while enhancing the accuracy and precision of the final implant. Consequently, this can lead to improved patient outcomes and increased patient satisfaction [88].

Furthermore, 3D printing also enables the creation of temporary implants that can be used during the healing process, further reducing the overall treatment time. This is due to advancements in 3D printing technology, materials science and engineering, biological science, and medicine [85]. Based on the materials used in the manufacturing process, 3D printing technologies can be divided into different categories. Stereolithography (SLA), Fused Deposition Modelling (FDM), Selective Laser Sintering (SLS), Digital Light Processing (DLP), Binder Jetting, Material Jetting and Bioprinting. The details of each method are given in the next section. Overall, 3D printing has significant potential to improve patient care, advance medical research, and reduce costs in the biomedical field.

In this review, an overview of the 3D printing technology used in biomedical applications, including the different printing techniques and materials used, is provided.

- To discuss the various biomedical applications of 3D printing, including tissue engineering, dental applications, orthopedic implants, prosthetics and orthotics, surgical planning and instrumentation, and drug delivery.
- To highlight the advantages and limitations of 3D printing in biomedical applications, including regulatory issues, biocompatibility, production time and cost, and limited resolution.
- To identify the challenges and future directions of 3D printing in biomedical applications, including advancements in materials and printing technology, integration with personalized medicine, and expansion to complex tissues and organs.
- To provide a comprehensive summary of the key findings and implications of 3D printing in biomedical applications and to make recommendations for future research and development in this field.

3.1 Biomedical polymers

Owing to their favorable characteristics such as biocompatibility, biodegradability, acceptable mechanical characteristics, abundance, and ease of processing biomedical polymers are widely used in 3D printing for biomedical applications, including tissue engineering, drug delivery, biosensors and wound healing. Polymers are long-chain compounds created by the combination of identical chemical building blocks (monomers) with covalent connections. Polymers can be classified as either natural or synthetic depending on where they came from. Both types are used in different 3D printing

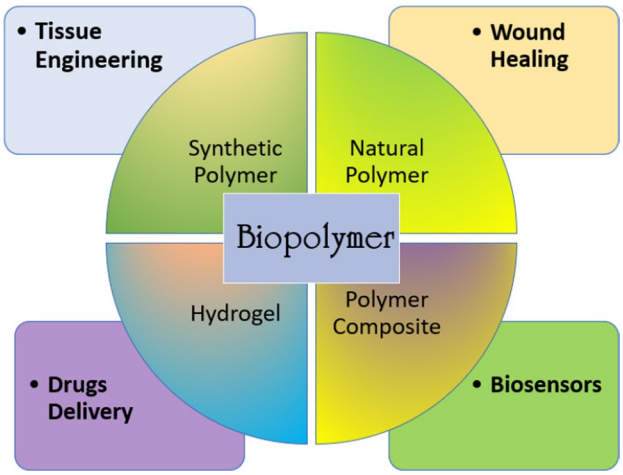


Fig. 3 Type of biopolymers and their biomedical applications

technologies to create a variety of biomedical products (Fig. 3). Natural polymers are frequently chosen for implantable devices because of their distinct characteristics. Natural biopolymers are frequently used in biomedical applications and come from non-mammalian sources including algae and seaweed as well as animal or human tissues. These organic polymers are well suited for biomedicine due to their inherent qualities. They show evidence of biocompatibility, biodegradability, and self-assembly. The extracellular matrix (ECM) of the human body closely mirrors their structural makeup, which creates a conducive milieu for cell adhesion, growth, and differentiation [35, 89]. Consequently, natural polymers are widely utilized in 3D printing for biomedical engineering. However, they often suffer from limitations such as weak mechanical properties, poor printability, and unstable structures. To overcome these challenges, a promising solution is to combine natural polymers with other biomaterials, such as synthetic biomedical polymers. This synergistic approach helps address the drawbacks associated with natural polymers. Currently, natural biopolymers like alginate, gelatin, chitosan (CS), collagen, silk fibroin, and fibrin are predominantly utilized as hydrogels in 3D printing. However, these materials also have limitations compared to synthetic polymers.

On the other hand, synthetic polymers have garnered significant interest due to their customizable chemical and physical properties. They offer advantages not found in natural polymers, such as the ability to control mechanical properties, slow degradation, and maintain structural integrity [90]. While concerns may arise regarding their biocompatibility and degradation byproducts in certain applications, synthetic polymers possess numerous benefits that make them attractive for additive manufacturing in the biomedical field.

In the realm of biomedical engineering, several popular synthetic polymers are utilized in 3D printing. Owing to their low melting and glass transition temperature polymer are better choice for 3D printing [91]. These include PLA, poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(e-caprolactone) (PCL), medical-grade silicone, poly(L-lactide-co-e-caprolactone), and poly(etheretherketone) (PEEK) [77, 86, 92–98]. These materials are non-toxic, biocompatible, biodegradable, and possess favorable mechanical properties. Consequently, they are frequently employed for the production of medical implants, prostheses, drug delivery systems, and tissue engineering scaffolds using 3D printing techniques such as 3D dispensing, fused deposition modeling (FDM), and selective laser sintering (SLS). In recent years, synthetic polymers like PLA and PCL have also been investigated as smart materials for 4D printing. However, they do have limitations, such as low bioactivity, as well as restricted cell attachment and proliferation abilities. Table 1 gives the values of thermal (T_g and T_m) and mechanical (tensile strength and tensile modulus) for various polymers along with their advantages and limitations in biomedical applications.

3.2 Hydrogels

Hydrogels are gel-like materials that contain water and consist of cross-linked polymer networks. The cross-linking can occur either through chemical or physical means. When molecules from a solution enter these polymer networks, hydrogels have the ability to swell significantly. Hydrogels have garnered considerable attention in the field of 3D printing for biomedical engineering due to their highly desirable properties. These properties include excellent biocompatibility and biodegradability, similarity to the extracellular matrix (ECM), possession of specific cell binding sites that promote cell attachment and growth, diffusion of hydrophilic nutrients and metabolites, the ability to undergo photo cross-linking

Table 1 Thermal and mechanical properties of various polymers along with their advantages and limitations in biomedical applications

Polymer	Density (g/cm^3)	Glass transition Temp (°C)	Melting point (°C)	Tensile strength (MPa)	Tensile modulus (GPa)	Advantages	Limitations	Ref.
PLA	1.21–1.25	45–60	150–162	21–60	0.35–3.5	Biodegradable and flexible, good mechanical properties	Slow degradation and low cellular adhesion	[99, 100]
PLDA	1.24–1.29	40–50	120–160	58–67	3.4–3.8	Good biocompatibility and mechanical property	Can cause allergic and inflammatory reactions in the body	[101]
PLLA	1.24–1.30	55–80	170–200	15.5–150	2.7–4.14	Good biocompatibility and mechanical property	Brittle, slow degradation rate	[102]
PCL	1.11–1.14	− 60 to − 65	58–65	20.7–42	0.21–0.44	Low cost, flexibility in processing and modification	Limited degradation, low cellular response	[102]
PEG	1.125	− 76	1–66	10–60	0.5–3.0	Good biocompatibility,	Low melting point, processing challenges, non-biodegradable, poor mechanical properties	[103]
PGA	1.50–1.71	35–45	220–233	60–99.7	6.0–7.0	Good degradation behavior in vivo	Low solubility and faster degradation, poor flexibility	[104]
PEEK	1.3–1.4	145–150	340–350	139	8.3	Superior biocompatibility, good mechanical property	Non-biodegradable, potential to catalyst reactions	[105, 106]

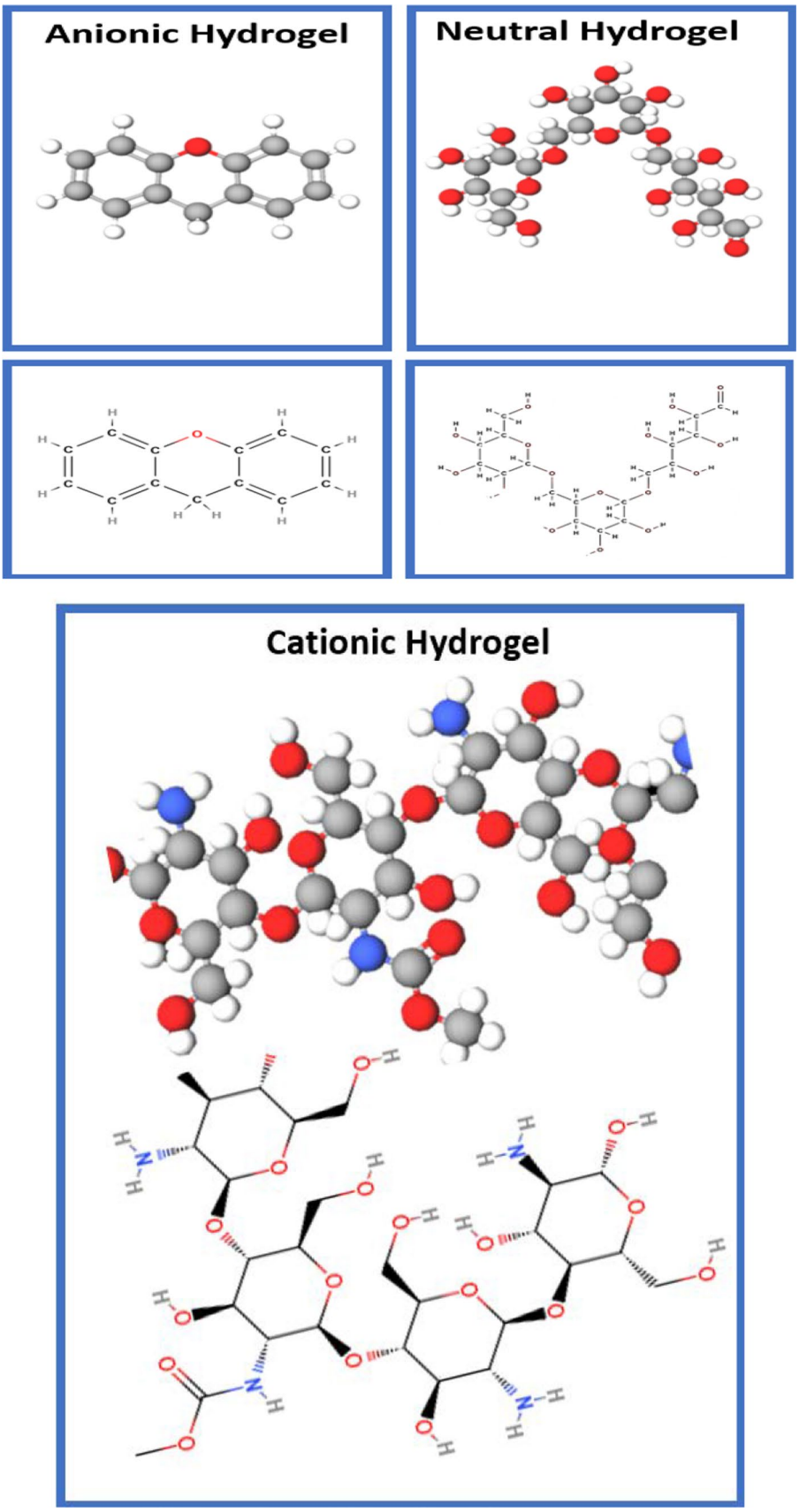


Fig. 4 Some example and 3D structures of anionic, neutral and cationic hydrogels

or ionic cross-linking, and the incorporation of living cells to form bioinks for 3D bioprinting [107, 108]. Hydrogels can be categorized based on their ionic charge as neutral (e.g., dextran), anionic (e.g., alginate and xanthan), or cationic (e.g., chitosan and gelatin). Additionally, the classification of hydrogels is done as either natural (e.g., alginate, chitosan, gelatin, and collagen) or synthetic (e.g., polyacrylamide, poly(ethylene glycol), and Pluronic) depending on their source [109]. These different types and their 3D structures are shown in Fig. 4.

