

Recent trends and advances in 3d printing for biomedical applications

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ABSTRACT

3D printing has revolutionized the technological field with its rapid growth and broad popularity throughout the globe. It is one of the most sought out techniques being used because of the speed and development it offers in production, customization features, and numerous diverse opportunities it provides in every field. It has found applications in fields ranging from automobiles to the architecture industry. It has also seen tremendous growth in the medical field in recent years, but the growth hasn't been significant as in other fields due to the limitations in the use of materials it can be integrated with. This review article provides the current scenario of 3d printing in medical fields, such as the bioprinting of tissues and the integration of nanotechnology in 3d-printing of biomaterials. Though the article focuses on tissue engineering, it also sheds light on the various 3d printing methods outlining how different forms of 3d printing techniques are contributing to the medical field. Various materials which have been used as biomaterials has also been discussed along with their usages and contribution in different 3d printing techniques and their respective advantages and disadvantages. Along with the industry trends and advantages of 3d printing in the medical field, this review article also discusses the limitations and potential threats of this technology.

Keywords: 3D printing; additive manufacturing; biomaterials; nanotechnology; tissue engineering; scaffold.

1. INTRODUCTION

The process of fabricating a 3-Dimensional body of an object through a digital file is 3-D printing [1]. Computer-based design software, termed as CAD (computer-aided design) such as Solidworks, ZBrush, and AutoCAD are used for designing 3-D digital copies of the required object for commercial as well as industrial needs. Other than the commercialized design software, 3-D design models are also created at cost-free platforms such as FreeCAD, Meshmixer, and SketchUp [2].

The most prominent feature of 3-Dimensional printing is a replica, generation of intricate geometrical designs, and the ability to design a custom pattern for different applications [3]. The low manufacturing cost and ability to create intricate designs are its benefits over conventional machining processes such as injection molding. The introduction of novel advanced materials used for 3D printing has significantly improved the quality of designed parts. Traditional materials such as metals, polymers, and ceramics are also used; the chemical and physical properties of these materials used must be consistent for producing parts of high fidelity [4-6].

The majority of applications from 3-D printing technology are limited to the aerospace and automotive industries [7-9]. However, with time the medical field has adopted the trend, and today, mostly anatomical models for learning and teaching purpose are manufactured by 3-D printing [10-12]. With the advancement in the adoption of biodegradable materials and the evolution of novel biomaterials for medical operations and pharmaceutical needs such as prosthetic and orthotic applications, the potential of 3-D printing has increased manifold [13-16].

Any material with the ability to interact with live biological systems is termed as biomaterials. Based upon various factors such as their origin type, physical and chemical structure, and

modification generation, the biomaterials are further classified. The biomaterials can be of natural or synthetic origin, built for interacting with biological systems, and has further applications such as augmentation, repair, or replacement of a tissue or an organ part of the organism at a given time [17-18].

The target tissue also is a significant factor in deciding the type of biomaterial. In recent years, the biodegradable material is much focused on research and engineering. The chemical composition of the material divides it into several categories, such as composite, polymer, and ceramics. Most of the inorganic metal compounds and calcium salts are made up of the ceramic material category. The majority of manufacturing units are of orthotic devices, widely available commercially [19-20].

The various benefits offered by 3-dimensional printing; are

- Customized surgical aids and biomedical models of patients,
- Personalized prosthetic and orthotic devices,
- Bioprinting of tissues and custom 3D scaffolds for regenerative medicine of additive manufacturing based 3-D printing has a broad base of clinical applications.

The most beneficial advantage offered by 3-D printing technology is the personal geometrical customization of the printed object, capable of engagement with the anatomical structure of an individual. This is achieved via data obtained through Computed Tomography (CT) & Magnetic Resonance Imaging (MRI) scans of the patient. This phenomenon helps in the design of many efficient, personalized, and robust medical devices, all by the generated 3-D information and its application in new modeling and simulation software available [21-23].

2. CURRENT SCENARIO OF 3D PRINTING

With the introduction of novel biomaterials, the advances in other industries have also begun [24]. Table 1 shows the most common applications of 3D printing in various industries. Other application of 3-D printing includes the chemical industry, for creating complex molecules and compounds [25]. The construction industry also benefits by creating small scale models; however, these applications are limited due to the commercial unavailability of biomaterial [26-27]. Bio fabrication is possible by four major 3D printing techniques- Extrusion Printing, Inkjet Printing, Selective Laser Sintering, and Stereolithography [28].

Table 1. Applications of 3D Printing in various industries.

| Industries Involved | Applications |
|---------------------|--|
| Automotive Sector | Prototypes, scale model & spare parts. |
| Medical Field | Surgical models, dental fixtures, live tissue scaffolds, tissue engineering, prostheses and orthotics. |
| Pharmaceuticals | Customised implants for drug delivery, oral drug devices. |
| Aerospace | Fairing, prototypes and parts. |
| Miscellaneous | Household objects, cutlery and clothing accessories. |

Extrusion and inkjet printing use liquid-like precursors, that can solidify *in-situ* after extrusion and can also encapsulate enclosing cells [29-31]. In the Selective laser sintering, the laser binds or melts dry powders one layer in time [32]. Stereolithography is based upon photosensitive aqueous solutions, capable of performing polymerization with patterned light and enclose cells [33-34].

Widely adopted extrusion-based FDM (Fused Deposition Modeling) works on the principle of melting a thermoplastic material and depositing into layer-by-layer manner upon a built-up platform; until the complete construction of body [35-36]. Other than FDM, another extrusion-based printing method is Bioprinting [37-38]. This technique is used for creating scaffold through a biomaterial, which is extruded under pressure via a nozzle in a layer-by-layer manner. The materials used for FDM are nylon, PLA (poly-lactic acid) and for bioprinting are chitosan, gelatin, and fibrin [39-42].

3. 3D PRINTING & BIOMATERIALS

Amongst all the types of 3D printing mechanisms available in the industry; the most commercially used techniques are FDM, Inkjet, & Polyjet in the medical and pharmaceutical fields [52-53]. FDM offers features such as dimensional accuracy and outstanding mechanical properties, which makes it suitable to be commonly adopted as the prototyping application. Novel features offered by extrusion-based Bioprinting are varied viscosities and high cell density aggregation of the printed object [54].

The polyjet printing mechanism deposits layers of photopolymer resin, upon the build platform and are treated continuously under UV rays [55-56]. The most prominent feature offered by the polyjet printer is the ability to jet multiple layers and cure them at the same time. This technique is used for creating complicated, multi-material based 3D objects. Alike, the FDM based techniques, these are also widely adopted in the medical and

A regular working of most of the 3D printer or similar techniques is shown in Figure 1

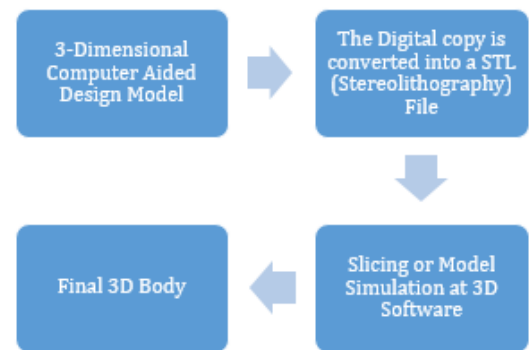


Figure 1. Common working of a 3D printer.

Recently, the SFF based 3D printing has gained popularity, sudden commercialization, and the printing machines are being made custom made for educational institutes, small scale industries, and domestic purposes. These machines are made specifically with lesser function complexity and economic investment. With the era of digitalization, the hardware accessories required, such as 3-Dimensional scanners and the availability of software such as CAD (Computer-Aided Design) and model simulations, it is convenient to fabricate the machine parts as well [43].

The integration of novel imaging techniques such as MRI and CT scanning with the CAD software, the whole fabrication process is accelerated and advanced due to the aid of rapid prototyping, providing both macro and micro-architecture control [44-45]. This has helped in building customized, complex, and more personalized biomedical devices, orthotics, and prostheses [46-48]. Sequentially, at the post-processing stage, most of the surface modifications are completed. For generating scaffolds, although the conventional methods are effective, by SFF, the generation of complex maxillofacial tissue is possible, making tissue engineering much exciting. However, tissue engineering is a new discipline that has many limitations as of now, and the final scaffold design depends upon biomaterial & printing technique used; and the specific requirements [49-51].

pharmaceutical fields mostly for creating anatomical models and pre-operation surgical plans and simulations [57].