Natural hydrogels can be made from either mammalian tissues or non-mammalian sources like algae and shrimp. Due to its beneficial biological features and physicochemical characteristics, collagen—the most abundant protein in mammals—is widely used in biomedical applications. It is an important component of connective tissues in the human body [110]. Inherent Arg-Gly-Asp (RGD) motifs and accessible active groups in gelatin, which is produced by denaturing collagen, promote cell adhesion and proliferation. However, pure gelatin has unstable structures at physiological temperatures, making its 3D printing challenging. Various approaches have been devised to address this constraint [111, 112]. Fibrin, derived from the enzymatic reaction between thrombin and fibrinogen, has been utilized in various areas of biomedical engineering, but its weak mechanical strength limits its application in 3D printing [113]. Hyaluronic acid (HA), a primary component of the ECM in cartilage and other connective tissues, suffers from poor mechanical properties, often requiring chemical modification or blending with other biomaterials when used as an ink for 3D printing. Alginate, an anionic polysaccharide derived from brown seaweed, is commonly employed in 3D biomedical printing, and various approaches are adopted to overcome its limitations, such as combining it with nanoclay or nanocellulose to improve printability and mechanical properties. Chitosan (CS) is a linear polysaccharide derived from partially deacetylated chitin and represents the sole cationic natural polysaccharide, exhibiting higher mechanical strength and stiffness compared to other natural materials like gelatin, collagen, and fibrin. Agarose, a natural polysaccharide extracted from marine algae or seaweed, shares temperature-responsive properties with gelatin and can be used as a sacrificial material in 3D printing. Silk fibroin (SF), derived from silk produced by silkworms, is another popular natural hydrogel employed in various biomedical applications. Improving the viscosity of SF for 3D printing often involves blending it with other substances like gelatin or adding additives such as mesoporous bioactive glass [114–116].

Natural hydrogels possess excellent biocompatibility and require biodegradability, making them highly attractive for numerous biomedical applications, including drug delivery systems, medical implants, and tissue engineering scaffolds. However, their low mechanical strength and stiffness, as well as poor printability, pose challenges for cell attachment and cell growth. To address these challenges, various effective strategies have been devised. Firstly, synthetic polymers can be combined with other biomaterials possessing excellent bioactivity and cell-friendly components, such as gelatin, collagen, and hyaluronic acid. Secondly, the addition of biomolecules like growth factors can enhance cell attachment, proliferation, and tissue regeneration. Finally, modifying synthetic polymers with bioactive components offers another approach to mitigate their limitations. Table 2 summarizes some advantages and limitations of hydrogels in the biomedical field.

3.3 Metals

Biodegradable metals are biomaterials specifically designed to gradually break down inside the body while simultaneously facilitating tissue growth. Once these metals have served their purpose in supporting tissue development, they completely dissolve. It is of utmost importance that the byproducts produced during the degradation process of biodegradable metals are not harmful and can be safely eliminated through the body's metabolic processes. Furthermore, the rate at which these metals degrade should align with the natural pace of new tissue formation and growth. The utilization of biodegradable metals offers several advantages, including the avoidance of costly and invasive procedures to remove implants since they naturally degrade after tissue repair. They also hold promise for use in young patients who are still in the growing phase, and they possess higher mechanical strength when compared to polymer-based biomaterials.

The primary focus of current research on biodegradable metals centers around magnesium (Mg) and iron (Fe) alloys. Magnesium is characterized by its lightweight nature, relative softness, and low elastic modulus. However, it undergoes rapid degradation in a physiological environment that contains high levels of chloride. This degradation process releases hydrogen gas, which can have adverse effects on the body [78]. To enhance its properties, magnesium can be combined with elements such as zinc (Zn), zirconium (Zr), and rare earth elements. Mg-based alloys are deemed suitable for medical applications but typically require indirect 3D printing methods due to the challenges associated with processing. On the other hand, iron-based alloys, formed by combining iron with manganese (Mn), palladium (Pd), and carbon (C), exhibit mechanical properties similar to stainless steel. The Fe-based alloys can be directly utilized for the fabrication of biomedical products through 3D printing methods.

Table 2 Some advantages and limitations of hydrogels in biomedical applications

Hydrogels	Advantages	Limitations	Ref.
Chitosan	Non-immunogenicity, easily metabolized, antibacterial activity, and biocompatibility	Low mechanical strength, brittle, stiff	[117, 118]
Cellulose	Good biocompatibility, and mechanical properties	Limited cell adhesion	[119]
Collagen	Excellent biocompatibility high porosity, good bioactivity	Low strength and stiffness and low antigenicity	[110]
SF	Biocompatibility, excellent mechanical characteristics, high tensile strength, bioactivity, high flexibility, and low immunogenicity	Brittle and have high degradation rate	[120]
Gelatin	Biocompatibility, bioactivity, ECM mimicked, poor immunogenicity, and better solubility	Low mechanical strength and high degradation rate, low solubility in solution with a high concentration	[121]
HA	Non-toxicity, easily modified through a chemical reaction, good biocompatibility	High degradation rate with low mechanical characteristics	[122]

Biodegradable magnesium (Mg)-based alloys and iron (Fe)-based alloys demonstrate contrasting degradation behaviors. Mg-based alloys degrade within a timeframe of 4–52 weeks in animal tests and 6–12 months when implanted in the human body. In contrast, Fe-based alloys degrade at much slower rates, with a notable portion of the implant remaining visible after 12 months in animals, and complete degradation requiring more than a decade in the physiological environment. In comparison, other biodegradable biomaterials like hydrogels degrade at a faster pace, typically losing a significant portion of their mass within a few days to 3 weeks during laboratory tests. In comparison to natural hydrogels, synthetic polymers like poly(lactic-co-glycolic acid) (PLGA) and poly(lactic acid) (PLA) offer greater structural stability and slower breakdown. They still degrade more quickly than biodegradable metals, though. Mg-based and Fe-based alloys have the potential to develop breakdown products during in vivo deterioration, which is cause for concern. Mg alloy implants initially produce too much hydrogen gas, which causes the formation of gas cavities. These cavities progressively disappear without the need for special care, but they may cause mild inflammation. Contrarily, Fe alloy implants rarely exhibit toxicity or inflammation after implantation, however regional iron deposition can occasionally cause mild inflammation. Biodegradable metals differ mechanically from non-degradable metals like stainless steel and cobalt-chromium (Co–Cr) alloys in in vivo tests, and titanium (Ti) alloys. As biodegradable metals degrade, their mechanical properties gradually decline. Therefore, it is crucial for biodegradable metals to maintain adequate mechanical strength until sufficient new tissue formation occurs. In contrast, the mechanical properties of non-degradable metals are largely unaffected by the in vivo conditions during implantation. Similarly, gold finds diverse applications in the field of dentistry and medicine. In restorative dentistry, gold is utilized for implants, fillings, wire fixings, and supports. It is also employed in ocular prosthetics, particularly for upper eyelid implant surgery, as well as in endovascular stents. Additionally, gold is used in soluble injectable compounds to alleviate rheumatoid arthritis and prevent bacterial infections. Properly installed, gold dental implants are known for their exceptional durability, outlasting other materials. Furthermore, gold nanoparticles exhibit unique physical and chemical properties due to their high surface-to-volume ratio, making them more reactive. As a result, a wide variety of functionalized gold nanoparticles have been explored for therapeutic and diagnostic purposes. Gallium and its alloys, characterized by their biocompatibility and liquid state at room temperature, offer advantages in biomedical applications where solid metals are impractical. These applications include vascular embolization tumor therapy, nerve reconnection, and flexible interconnects. Furthermore, gallium alloy nanoparticles can be functionalized with a metal thiolate complex for use in drug-delivery applications. The self-healing property of Ga alloys is particularly beneficial in antennas and electrodes for biomedical purposes. For instance, if a channel filled with a Ga alloy is cut, the alloy generates a protective oxide at the cut, preventing the liquid metal from retracting or dripping. Upon reconnection, the liquid metal coalesces, restoring electrical conduction. If the channel is composed of a self-healing polymer, both electrical and mechanical healing can occur [123].

The most widely used metal and alloys for biomedical applications are Ti and its alloys and stainless steel. Titanium and its alloys, along with stainless steel, stand as the predominant choices for biomedical applications. Stainless steel, comprising steel infused with at least 11% chromium, is highly favored in biomedical applications for its cost-effectiveness, commendable mechanical properties, and resistance to corrosion and wear [124]. Despite its advantages, its superior mechanical strength compared to bone can lead to stress shielding when used in orthopedic implants, and corrosion within the body may result in implant failure and the release of harmful metallic ions, triggering inflammatory reactions. To address these concerns, stainless steel can be alloyed with other metals, with 316 L stainless steel emerging as a popular choice due to its low nickel content and high nitrogen content, offering enhanced mechanical properties and biocompatibility at a reasonable cost. Alloying elements such as chromium, carbon, nickel, and various others further augment corrosion resistance and mechanical strength, while manganese addition strengthens the material and improves durability, making stainless steel alloys a versatile and reliable option for medical applications [125]. Stainless steel alloys stand out as among the most utilized metal alloys for surgical instruments due to their significant anti-bacterial and anti-staining properties, which are crucial in preventing contamination in medical settings. These alloys find widespread use in various medical applications including orthopedic implants, bone fixations, artificial heart valves, syringes, needles, sensor probes, catheters, otolaryngology ear scope nozzles, and more. The advent of 3D printing technology has enabled the creation of customized orthopedic implants such as crowns, bridges, and bit splits, tailored precisely to match each patient's anatomy. Additionally, innovative stainless steel surgical instruments, such as those designed for keyhole heart surgery, have been developed, benefiting from the precision of 3D printing technology, allowing for dismantling and passage through tiny holes in the heart. Medical devices crafted through 3D printing using stainless steel and its alloys not only offer ease of cleaning and sterilization but also boast longevity, making them well-suited for use in medical facilities [125].