In Material Sintering, the process principle involves the fusion of laser with the powdered material, which eventually forms a layer-by-layer pattern, creating the final 3- Dimensional body [58-59]. EBM (Electron Beam Manufacturing), SLS (Selective Laser Sintering), and SLA (Stereolithography) are the processes commonly adopted. In the SLS process, the high-powered laser beam is employed, and the materials used are nylon and polyamide. Laser-focused upon the photopolymer resins is the UV laser beam, employed at SLA, and high-powered electronic beams are employed for EBM applications; the materials used for both the processes are photopolymers and titanium, cobalt-chrome alloy respectively [60-62].

The material suited for Bioprinting and 3D printing of biomedical devices needs to have distinctive cell-material interaction, chemical, material & mechanical properties, along with FDA approval and processing methods. The three most crucial features for suitable biomaterials are as follows, 1) Biocompatibility, 2) hassle-free printing process, along with regulating degradation rates and 3) the ability to mimic the morphological structure of live tissue.

Generally used ceramic based biomaterial is β -TCP (β -tricalcium phosphate), α -TCP (α -tricalcium phosphate), HA (hydroxyapatite), BCP (bi-phasic calcium phosphate, a mixture of β -TCP and HA), CPC (calcium phosphate cement), CS (calcium sulphate) [62-64] and titanium [65-66]. Due to the brittle nature of ceramics, they are often added with polymers. Biomaterials, constituting both polymers and ceramics, are termed as composites. [67]. The biomaterial used for 3-D printing is dependent upon the requirement and applications of the final product. The 3-D mechanism required for building orthopedic and dental structures employs biomaterial, which supports robust mechanical strength and low biodegradation rates. Contrarily, the dermal and visceral organ demands the biomaterial with features such as flexibility and high biodegradation rate. Table 2 compares the various biomaterials types, along with their advantages and disadvantages.

Most of the applications of the 3-D printing mechanism, from the medical and pharmaceutical field, are limited to orthodontic applications, and the bio-materials used are the

4. TRENDS IN TISSUE ENGINEERING

After enduring some damage to the body, the capability to regenerate lost tissues and cells is an incredible ability of the human body. This regeneration phenomenon is dependent upon critical conditions such as the availability of growth hormones for differentiation and tissue type. Another crucial factor upon which this phenomenon is dependent upon is the physical size (critical defect) of the tissue. External support is required for tissue growth if the injury exceeds this critical defect. TE (Tissue Engineering) is the phenomenon of supporting tissue regeneration, externally beyond this critical size [70-71]. This is often also termed as RM (Regenerative Medicine) [72]. The supports provided externally, to promote the regeneration of tissues are termed as scaffolds. The scaffold builds a stage for body cells, for migration to the field, the site of regeneration of new tissue [73-75]. For enhancing the regeneration ability of tissues, the hastened differentiation of cells takes place in order to prefer the lineage type, which promotes the generation of new tissue. This is possible due to the added growth factors to the scaffold. The cell proliferation and its viability depend upon the chemical and physical composition of the respective scaffolds.

ECM (Extracellular Matrix) supports the cell functionality and viability, which acts as a hindrance for biomaterial applications of TE and RM, as they copy the ECM. Biomaterial features such as its contact-angle, rigidity, surface charge, chemistry, reactivity, and roughness are critical, as the cell-cell & cell-biomaterial interactions depend upon them. Due to an efficient cell-biomaterial & cell interaction, cell attachment, differentiation, and viability are proportionally determined, which eventually evaluates the scaffolds' success [76]. Other than these critical features, some physiochemical requirements for effective growth are therapeutic

conventional metal-ceramics, hard polymers, and stiff composites. With the introduction of novel biomaterials such as soft polymers and hydrogels, the applications of 3D printing mechanisms have been used for generating tissues and fabricating organs of an organism [68-69]. The reason for the need of such novel materials is their unique property of mimicking the Extracellular Matrix of live tissue.

Table 2. Comparison of different biomaterial types along with their advantages and disadvantages.

| Biomaterial Type | Advantages & Disadvantages |
|--|---|
| Metal & its Alloys e.g. (Gold, Platinum, Steel, Cobalt & Chromium) | <ul style="list-style-type: none"> • High material strength, • Ease in fabrication and sterilization. • Corrosive and excessively elastic. |
| Ceramic & Carbon-based Compounds, e.g. (Calcium Phosphate Salts, Glass and Oxides of Aluminium & Titanium) | <ul style="list-style-type: none"> • High material strength, • Biocompatibility and corrosion resistance. • Hard molding process and excessive elasticity. |
| Polymers e.g. (Polycarbonates and Polyurethanes) | <ul style="list-style-type: none"> • Biocompatibility, • Biodegradability, • Easy molding process and availability. |
| Composites, e.g. (carbon fiber-based composites) | <ul style="list-style-type: none"> • Robust mechanical strength, • Efficient mechanical properties and corrosive resistant. |

delivery, biocompatibility, cell adhesion promotion, and cell stimulation response, the survival of supporting cell, biodegradability, serializability, differentiation and mechanical strength.

The scaffolds' structure and its surface chemistry significantly affect the cell function and its viability; also the cells of mammals are viably dependent upon an anchorage, making a substrate essential for the cell's growth. If a substrate is not provided for cell attachment, it could even die. In order to enhance the growth of the cells, the cell adhesion is stimulated via modifying biomaterials and scaffolds [77-78]. This is done through 3 processes: chemical modification, physical modification, and coating of the surface. The chemical modifications are carried out via acetylation, alkali hydrolysis, and substitution of glycidyl groups, UV radiation, and oxidation methods. The biomaterials surface chemistry is altered through these chemical reactions and radiations. Also, the addition of several RGD (arginine-glycine-aspartic acid) based groups upon the material surface enhances cell adhesion [79-80]. Chemical modification via several functional groups enhances cell adhesion and proliferation. The structural changes made upon the surface of the biomaterial are termed as physical modifications. These methods are adopted for engineering the materials surface roughness and topography; via employing techniques such as mechanical polishing, sandblasting, photolithography, and plasma etching.

The methods employed for surface coatings are Surface-grafting, solvent casting, sol-gel coating, precipitation, and several dipping coating of scaffolds structure [81-85]. These processes result in efficient cell-biomaterial interaction and influence multiple scaffolds' surface properties. For the fabrication of scaffolds, many

methods and techniques are adopted and employed upon the biomaterials, transforming them into scaffolds. The TE (tissue engineering) requires biomaterial with certain specific properties, and not all the biomaterials are compatible with a specific fabrication process, due to which they are constantly modified to

render them for use. This is achieved via several chemical and physical processes, modified explicitly for TE. Additive manufacturing, Electrospinning, solvent casting, and freeze-drying are some of the conventional fabrication processes, used today.

5. 3D PRINTING & TISSUE ENGINEERING

The kidney is the most crucial organ in the human body and has very high transplant rates. Since the 3-D printing of the scaffolds is complicated, they are under the subject of UV-crosslinking and seeded with HEK (human embryonic kidney cells). The scaffolds exhibit cell viability by creating a conducive environment for kidney TE. These scaffolds offer proliferation and high cell viability. This study promises the fabrication of TE to be much competent and easy [85-87].

In medical applications, FDM has certain specific applications, such as the construction of personalized body implants, prosthetics, and fabrication of anatomical models and surgical guides [88-91]. The biomaterial, most widely adopted for the FDM process, is ABS [92-94]. Other than the ABS, conventionally employed printing filaments are PLA, nylon, polycarbonate (PC), and polyvinyl alcohol (PVA). Well-known polymers are lactic acid-based, such as PLA and PCL; these polymers support biocompatibility and have efficient, biodegradable properties, due to which they are widely adopted for medical and pharmaceutical applications [95-96]. Thermoplastic polyurethane (TPU) and ABS based biomaterials are used for printing pre-operation surgical planning models and simulations. The most prominent biomaterial for bioprinting is the polymer, and certain numbers of polymers are being studied with intent to make them commercially feasible; through the Bioprinting technique. Some of the polymers, of natural origin used for bioprinting, are collagen, gelatin, alginate, and hyaluronic acid (HA) [97-101].