Titanium emerges as another frequently utilized metallic biomaterial, often employed in its pure form, as alloys, or in combination with bioceramics. The categorization of titanium materials hinges on their equilibrium state structure. Presently, titanium alloys with α and β structures find applications, particularly valued for their high biocompatibility and similar Young's Modulus to human bone, aiding in the reduction of stress shielding [126]. Nonetheless, titanium and its alloys exhibit chemical reactivity with atmospheric gases and poor wear resistance, necessitating surface treatments for some titanium-based biomaterials. In a study by Elsayed et al., bioactive coatings were applied to titanium substrates using airbrush spray technology with preceramic polymers containing nano-sized precursors, resulting in crack-free coatings post-deposition and subsequent heating [127]. Similarly, titanium (IV) oxide nanotubes have been utilized as surface modifications under low pressure non-thermal oxygen plasma conditions, rendering the surface suitable for blood-contacting devices due to the absence of platelet adhesion or activation. Notably, common titanium alloys like Ti–Nb, Ti–Cu, and Ti–Mo offer diverse properties such as shape memory, enhanced antibacterial attributes, hardness, and corrosion protection when combined with copper, along with low Young's modulus and desirable mechanical properties in Ti–Mo alloys. These titanium alloys can undergo various processing techniques like hot rolling, annealing, and solution treatment to achieve tailored mechanical properties such as varying hardness and Young's modulus. Titanium-based materials are widely favored due to their superior mechanical and biological attributes, making them exceptionally biocompatible among metals. Notably, titanium exhibits a low Young's modulus akin to bone, minimizing stress shielding effects [128]. In additive manufacturing, titanium-based biomaterials have found extensive application in orthopedics and dentistry. For instance, C-shaped titanium nails have been recommended for certain long bone fractures, while shape memory Ni-free beta-type Ti–Nb alloys have been proposed for specialized applications in hard tissue surgery. Further advancements include beta-type titanium alloys modified with elements like silicon, zirconium, and tantalum, catering to dental and orthopedic implant needs. Personalized implants crafted from titanium involve a meticulous process, beginning with computed tomography (CT) imaging to diagnose bone fractures, followed by collaborative efforts between surgeons and additive manufacturing (AM) engineers to design precise titanium implants. Subsequently, 3D models are generated from diagnostic images using specialized software for biomedical 3D printing. Post-printing, implant components undergo powder removal via specialized techniques like powder recycling systems or ultrasonic cleaning, followed by heat treatments to alleviate residual stresses. Upon finalization, the implants undergo sterilization before implantation, encompassing various orthopedic devices such as clavicle implants, mandibular implants, and hip replacements, including flanged acetabular cup implants [129].

Table 3 lists out the various advantages and disadvantages of using metals and their alloys in biomedical applications.

3.4 Ceramic materials

Ceramic materials, composed of inorganic salts like calcium and phosphate, find application in bone and dental treatments due to their osteoconductivity. However, ceramics are prone to brittleness, making them difficult to handle and implant independently. To overcome this challenge, ceramics are combined with a polymeric binder in biofabrication processes such as extrusion bioprinting or 3D powder printing [133, 134]. Tricalcium phosphate (TCP), hydroxyapatite (HAp), bi-phasic calcium phosphate (BCP), poly(methyl methacrylate) (PMMA), and bioglass are examples of ceramics commonly used in the printing process. For bone replacement, tetra calcium phosphate (TTCP) shows promise and exhibits high resorbability under low pH conditions. A study by Mandal et al. demonstrated the use of TTCP with a phytic acid binder. After printing and post-hardening with an additional binder solution, TTCP remained the primary ceramic phase, but there was also evidence of an amorphous calcium phosphate phase, suggesting a reaction between the ceramic powder and binder [135].

Ceramics have also been utilized to enhance the properties of polycaprolactone (PCL) by blending powdered ceramics with the polymer. This mixture is melted to form a liquid and extruded into filaments, enabling the creation of multilayered scaffolds. In a particular study, PCL combined with natural ceramics, such as decellularized bone matrix and Bio-Oss (a bovine-derived bone mineral), exhibited superior osteoinductive capabilities compared to synthetic ceramics like HAp and TCP [136].

3.5 Composite materials

Biomedical materials need to possess certain characteristics to fulfill their intended purpose. They should exhibit biological compatibility, resistance to corrosion, and adequate mechanical strength and toughness. Biocompatibility specifically

Table 3 Some advantages and limitations of metals in biomedical applications

Metals	Young's modulus (GPa)	Tensile strength (MPa)	Advantages	Limitations	Ref.
Ti	110–114	895–930	Good binding with host tissue, good corrosion resistance, high specific strength	High stiffness, stress shielding effect	[124]
Zn	90–110	37	Promotes tissue regeneration, involves in enzyme growth, low toxicity and high biocompatibility, intermediate degradation rate, good corrosion resistance	Poor mechanical properties, low fatigue strength and creep resistance	[130]
Zr	96.6–99.1	230–330	Low toxicity; improves corrosion resistance	–	[131]
Co–Cr	220–250	600–2280	Inert, high corrosion and wear resistance, low cost	Longevity is questionable	[124]
SS 316L	189–205	490–1731	Controllable mechanical properties	Suffer corrosion pitting, corrosion fatigue, stress corrosion cracking, poor wear resistance	[124, 125]
Mg alloy	10–45	90–280	Promote native tissue growth, fully absorbable by the body, excellent biomechanical compatibility with body, osteopromotive properties	Hydrogen bubble generation, highly flammable	[132]
Fe alloy	188–215	357–412	Good tissue growth, excellent mechanical properties, and biodegradability, high ductility, high fracture strength, high hardness	Toxic at high concentrations, slow degradation rate	[124]

refers to the material's ability to elicit an appropriate response from the host, ensuring that the presence of the material does not cause adverse reactions in a particular application. Composite materials for biomedical applications are designed by combining two or more different materials to produce a novel material that exhibits improved properties and functionalities. These composites offer unique advantages such as improved mechanical strength, biocompatibility, bioactivity, and tailored properties for specific biomedical applications. Here are some examples of composite materials used in biomedical applications:

3.5.1 Polymer matrix composites

Polymers, including both synthetic and natural, as well as hydrogels and their combinations, have been widely utilized in biomedical engineering for 3D printing applications. However, individual polymers may have limitations that restrict their suitability for specific applications. To overcome these limitations, one effective approach is to incorporate another material, known as a "reinforcement," into the polymer matrix. This results in the formation of polymer matrix composites, which exhibit enhanced performance, such as improved mechanical properties, enhanced printability, bioactivity, or other desirable functions or properties that cannot be achieved with the polymer alone. The reinforcement materials can take the form of particles, fibers, or even sheets.

For instance, the addition of bioactive components like hydroxyapatite (HAp) and tricalcium phosphate (TCP) micro- or nanoparticles to polymers can improve their mechanical properties and impart bioactivity [137]. Laponite XLG or RD particles have been investigated as viscosity modifiers to enhance the printability of hydrogels, such as alginate, PEGDA, gelatin, and GelMA. Incorporating materials like PCL nanofibers, PLA nanofibers, gelatin/PLGA nanofibers, graphene fibers, and carbon fibers into biomaterials has been employed to enhance their mechanical properties [138–141]. Cellulose nanofibrils, used as rheological modifiers, can enhance the rheological properties of hydrogels, enabling them to be more suitable for 3D printing [142–144]. The mechanical properties of reinforced polymers are significantly influenced by the characteristics of the reinforcing agents and the interface between the reinforcement and the polymer matrix. Particle size, shape, and distribution within the composite are critical factors for tailoring the mechanical properties of particle-reinforced polymer composites. In fibrous polymer composites, the length and orientation of the fibers play a crucial role in determining the composite's mechanical properties. During the 3D printing process, the flow of viscous ink through the nozzle can induce fiber alignment along the extrusion direction, resulting in anisotropic composites. Cellulose nanofibrils, for example, undergo shear-induced alignment during 3D printing, leading to textured composites with enhanced mechanical properties along the printing direction. The interface between the reinforcement and the polymer matrix is another critical factor that affects the mechanical properties of polymer composites. A strong interface can result in high mechanical strength but low toughness, while a weak interface may lead to reduced strength of the composite [138, 145].

Another significant improvement achieved by incorporating a reinforcement into a polymer is enhanced printability, which is accomplished through improved rheological properties. In many cases, a single polymer, whether natural or synthetic, exhibits very low viscosity, making it unsuitable for extrusion-based 3D printing. However, the addition of nanoparticles or nanofibers to polymer solutions increases their viscosity. For instance, the viscosity of a 20% w/v PLLA/dichloromethane solution increased from 45 to 128.8 Pa/s with the addition of 15 wt% calcium phosphate nanoparticles. Similarly, by incorporating 2% w/v cellulose nanofibers, the viscosity of alginate or GelMA hydrogels can reach several thousands of Pa/s from an initial few Pa/s, resulting in a gel-like state that is ideal for 3D printing [138].

3.5.2 Metal matrix composites

While metallic biomaterials are widely employed in biomedical applications, they do have limitations such as a lack of bioactivity and the potential for stress shielding. To address these drawbacks, researchers are exploring the development of metal matrix composites by combining metallic biomaterials with suitable inorganic biomaterials. In this approach, bioceramic particles, whiskers, or fibers are typically incorporated as the inorganic phase in these composites.

Metallic composites leverage the mechanical strength of the metal matrix for load-bearing applications, while the bioceramic component (particles, whiskers, or fibers) enhances bioactivity and reduces stiffness. For example, hydroxyapatite (HAp) particles have been introduced to 316L stainless steel, titanium (Ti), and Ti-6Al-4V alloys, resulting in HAp-reinforced metallic composites that exhibit improved bioactivity and decreased stiffness [146, 147]. Additionally, various titanium-based compounds, apart from calcium phosphates, have been combined with metals to achieve composites with enhanced mechanical properties. For instance, titanium boride (TiB or TiB2) particles and titanium carbide

(TiC) particles, characterized by biocompatibility, thermodynamic stability, and mechanical stability, have been utilized as a non-continuous phase in metallic composites. These composites can be processed using techniques like selective laser melting (SLM) or electron beam melting (EBM) [148]. Due to their natural degradability in the body, Mg and its alloys increasingly attract attention for orthopedic and cardiovascular applications. Incorporating Mg micro-nano-scale particles into biodegradable polymers dramatically improves scaffolds and implants' strength, biocompatibility, and biodegradability. Polymer biodegradable implants also improve the quality of life, particularly for an aging society, by eliminating the secondary surgery often needed to remove permanent implants and significantly reducing healthcare costs [77].

3.5.3 Ceramic matrix composites

Despite the use of bioceramics like alumina, hydroxyapatite (HAp), beta-tricalcium phosphate (b-TCP), and calcium sulfate in 3D printing for human tissue replacement and regeneration, these materials have inherent limitations. Examples include poor osteoconductivity in the case of alumina, brittleness, and low mechanical strength. However, these drawbacks can be addressed by combining bioceramics with a compatible secondary component. Studies have indicated that the addition of a small amount of magnesium (Mg) can enhance the mechanical properties of calcium silicate. By substituting 6–10 mol. % of calcium in calcium silicate with Mg, optimal mechanical properties matching the requirements of load-bearing bones can be achieved [149]. Composite scaffolds of Mg-calcium silicate, fabricated through robocasting, have exhibited mechanical strength comparable to that of natural bone [150]. To further improve the bone regeneration capacity without compromising mechanical strength, tricalcium phosphate (TCP) can be added to the Mg-calcium silicate composite [149]. In addition, other materials such as SiO_2/ZnO and pearl have been incorporated into bioceramics to enhance their performance. Trace elements like Si and Zn, which are naturally present in bone, promote both osteogenesis and angiogenesis. The inclusion of SiO_2 and ZnO can confer osteoinductive properties to calcium phosphates. Moreover, calcium sulfate scaffolds incorporating pearl, fabricated via 3D printing, have demonstrated improved compressive strength and osteogenic properties [151].

4 Applications of 3D printing in biomedical

Researchers have recently become interested in the use of 3D printing in biomedical applications, and numerous businesses all over the world have aided in this development with their research facilities and lab work. Due to the capability of manufacturing the optimal product in accordance with patient-specific requirements, this technology offers substantial advantages for biomedical applications and devices. Biomedical uses include artificial kidneys, hearts, teeth, knee prostheses, lenses, pacemakers, and hips, among others. For these medical applications, printing enables customized implant shapes and on-demand production, which can lead to a significant reduction in cost and stock. Due to its various benefits, this technology is increasingly being used in biological applications. It is utilized in biological applications like tissue engineering and implants, drug transport, early diagnosis instruments, and others.

4.1 Tissue engineering

Tissue engineering is a multidisciplinary field that encompasses life sciences, engineering, and clinical medicine [152]. It offers promising solutions to challenging medical issues related to tissue and organ loss by developing biological substitutes that can restore, maintain, and enhance tissue and organ functions. Since the late 1980s, researchers have extensively explored tissue engineering strategies and technologies to provide effective therapies for repairing various human tissues (e.g., skin, bone, cartilage, muscle, tendon, and ligament) and restoring organs (e.g., heart, kidney, and liver) [153, 154].

One significant area within tissue engineering focuses on the application of advanced manufacturing technologies like microfabrication, microfluidics, and 3D printing [155, 156]. The use of 3D printing in tissue engineering has gained considerable attention and is currently a prominent area of research and design. 3D printing enables precise and comprehensive control over the fabrication of artificial tissue and organ substitutes by leveraging computer-based medical imaging technologies such as CT and MRI, well-established computer-aided design and computer-aided manufacturing (CAD/CAM) techniques, and both established and emerging 3D printing technologies.

Extrusion printing has been used extensively for musculoskeletal tissue applications in addition to conventional multilayer scaffolds. In a recent instance, Kundu et al. produced biodegradable PCL-alginate scaffolds for tissue-engineered cartilage using a multi-head method [157]. Both chondrocytes and TGF- were successfully patterned into the scaffolds in the study, improving cartilage production in vivo and maintaining bioactivity. Another instance involved the development by Zopf et al. of a patient-specific resorbable PCL-based airway splint for implantation in a newborn with tracheobronchomalacia, a soft tissue disorder that can cause the walls of the airways to collapse or narrow [158]. After a year of follow-up, the patient had started to replace the construct with native tissue and no issues had shown up.

4.1.1 Orthopedic implants

With the rise of three-dimensional (3D) printing, various aspects of medicine are being influenced, and novel techniques and applications are being integrated into clinical processes. Notably, the technology of 3D printing enables personalized patient care by producing surgical guides, anatomical models tailored to individual patients, and practice models for simulation purposes [159]. One of the main benefits of 3D-printed orthopedic implants is personalization. Each patient's anatomy is unique, and 3D printing enables the design and production of implants tailored precisely to an individual's specific needs. This customization results in a better fit, reduced risk of complications, and improved overall patient outcomes. Moreover, 3D printing allows for complex geometries that were previously difficult or impossible to achieve with conventional manufacturing techniques. This flexibility enables the creation of implants with intricate internal structures, such as lattice-like designs, which can promote bone ingrowth and enhance implant stability. Additionally, another significant advantage of 3D-printed orthopedic implants is the ability to use biocompatible materials, including titanium and various biodegradable polymers. These materials have excellent mechanical properties and compatibility with the human body, ensuring that the implants are durable and well-tolerated by the patient's tissues [160–162]. 3D printing facilitates rapid prototyping, allowing orthopedic surgeons to create and evaluate implant designs before final production. This iterative process ensures that the implant's fit and functionality are optimized before it is implanted in the patient, leading to better surgical outcomes [160].

One intriguing and potentially groundbreaking use of 3DP in orthopedics is the development of patient-specific implantable devices [163]. Customized 3D-printed titanium plates have been utilized to improve physical function and knee flexion. The scope of applications extends beyond traditional structures like plates and screws, as researchers are increasingly exploring their use in more complex scenarios. Researchers are exploring filaments that are printable and have the potential to be used as composite biomaterials for 3D-printed bone implants [164]. Illustrative instances comprise the development of personalized knee arthroplasty implants that closely mirror the patient's natural knee or tailored spinal implants and implant guides designed for pediatric spine patients, as shown in Fig. 5a, b, respectively.

While patient-specific implants hold significant potential, it is important to acknowledge certain limitations, such as prolonged postprocessing time, cost, and limited material options. But as printer technology has advanced, printed materials have become more accurate and stable, necessitating less postprocessing overall. Even though

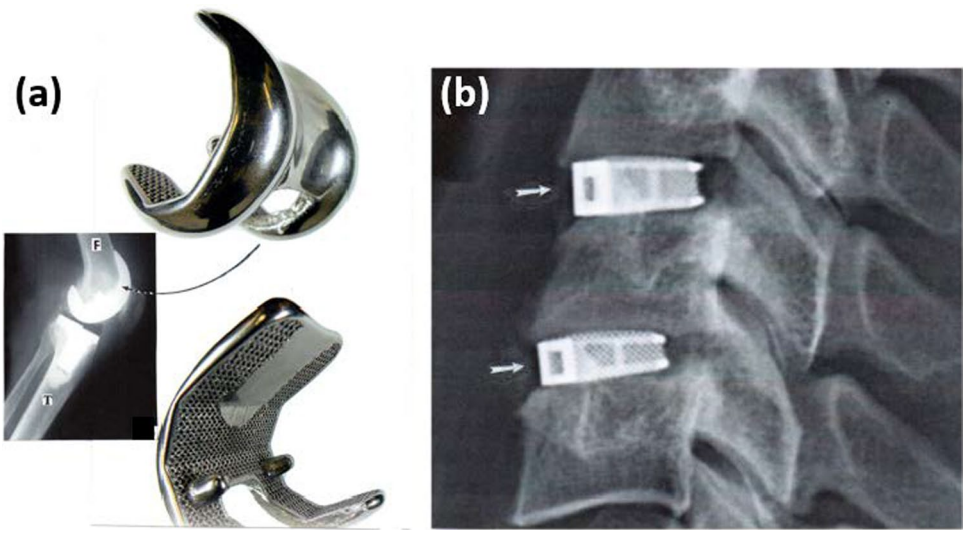


Fig. 5 **a** 3D printed Co–Cr–Mo alloy femoral mesh appliance as a component in total knee arthroplasty with the knee X-ray image reproduce with permission from [165] and **b** X-ray image for customized 3D printed Ti-6Al-4V spinal mesh inserts (support cages) (arrow) implanted in a patient's spine (https://3dprintingindustry.com/news/eit-3d-printed-titanium-cage-portfolio-receives-fda-approval-118555/)

certain 3D printers still have significant upfront costs, cost savings from things like shorter operating room times make them a viable option [87]. The ability of 3D printers to use a variety of materials, such as metal or metal alloy powders, concrete cements, composites, polymers, and bioinks, has been significantly improved. The use of 3D printing (3DP) in orthopedic surgery is probably going to increase as logistical and financial constraints get better. Furthermore, the advancement of bioresorbable materials holds promise because it does away with the requirement for implants inside the bodies of patients [166].

4.1.2 Skin

The skin is the largest organ in the human body, composed of three layers: epidermis, dermis, and hypodermis. It has essential functions in maintaining temperature, fluid balance, pathogen protection, and other physiological processes. Skin injuries like wounds and burns can impair its functions and necessitate the replacement of damaged skin using grafts or substitutes. Three-dimensional (3D) printing offers advantages over traditional grafting methods by enabling the production of adaptable, readily available, and personalized artificial skin or skin substitutes.

Scientists have employed 3D printing to create skin substitutes that replicate the structure and components of natural skin. Hydrogels, especially collagen, are commonly used as the framework for 3D printed skin tissue engineering. Keratinocytes and fibroblasts can be incorporated into the epidermis and dermis, respectively. Researchers have also explored vasculature and hypodermis in 3D printed skin models. These constructs have demonstrated promising similarities in terms of morphology and biological characteristics to real human skin tissue.

Various techniques have been utilized in 3D printing skin substitutes, such as laser-assisted bioprinting and the use of bioinks containing collagen, gelatin, fibrinogen, and cells. The incorporation of growth factors, such as fibroblast growth factor 2 (FGF-2), has been investigated to enhance the growth of the epidermis and the formation of new blood vessels in the dermis. Additionally, researchers have investigated the use of stem cell-encapsulated hydrogels for skin repair, showing faster wound closure and improved angiogenesis compared to conventional gel treatments.

The optimal bioink formulation must meet specific criteria related to both material and biological aspects. Material properties include printability, mechanics, degradation, and functionalizability. Biological requirements focus on biocompatibility, cytocompatibility, and bioactivity. Among material properties, printability is identified as the most crucial parameter, comprising the processability of the bioink formulation and print fidelity associated with the mechanical strength required for the printed construct to maintain a 3D structure post-printing [167].