Bioprinting fabrication is based upon the principle of layer-by-layer deposition of biomaterial in the liquid state; until the completion of the entire object. The instant the liquid biomaterial exits the print head, it solidifies and retains the desired shape. The sol-gel phase conversion process is the critical element for biomaterial compatibility; the transformation capability of the biomaterial is what makes it adaptable for bioprinting [102-103]. Composites and polymers have most applications as the biomaterial due to their ability to polymerize via several methods, making them an efficient 3D printable material [104-106]. The rheological properties of the material and crosslinking methods adopted for the fabrication are crucial and depend upon the bioprinting method employed. For instance, the bio-ink employed for inkjet printing and the extrusion-based printing technique has different requirements. Also, the natural constituent of biomaterial directly affects the printing outcome and technique properties. Other than the rheological properties of the material, other physical aspects such as the shear forces acting on the live bioink cells also need consideration. Whilst designing novel biomaterial of hydrogel and polymer-based materials, for bioprinting applications, certain

Rheological material properties such as the Barus effect, viscosity, non-Newtonian behavior, and crosslinking method are considered. Researchers have discussed the features such as low viscosity under shear stress and time-independent offered by thinning non-Newtonian fluids. This is a novel feature as, during the 3-D printing process, the biomaterial undergoes shear and is pressurized; and since the shear thickening fluids under such conditions exhibits high viscosity, clogs the printer nozzle [107]. Likewise, the same behavior is displayed by thixotropic fluids, as they have viscosity as a time gradient; eventually, this results in non-uniform particle distribution, resulting in inhomogeneous structures [108]. After ejection from the print head nozzle, the polymer expands; this phenomenon is termed as the Barus effect. In order to preserve the resolution of the 3-D printed object, very little or none of the Barus effects is considered for Ideal bioinks.

The materials used for 3-D Printing are Calcium polyphosphate [109] and PVA, HA and TCP, TCP, TCP with SrO and MgO. The apatite-wollastonite glass-ceramic (water-based binder) [110], doped along with HA, collagen as the binder material along with calcium phosphate, PLGA and Mg₃(PO₄)₂ (Farringtonite powder) were used for several studies. The polymers of synthetic origin, such as PEG (polyethylene glycol) [111] and PVA, find their applications as novel Biomaterial for 3D printing, known as bioinks [112]. They demonstrate the capability of post-processing via crosslink of UV and chemical methods to enhance the mechanical robustness of the device structure. The applications of polymers in 3D printing have made possible the creation of biological tissues and scaffolds of varied complexities. Tappa, K., discusses the fabrication of gelatin-based ovarian implants. These implants were capable of creating normal ovarian functions and even produced offspring of a sterilized mouse [113]. The regeneration of bone, aortic valve, skeletal muscle, cartilage, neuronal and other tissues is possible via extrusion bioprinting. Despite these advancements and innovation, the vascularisation of complex body tissues is not achieved. The lack of biomaterial with desired properties and mechanical strength for a different type of fabrication requirements is a major concern, Nano-fibrillated cellulose (NFC) + alginate and NFC + HA are the biomaterials used for Bioprinting. It is also capable of high-resolution printing objects with varied modular strengths and high dimensional accuracy. Unlike other inkjet-based techniques, it does not require post-processing of the final object [114-116]. Biomaterial used for polyjet technique is termed as photopolymers; ABS, veroclear, verodent and fullcure are some of the photopolymers used in medical and pharmaceutical fields [117].

6. NANOTECHNOLOGY IN 3D PRINTING

With the introduction and emergence of nanotechnology with various conventional processes, techniques, and materials, many revolutionary devices are made [118-119]. The use of

nanotechnology for 3D printing of biomaterial guarantees the development of efficient and smart medical devices, with a better possibility to enhance the device- biomaterial-cell interaction

performance. Most of the body cells are on a range of 100–1000 μ m and their components on a nanoscale. As the interaction between cell-cell and the Biomaterial-cell interactions are performed upon microscale, the nanotechnology has the potential to develop smart devices, capable of interacting with cell upon micro and nanoscale. This phenomenon increases the threat of entire tissue, and organs, simultaneously decreasing the inflammatory response, whilst providing better treatment to the target problem. This promises the wide adoption of nanotechnology-based in biomedicine via nanomaterials. Various kind of materials is used as a nanomaterial, for instance, gold, SiO₂ gold-based nanoshells, hydrogels, starch-based powders, water-soluble polymers, and fibrins [120-123]. These bio-materials has many applications, and it is also used for fabricating neuron-adhesive patterns, collagen scaffolds, biodegradable synthetic scaffolds, and fibrin channels [124]. Amongst all the nanotech-based manufacturing processes, 3D printing is the most sought for its prominent features such as rapid fabrication, dimensional and geometrical precision.