Depending on the printing method, achieving printability may involve considerations such as solution viscosity, surface tension, and cross-linking properties. Viscosity plays a significant role as it affects both print fidelity and cell encapsulation efficiency. High-viscosity polymer solutions, while maintaining the printed structure's shape for an extended period post-printing, require higher pressures for flow, limiting gauge size and the smallest achievable print size, particularly in Direct Ink Writing (DIW). For example, Tirella et al. investigated alginate hydrogels using pressure-assisted microfabrication (DIW technique), successfully creating a 3D phase diagram depicting the interplay between bioink viscosity, print velocity, and applied pressure to achieve high print fidelity [168].

An ideal bioink formulation should have tunable viscosity to accommodate various bioprinters. For instance, bioinks for inkjet or droplet-based bioprinters typically have viscosity values around 10 mPa·s, while viscosity for extrusion-based DIW bioprinting ranges from 30 to 6×107 mPa·s. Laser-assisted bioprinting bioinks generally exhibit viscosity in the range of 1–300 mPa·s. In extrusion and droplet-based printing with high-viscosity bioinks, a shear-thinning characteristic is desirable to counteract the high shear stress associated with elevated viscosity [169, 170].

Overall mechanics, especially achievable stiffness, are crucial not only for constructing self-supporting constructs but also for controlling and directing cellular behavior. Degradation is essential for the functional integration of the printed construct in vivo, allowing cells to gradually replace the construct with their extracellular matrix (ECM). Both the bioink and its degradation products should lack materials that induce inflammatory host responses when implanted. Functionalizability is necessary to incorporate biochemical cues, i.e., bioactivity, guiding cellular behavior such as adhesion, migration, and differentiation.

In addition to biocompatibility and cytocompatibility, maintaining high cell viability, both before and after printing, is critical for the ink formulation. Notably, a recent study highlighted the importance of the print substrate

for live cell inkjet printing. Computational and experimental studies indicated that the print substrate's stiffness directly influences the impact forces on the droplet, thereby affecting overall cell survival.

The current state-of-the-art in bioprinted skin has made significant strides in replicating the complex structure and function of native human skin. Here's a discussion on each aspect:

4.1.3 Skin pigmentation and hair follicles

Bioprinting technologies have advanced to include methods for incorporating melanocytes, the cells responsible for skin pigmentation, into printed skin constructs. Researchers have achieved success in mimicking the coloration of human skin through precise deposition of melanocytes within the dermal layers of bioprinted skin [171]. However, achieving natural skin coloration and uniformity remains a challenge, as it involves replicating the intricate spatial distribution and functionality of melanocytes across different skin types and ethnicities. Integrating functional hair follicles into bioprinted skin remains a significant hurdle. While early research has demonstrated the feasibility of printing dermal papilla cells and keratinocytes in close proximity to simulate hair follicle structures, the challenge lies in inducing proper hair growth and cycling within these constructs. Recent advancements in bioprinting techniques aim to incorporate mesenchymal stem cells and growth factors to support follicle formation and hair regeneration, but achieving fully functional and aesthetically pleasing hair growth remains an active area of research [172]. Bioprinted skin models have also progressed towards incorporating sweat gland structures. Sweat glands play a crucial role in thermoregulation and skin hydration. Researchers have developed methods to print sweat gland precursor cells and epithelial cells within the dermal layers, aiming to recreate functional glandular structures capable of secreting sweat. However, achieving the spatial organization and physiological response of native sweat glands remains challenging, particularly in regulating sweat composition and secretion rates.

Despite the advancements in 3D printing technology for skin tissue engineering, there are considerations regarding prolonged postprocessing time, cost, and limited material choices. Nonetheless, advancements in printer technology, reduced postprocessing requirements, and the availability of a wider range of materials, including bioresorbable materials, are making 3D printing increasingly viable for skin surgery.

4.2 Organ printing and cancer treatment

3D printing is revolutionizing both organ printing and cancer treatment through its innovative applications in personalized medicine, tissue engineering, and surgical planning. 3D printing facilitates the creation of scaffolds that mimic the extracellular matrix, supporting cell growth and tissue formation. This technology also enables bioprinting, where living cells and biomaterials are printed layer by layer to construct tissue-like structures, including skin, cartilage, and early-stage organ constructs. Personalized implants are another significant advancement, allowing for custom-made implants and prosthetics tailored to a patient's specific anatomy, thereby improving integration and functionality. Additionally, 3D-printed organ prototypes help researchers study organ functions and test medical procedures, with the ultimate goal of creating fully functional organs for transplantation [173].

In cancer treatment, 3D printing enhances personalized medicine by producing patient-specific tumor models based on medical imaging data. These models facilitate personalized treatment planning and testing of surgical techniques. Customized drug delivery systems, created through 3D printing, can release chemotherapeutic agents directly at the tumor site, minimizing side effects and improving efficacy. For surgical planning and training, 3D-printed models of tumors and surrounding tissues allow surgeons to visualize and practice complex procedures, thereby reducing risks during actual surgeries [174, 175]. Customized radiation shields and molds produced through 3D printing protect healthy tissue during radiation therapy by ensuring precise radiation dose delivery to the tumor. Furthermore, in the field of immunotherapy, researchers are exploring 3D-printed scaffolds that enhance the activation and proliferation of immune cells, potentially improving the effectiveness of immunotherapy treatments [175].

4.3 Drugs delivery

Drug delivery involves various methods, technologies, and formulations to administer pharmaceutical compounds safely for therapeutic purposes. It has expanded to include bioactive molecules and genes, focusing on targeted-release and controlled drug delivery systems tailored to individual patients [176, 177]. 3D printing is a promising technique for

controlled drug release, offering advantages such as precise distribution of active ingredients, minimal drug consumption, complex release patterns, reduced waste, and efficient production of customized drug delivery systems [178].

The use of 3D printing in developing drug delivery systems brings several benefits. Factors like drug encapsulation strategies, biomaterial properties, and system design influence the drug release behavior of 3D printed structures. By adjusting these factors, customized drug release profiles can be achieved for specific therapeutic goals [179]. For instance, researchers successfully created vancomycin-loaded porous scaffolds by printing gelatin and Si-doped HAp, effectively inhibiting bacterial growth. System design also influences drug release, as demonstrated by oral dual drug delivery devices fabricated with 3D printing. 3D printed drug delivery systems hold promise in cancer treatment as well. For example, PLGA scaffolds loaded with specific drugs showed sustained release for 30 days and inhibited tumor growth in orthotopic breast tumor mouse models.

In 2015, Melocchi et al. pioneered the production of the initial 3D-printed capsular devices. The process involved the creation of filaments containing hydroxypropyl cellulose through hot-melt extrusion, followed by the 3D printing of these filaments. The resulting capsules were designed for oral pulsatile drug release, exhibiting swellable and erodible characteristics [180]. Capsules were manufactured using fused deposition modeling and inkjet printing, employing diverse polymer formulations. Each capsule comprised three parts: two hollow sections with a cylindrical closed end and a rounded open end, and a central part serving as both a joint and a partition. The hollow parts varied in geometry and wall thickness. The capsules were then filled with model Active Pharmaceutical Ingredients (APIs). The outcomes demonstrated the device's efficacy in successfully releasing the model APIs in pulsatile fashion within a 2-h timeframe [181].

In summary, 3D printing offers a valuable approach for advanced drug delivery systems, enabling precise control of drug distribution, reducing drug consumption, supporting complex release patterns, and customization for individual patients. This technology has significant potential to improve therapeutic outcomes and address the needs of the pharmaceutical industry.

4.4 Early diagnosis tools

The timely detection of diseases enables the selection of appropriate treatment methods and prevents issues like drug resistance. It also plays a crucial role in disease treatment by preventing the spread of diseases and even pandemics in some cases. Effective diagnoses, particularly in bacterial infections, can help avoid the overuse of antibiotics and render such treatments ineffective against infections [182]. A further step in 3D printing is the creation of functional devices that has led to advancements in diagnostic platforms. Diagnostic applications often involve complex and high-performing analytical devices that typically require advanced laboratory settings and skilled technical personnel to operate the equipment. Additionally, samples are often transported to centralized laboratory facilities, hindering real-time monitoring of crucial metabolic and diagnostic information on-site [183]. However, the development of cost-effective and dependable diagnostic platforms through 3D printing enables the simplification and acceleration of these diagnostic tools. This allows for streamlined and efficient diagnostic processes, eliminating the need for extensive laboratory facilities and facilitating on-site monitoring of essential information. 3D printing approaches have made it possible to develop sensors and sensor arrays with high sensitivity in a shorter timeframe [184]. Dentistry, among other fields, has also embraced 3D printing technology to simplify the diagnosis process by creating complex structures that closely resemble real-life dimensions, which is not achievable through other methods [185]. Similarly, 3D printed sensors are in common use for early diagnosis using biological fluid (e.g., blood, urine, saliva, sweat, and tears) [186]. Cao et al. utilized post-modified 3D printed sensor for dopamine analysis using fast-scan cyclic voltammetry following stimulation in the brain of an adult fly [187]. These remarkable electrochemical sensors exhibited consistent and reliable detection of stimulated dopamine within the range of 10 to 50 μM. In order to create a paper-based analytical instrument that can detect the presence of glucose in urine, Zhang et al. presented a novel method. On Whatman chromatography filter paper used in their investigation, the researchers used wax printing to produce a hydrophobic barrier. They then used inkjet printing to successively implant the enzymes horseradish peroxidase (HRP) and glucose oxidase (GOx). These enzymes were essential in enabling the reaction between the chromogenic substrates and glucose. The HRP catalyst helped the interaction between glucose and the chromogenic substrate, which in turn caused a significant color change when urine samples with various glucose concentrations were applied to the printed portions [188]. Similar to this,

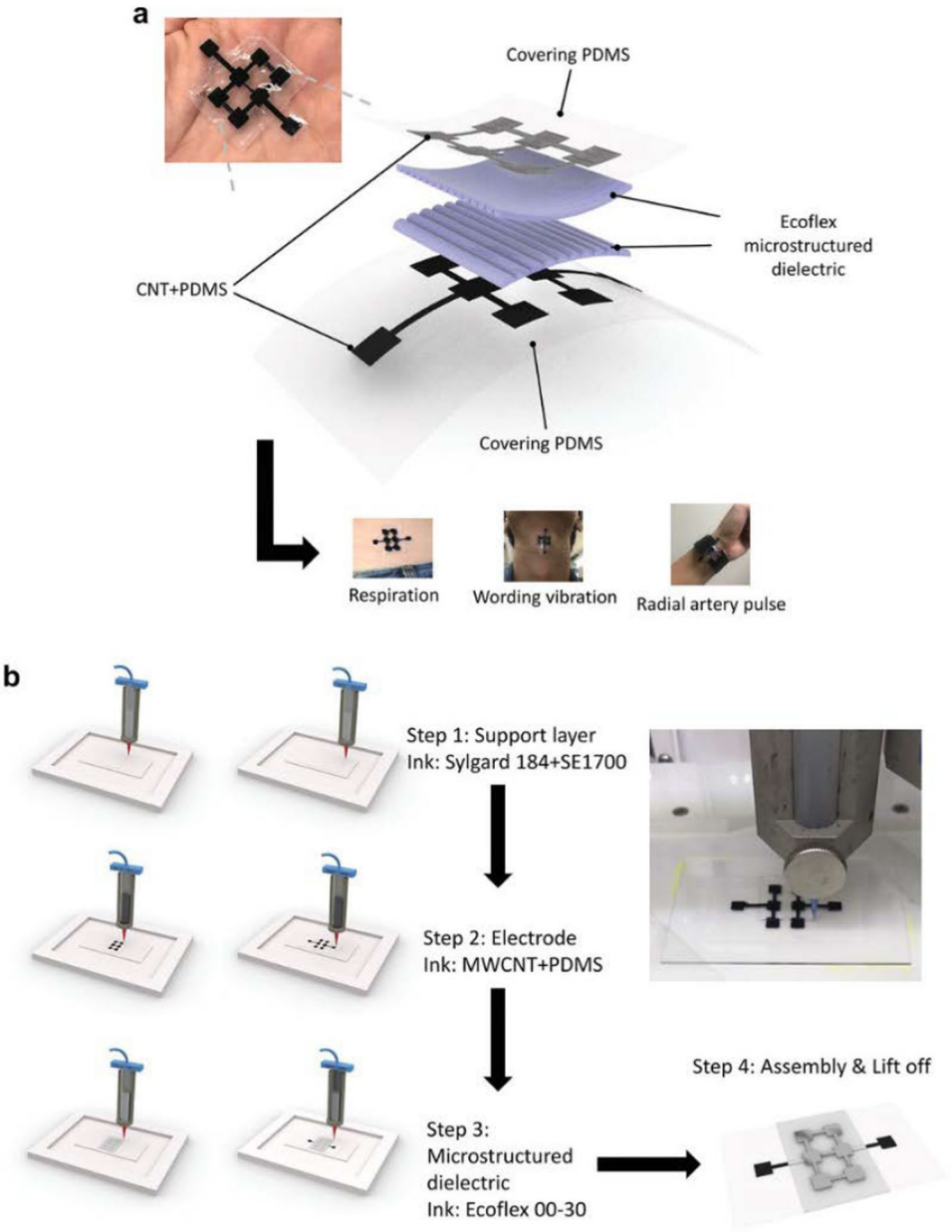


Fig. 6 Description and process of multimaterial all-3D-printed nanocomposite-based (M2A3DNC) flexible wearable pressure sensors: **a** an image and diagram illustrating the M2A3DNC pressure sensor designed for monitoring multiple physiological signals, showcasing its exploded view. **b** A diagram demonstrating the step-by-step 3D printing process for creating the M2A3DNC sensor's multilayered structure. Step 1 involves directly printing the PDMS supporting layer, followed by step 2, which entails the direct printing of the conductive layer composed of multi-walled carbon nanotube (MWCNT) mixed with PDMS. Step 3 involves the direct printing of the microstructured dielectric made from Ecoflex 00-30, and finally, step 4 covers the assembly of two capacitor pieces, which are detached by dissolving the precoated PVA layer in a hot water bath. An additional inset shows an optical image of the 3D printing process for the hemicylinder patterned Ecoflex 00-30 dielectric layer [189]

Malekghasemi et al. created microfluidic paper-based analytical devices (μPADs) by combining 3D printing and microwave irradiation techniques which are easy-to-use, faster, and cost-effective with longer shelf life.

Yi et al. [189] developed a groundbreaking innovative wearable pressure sensor referred to as the Multimaterial and Multilayer All-3D-Printed Nanocomposite-Based (M2A3DNC) micro-engineered sensor. This flexible, hybrid, and soft sensor was designed to record various physiological signals with exceptional sensitivity, enabling real-time monitoring of human health. The sensor's structure and functionalities are depicted in Fig. 6.

5 Optimization of 3D printing process for biomedical applications

There are several challenges in bringing additive manufacturing processes to be fully implemented for biomedical applications that need to be addressed to ensure reliable and high-quality production. Some of the key challenges include:

5.1 Materials selection

When considering materials for 3D printing in biomedical applications, several important properties are prioritized. These properties ensure that the materials are safe, functional, and compatible with biological systems. Although there are a wide variety of materials that can be utilized in 3D printing, the range of available materials is still somewhat limited compared to traditional manufacturing methods. Biocompatibility, mechanical properties, sterilizability, and regulatory compliance are critical considerations. Limited availability of biocompatible materials with suitable properties and processability can be a challenge. This may restrict the usefulness and design potential of 3D-printed medical equipment. Figure shows some of the important properties of biomedical materials for 3D printing.

In biomedical applications, the properties of 3D printed materials play a vital role. Biocompatibility is essential, as the material must not cause any adverse reactions or toxicity when in contact with living tissues or bodily fluids. This property is particularly crucial for implants, prosthetics, and tissue engineering scaffolds. Additionally, sterilizability is important to ensure that the material can withstand common sterilization methods, such as autoclaving, gamma irradiation, or ethylene oxide gas sterilization. Proper sterilization eliminates bacteria, viruses, and other microorganisms, ensuring the safety of the printed biomedical devices or implants for clinical use. Printability is another key property that the material must possess. It should have suitable rheological properties, allowing it to be extruded, deposited, or cured layer-by-layer during the 3D printing process. Factors like viscosity, flowability, and solidification behavior influence printability and affect the material's ability to form precise and accurate structures. Mechanical strength and stability are crucial properties, especially for load-bearing applications like bone implants or prosthetics. The material should exhibit sufficient strength and stability to withstand the physiological conditions and loads it will encounter within the body.

If the application requires temporary implants, tissue scaffolds, or drug delivery systems, the material should be designed to degrade over time in a controlled manner. Degradability enables the gradual absorption of the material by the body as new tissue forms, reducing the need for surgical removal. In some cases, materials with bioactive properties

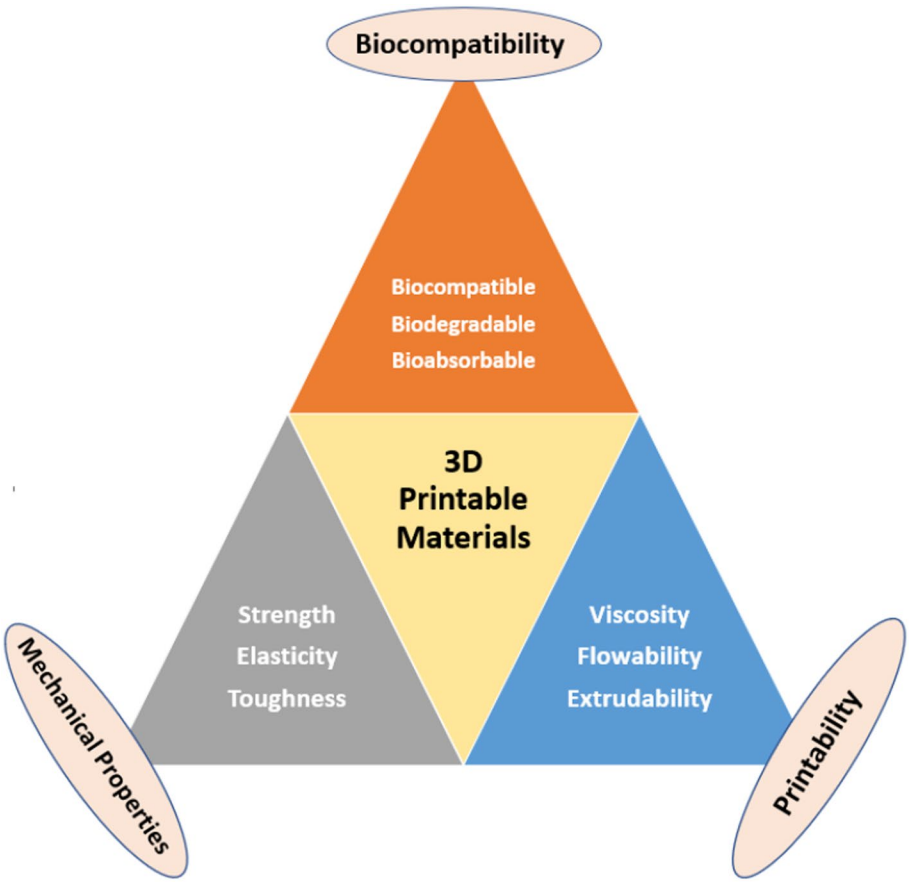


Fig. 7 Material consideration for 3D printing in biomedical applications

are desirable. These materials can interact with biological systems, promote cell adhesion, proliferation, and tissue regeneration. Bioactive materials find applications in tissue engineering and regenerative medicine.

Furthermore, materials used in 3D printing for biomedical applications must meet regulatory requirements and have appropriate approvals from organizations such as the FDA. Compliance with safety and quality standards is crucial to ensure patient safety. Figure 7 depicts the material considerations that have to be taken in 3D printing for biomedical applications.

It's important to consider that no single material can meet all the requirements for every biomedical application. Material selection, such as biocompatible polymers, bioceramics, or metal alloys, should be based on the specific application and intended use, considering a balance between the desired properties and the requirements of the biomedical application at hand.

5.2 Surface modification

Surface modification of the scaffolds play a vital role in many biomedical applications as the surface have a direct impact on cellular response and the subsequent regeneration of tissues [190]. A desirable tissue engineering scaffold should replicate the extracellular matrix (ECM) and promote favorable interactions with cells, including enhanced cell adhesion, growth, migration, and differentiated functionality. Although synthetic biodegradable polymers have been widely employed as scaffolding materials in tissue engineering, they often lack biological recognition. Incorporating composite materials, such as the growth of bone-like apatite on the pore surfaces of scaffolds as mentioned earlier, represents an effective approach to enhance cellular interactions. Usually, bulk or surface modification is employed for achieving good cell attachment and proliferation, and cell interaction. For bulk modification is achieved by either doping, copolymerization, composite making or functional group attachment before scaffold preparation. As a result of bulk modification not only the chemical but the mechanical property of the scaffold also changes which is not required in most of the cases [191]. In contrast to bulk modification, surface modification can be performed after scaffold fabrication. Consequently, mechanical properties and scaffold structure are not significantly affected [56]. The surface of 3D-printed components can be modified using different techniques, either to activate or passivate them, depending on the desired application.

5.2.1 Surface activation

Surface activation of 3D-printed components involves the application of functional materials through conjugation or deposition. These functional materials encompass biologically active molecules such as growth factors, antibodies,

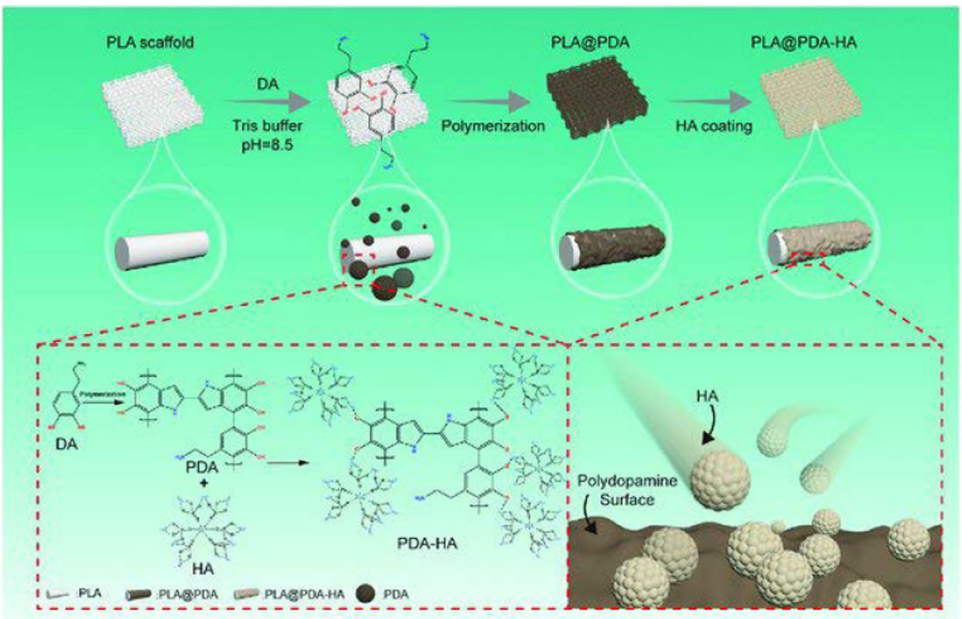


Fig. 8 Surface modification of 3D printed PLA scaffold [197]

peptides, nucleic acids, or their derivatives. Alternatively, a coating that is biocompatible or chemically active can be employed to facilitate interaction between the 3D-printed components and biological entities.

Surface activation techniques have been successfully employed in the field of 3D-printed tissue engineering scaffolds. Lee et al. utilized polydopamine chemistry to immobilize a growth factor called human bone morphogenic protein-2 (rhBMP-2) onto a 3D-printed polycaprolactone (PCL) scaffold, resulting in the promotion of osteogenic differentiation [192]. Yeh et al. immobilized an active compound extracted from the traditional Chinese medicine herb Xu Duan onto a 3D-printed PLA scaffold, leading to an upregulation of osteogenic and angiogenic markers in bone marrow stem cells [193]. Both studies utilized the strong adhesion properties of polydopamine, which exhibits a bio-inspired nature and can adhere to various surfaces [194]. The polydopamine coating contains hydroxyl and amine functional groups that enable the covalent conjugation of proteins and other active compounds. Additionally, polydopamine itself possesses biological activity. Kao et al. coated a PLA scaffold with polydopamine and observed enhanced cell adhesion and proliferation on the scaffold [195]. Polydopamine also exhibits sufficient reducing capability for electrodeless plating [194]. By immersing the 3D-printed components with a polydopamine coating in a solution containing gold salt, gold plating can be easily achieved, enabling biomolecular self-assembly through gold–thio interactions [196]. This process can be applied to metallize the 3D-printed components for built-in electrochemical sensing. Furthermore, polydopamine can facilitate the immobilization of a wide range of materials through a one-pot reaction, resulting in versatile chemical functionality. Due to its simple coating procedure and versatile capabilities, polydopamine represents an ideal technique for post-3D printing surface functionalization. Figure 8 depicts the surface modification process applied to three-dimensional 3Dprinted PLA scaffolds. Initially, the PLA scaffold was constructed using material extrusion-based 3D printing technology, resulting in a rectangular porous structure. Subsequently, a uniform coating of polydopamine (PDA) was applied to the surface of the PLA scaffolds. This was achieved by immersing the scaffolds in a dopamine solution (tris buffer, pH = 8.5) and simultaneously stirring them for 24 h, allowing the self-polymerization of dopamine (DA) particles to form PDA. In addition, nano-hydroxyapatite (nHA) particles were effectively immobilized onto the as-synthesized PDA coatings through the presence of catechol functional groups. Ultimately, the resulting PLA scaffolds were functionalized with nHA after the completion of the surface modification process [197].

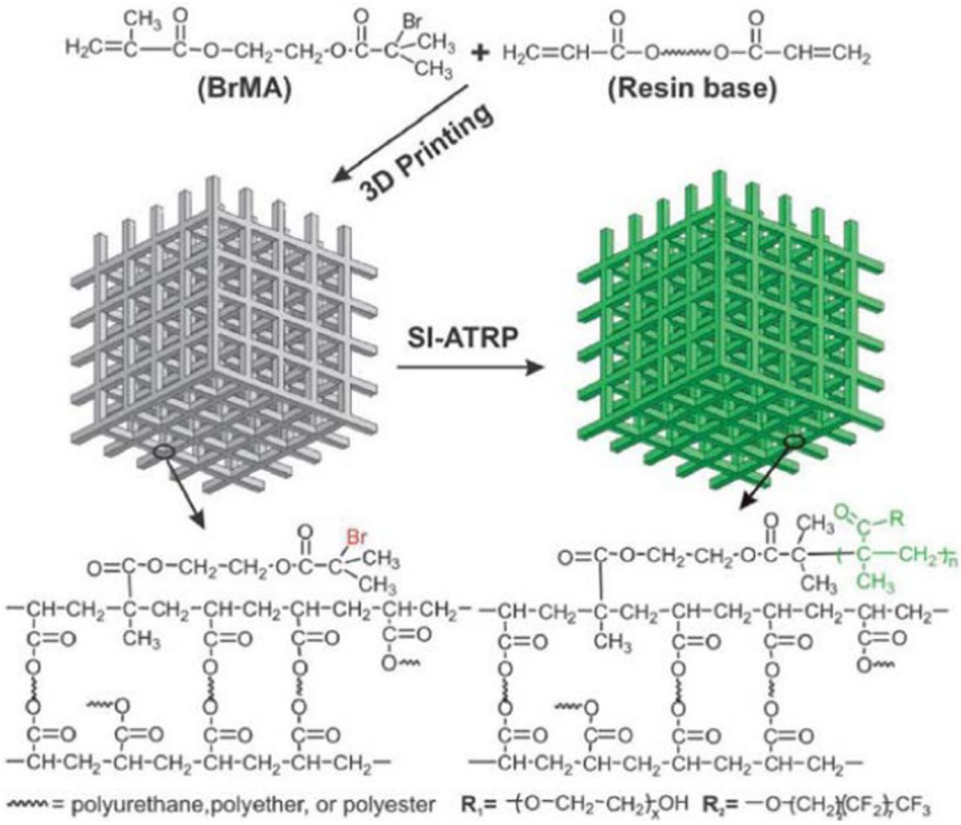


Fig. 9 Schematic illustration of initiator integrated functional groups on 3D-printed parts [201]

5.2.2 Surface passivation

The implants residing inside the human body face various problems, such as foreign body reactions, bacteria fouling, and protein fouling. Various techniques have been implemented to avoid these problems. For example, the use of polyethylene glycol (PEG) coating is an effective technique to prevent protein adsorption [108]. Similarly, for bacterial fouling prevention silver nanoparticles embedded polymer coating was used as an antimicrobial thin film. Certain resins commonly used in 3D printing, such as acrylate and its derivatives, have been identified as having cytotoxic properties and the potential to cause developmental malformations and other adverse effects. While the large-chain acrylate polymers that form the 3D-printed components are generally less toxic, there is still a notable presence of acrylate monomers and short-chain polymers within these components. These small molecules can potentially leach out and inflict damage on biological entities. Post-3D printing modification through UV curing can crosslink the small molecules, transforming them into long-chain polymers and thereby reducing the cytotoxicity of the 3D-printed components. Figure 9 gives a schematic illustration of initiator integrated functional groups on 3D-printed parts. In this approach, functional compounds are incorporated into the 3D-printable resin, allowing the functional groups to become available on the surface of the 3D-printed components. During the 3D-printing process, the functional compound becomes embedded in the final product. The authors of the study demonstrated the use of surface-initiated atom transfer radical polymerization for post-printing surface modification by incorporating Br-containing vinyl-terminated initiator [198]. If 3D-printable materials can be designed to carry carboxyl groups for carbodiimide coupling or other functional groups for the conjugation of proteins and biomolecules to the surface using well-established click chemistry [199], this technique could potentially offer a wide range of chemistry for surface modification of 3D-printed parts in a straightforward manner. However, further research is necessary to thoroughly investigate the biocompatibility of 3D-printable materials both before and after printing [200]. Additionally, exploring new methods to mitigate the toxicity of 3D-printed components should be a focus for future studies.

5.2.3 Sterilization

Sterilization is a crucial stage in the processing of any medical implant. Its primary objective is to completely eradicate all biological pathogens, such as bacteria, spores, viruses, and fungi, from the surface of the implant. This critical step significantly reduces the risk of infection associated with the implant. Various sterilization methods are available for orthopedic implants, each with its own advantages and disadvantages.

Ethylene oxide (EO) sterilization is a widely used method for orthopedic implants [202]. This process involves exposing the implant to EO gas in a low-temperature, low-pressure environment. EO gas is highly effective in eradicating microorganisms and can penetrate the porous structure of magnesium-based implants, ensuring thorough sterilization. However, EO sterilization has drawbacks. Residual EO may remain on the implant, leading to potential allergic reactions and other adverse effects. Additionally, EO sterilization requires a lengthy cycle time and can be costly.

Gamma irradiation is another commonly employed sterilization method [203]. It entails subjecting the implant to high-energy radiation, which damages the DNA of microorganisms and inhibits their growth. Gamma irradiation is effective in sterilizing a wide range of materials, including magnesium-based implants, and offers a short cycle time. Nevertheless, it has the drawback of potentially causing degradation in the material properties of the implant, such as reduced mechanical strength and compromised corrosion resistance, which may impact its long-term performance.

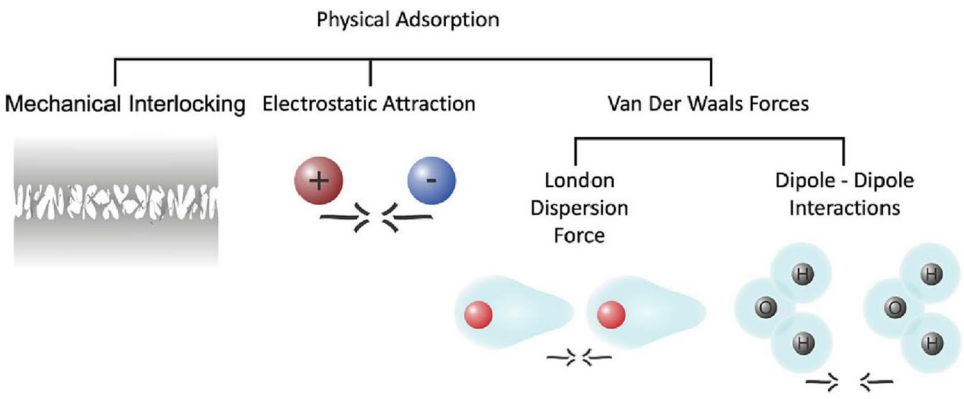


Fig. 10 Schematic illustration of the interactions involved in physisorption [204]

5.2.4 Physical adsorption

Physical adsorption, also known as physisorption, offers a straightforward approach to attaching biomolecules onto 3D printed structures. Physisorption involves immobilizing molecules onto solid surfaces through mechanical interlocking and relatively weak physical binding forces, without involving chemical reactions as represented in Fig. 10. These weak physical interactions encompass various forces, including electrostatic attraction, hydrogen bonding, hydrophobic interactions, and Van der Waals forces [151–153]. Biomolecules can be physisorbed by exposing the surface to a solution containing the biomolecules or by incorporating the biomolecules into the bulk material used to create the structure. The advantage of physisorption lies in the relatively weak nature of these interactions, which makes it particularly suitable for applications involving drug release.

Physisorption strength relies on several factors, including surface roughness, electrostatic attraction, and Van der Waals forces. Electrostatic attraction becomes more robust as the charge and proximity between oppositely charged ions and molecules increase. Van der Waals forces, including London Dispersion and Dipole–Dipole interactions, exhibit greater strength when there is a larger electronegativity difference between atoms in a molecule. Hydrogen bonds represent the most robust example of dipole–dipole interactions, forming when hydrogen atoms bond with atoms possessing high electron affinities. Hydrophobic interactions occur when polar and nonpolar components of surfaces adjust their shape to minimize exposure to the polar aqueous phase. This phenomenon, referred to as the "hydrophobic force," can result in a strong physical attachment between the hydrophobic regions of a molecule and a hydrophobic surface. In general, the strength of physisorption depends on the bond types and the number of bonds formed, with a higher strength associated with stronger bond types and a greater quantity of bonds.

6 Challenges, and future directions

A key concern revolves around enhancing current 3D printing methods and potentially developing novel techniques specifically designed for biomedical engineering applications. Currently, numerous existing 3D printing technologies possess drawbacks such as slow printing speeds, restricted resolution, complicated modeling processes, limited portability, and high costs. It is essential to improve and overcome limitations in existing 3D printing technologies. Figure 11 lists the major challenges that still need to be addressed in this domain. A major issue is the slow printing speed, which hinders its use in emergency surgeries and large-scale production during medical crises and emergency situations. However, speeding up the process can result in reduced resolution, increased heat generation, and complications with multi-material printing. Recent endeavors to enhance speed involve techniques like using a loop flow system for cooling and employing a rotating tube with evolving light patterns. Nevertheless, concerns persist regarding the use of potentially harmful substances and the need to demonstrate successful fabrication of large objects.

Another significant challenge is achieving higher printing resolution, currently limited to the micrometer scale in biomedical engineering. Advancements in light sources and nozzle sizes are necessary to attain nanoscale resolution. Additionally, the complex and time-consuming process of designing 3D virtual models using CAD software presents difficulties for medical professionals. To improve efficiency and clinical outcomes, it is important to develop user-friendly modeling environments and provide biomedical engineering education to medical professionals.

The size, weight, and cost of 3D printers, particularly bioprinters, restrict their broad implementation in biomedical applications. While portable and affordable FDM printers are commonly used, they have inherent limitations. Overcoming these limitations and reducing the size and cost of various types of 3D printers, including bioprinters, pose significant challenges that require advancements in diverse disciplines such as computer science, control and automation, and mechanical engineering. Emphasizing the design and development of dedicated bioprinters from the start is crucial to

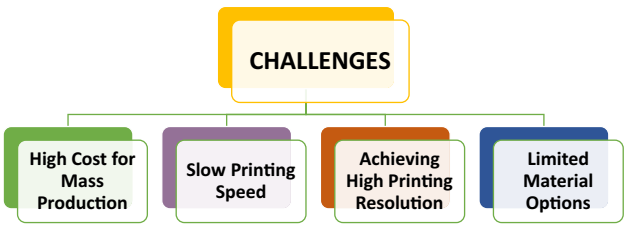


Fig. 11 Challenges in 3D printing for biomedical applications

Table 4 Comparison of different 3D printing methods, their pros and cons as well as the limitations for biomedical applications

3D printing method	Pros	Cons	Limitations for biomedical applications	Ref.
Fused deposition modeling (FDM)	– Cost-effective – Wide range of materials – Simple to operate – Good for prototyping	– Limited resolution and surface finish – Not suitable for high-temperature or bio-compatible materials	Limited suitability for creating complex and intricately detailed biomedical implants due to lower resolution and surface finish	[205]
Stereolithography (SLA)	– High resolution – Smooth surface finish – Wide range of materials	– Expensive equipment and materials – Limited build size – Post-processing required for some materials	Limitation in size of printed objects may restrict the production of larger biomedical implants or structures	[19]
Selective laser sintering (SLS)	– High resolution – No support structures required – Wide range of materials	– Expensive equipment and materials – Limited surface finish – Not suitable for bio-compatible materials requiring post-processing	Limited surface finish may necessitate additional post-processing for biomedical applications requiring smooth surfaces	[206]
Electron beam melting (EBM)	– High precision – Excellent material properties – Good for complex geometries	– Expensive equipment – Limited material choices – Not suitable for small-scale production	Limited availability of materials may restrict the diversity of applications in biomedical settings	[207]
Material jetting	– High resolution – Multi-material printing – Smooth surface finish	– Expensive equipment and materials – Limited build size – Support structures may be required	Limitation in build size may restrict the production of larger biomedical implants or structures	[208]
Direct metal laser sintering (DMLS)	– High precision – Excellent material properties – Suitable for metal alloys – No post-curing required	– Expensive equipment and materials – Limited build size – Surface roughness may require post-processing	Limitation in size of printed objects may restrict the production of larger biomedical implants or structures	[209]

meet the demanding requirements of bioprinting. Such efforts can benefit the research community and enable clinical applications of bio-printed products.

Different 3D printing methods offer various advantages and drawbacks for biomedical applications. Fused Deposition Modeling (FDM) is cost-effective and versatile but lacks resolution for intricate designs [205]. Stereolithography (SLA) provides high resolution and smooth surface finish but is costly and limited in build size [19]. Selective Laser Sintering (SLS) offers good resolution and material variety but may require post-processing for surface finish [206]. Electron Beam Melting (EBM) offers high precision but limited material choices and scalability [207]. Material Jetting provides high resolution and multi-material capabilities but is expensive and limited in build size [208]. Direct Metal Laser Sintering (DMLS) offers high precision and material properties suitable for metal alloys but is costly and may require post-processing [209]. Each method presents specific limitations such as size constraints, material availability, and surface finish requirements that impact their suitability for biomedical applications. Below is a table comparing the pros and cons of different 3D printing methods, as well as the limitations of each method for biomedical applications (Table 4).

There are numerous challenges hindering the further expansion of medical applications, including issues with insurance, medical device authorization, and the absence of standardized technology. Regulatory bodies in many countries have published various technical specifications and guidelines to address medical device authorization. The Korean Ministry of Food and Drug Safety (MFDS) has issued comprehensive technical specifications, guidelines, and regulations for the approval of 3D-printed medical devices, covering areas like orthopedics, dentistry, and bio-printing. These regulations ensure that 3D-printed devices meet the same safety and performance standards as traditional medical devices. Manufacturers must submit detailed applications including design, material, usage, and safety data to obtain authorization. The MFDS also requires adherence to ISO 13485-compliant quality management systems and recently published good manufacturing practices (GMP) regulations, addressing medical image data processing, design, manufacturing, post-processing, testing, and quality control. Similarly, the US FDA provided guidance in 2017 on technical considerations for additive manufacturing, focusing on design, manufacturing, and device testing [210].

Similarly, the integration of machine learning (ML) with advanced additive manufacturing (AM) holds significant promise for revolutionizing the biomedical industry. Machine learning techniques enhance various aspects of additive manufacturing processes, from design optimization and process control to quality assurance and predictive maintenance. When integrated with additive manufacturing (AM), machine learning (ML) creates new opportunities to improve the entire manufacturing workflow, including material formulation, design, process optimization, and quality control [211]. The combination of ML and AM has the potential to transform how AM-printed components are designed and produced. By utilizing the extensive data generated during the process, ML algorithms can provide valuable insights that lead to better design optimization, accurate material property predictions, and enhanced production quality. Modern additive manufacturing techniques can produce complex, multi-scale, multi-material, and multi-functional products that are challenging to create with conventional methods. However, there are still challenges in aligning theoretical design expectations with practical manufacturing capabilities. Recent research has focused on addressing these challenges using traditional optimization and simulation approaches. This review explores advanced algorithms in additive manufacturing and suggests potential applications leveraging cutting-edge artificial intelligence techniques [212].

7 Conclusion

Three-dimensional (3D) printing has undeniably revolutionized biomedical engineering over the past two decades, offering substantial benefits in the creation of tailored biomedical products with high precision, efficiency, and cost-effectiveness. However, the current state of 3D printing still faces significant hurdles that need to be addressed to fully realize its potential in producing high-quality biomedical goods. Critical challenges remain in optimizing 3D printing processes, materials, and applications to meet the intricate demands of the biomedical field. Addressing these challenges requires an interdisciplinary approach, integrating advancements from physics, materials science, engineering, biological sciences, and medicine. This review comprehensively examines these issues, highlighting the existing difficulties and proposing future research directions. While 3D printing holds great promise for generating a broad spectrum of beneficial biological products, ongoing research and development are essential to overcome current limitations and enhance its application in biomedical engineering.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate This study does not contain any studies with human or animal subjects performed by any of the authors.

Competing interests The authors declare no competing interests.

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