The rapid, dimensionally correct fabrication of the desired 3D object is the best feature of 3-D printing, which is possible due to the hassle-free operation process, consider instant it does not require additional clamp tools to hold, for stabilizing the whole operation. The only time required is for carrying out four operations of the process rate: deposition of powder layers, binder printing, the binder infiltration into powder, and the drying of the binder. Accurate geometrical dimensions are achieved through 3D fabrication, the final body dimensions are determined by the local and accumulative precision of the layer deposited., droplet placement, and the ability to replicate the dimensional modifications due to binder cure. The factors which affects the geometrical dimensions of the final objects are powder shape, binder diversity, binder material used, droplet velocity, the powder-packing density and temperature of the binder [125-127]. The 3-D printing techniques adopted for the fabrication of novel biomaterial fabrication are- Inkjet printing, usually used with printers such as the NP 2.1 (GeSim, Germany) & the Z40 (Zcorp, USA) and the

Nanoimprint lithography along with usual printer EVG620 nano imprinter and 520 hot embossers.

In the inkjet material binding process, a bed consisting of material powder is constantly poured with a liquid-based binding agent. This process results in the formation of liquid bound, a powder-based, 3-Dimensional object of the required material and unique features. Materials used for the power bed are starch, gypsum, and water as the binding agent. Other types of 3D printing technology include LOM (Laminated Object Manufacturing) [128-129], Poly-jet Material Binding, and CLIP (Continuous Liquid Interface Production) [130].

A wide variety of biocompatible nanomaterials, such as ceramics, metals, polymers, and metal alloys, are available, and they have potential applications, infused into novel fabrication techniques with processing composite materials, along with biological and synthetic based materials; like cells and proteins. Several applications of 3D printing, commercially available and widely used are concentrated around some specific industries. Abundant research, technological advancement nanotechnology, and the basic understanding of nano biomaterials have paved the way for the introduction of new, novel techniques and intelligent biomaterials. Researchers have discussed the prospective applications of 3-D bioprinting such as bones, organ valves and vessels and lastly an artificial ear; given the features of bioprinting it is an efficient method for the development of various biomedical and pharmaceutical applications as it provides n number of options along with a large variety of materials to choose from [131-134]

As 3D printing is developed from Rapid Prototyping (RP) technique, it has advantages like the RP solutions. The preprocessing and post-processing of 3-D printing are similar to the RP, powder-based processes. However, it also offers features such as the generation of more intricate designs and geometries.

Nanoimprint lithography is a novel technique for stacking structure patterns via transferring structures numerous times on the same substrate, eventually building the 3D structure. This method is very much cost-efficient [135].

7. LIMITATIONS OF 3D PRINTING OF BIOMATERIALS

Along with their advantages, unique features, and prominent compatibility, certain factors limit the applications of biomaterials, such as porosity in the final body and post-processing requirement in several 3D techniques.

Due to a lack of biomaterials, a novel technique such as 3-D printing has limited applications in the field of medical and pharmaceutical fields, specifically the fabrication of biomedical implant devices. This results in the employment of material processing technique, which is not compatible with the available biomaterial and hence results in the inadequate 3-D printing. Although where the biomaterials are both available and compatible with the printing technique, the advantages are unique, personalized, and economical devices.

8. CONCLUSION

To end with, 3-Dimensional bioprinting has several applications in the medical and pharmaceutical fields, including Tissue Engineering, scaffold production, and manufacturing of the novel biomedical device. Other applications include customized

The term biosafety refers to the threat possessed to the identity and personal privacy of the individual. The 3-D printing is capable of replicating geometrical structures in organisms as well as the biological characteristics. This could be a potential threat to the individual's health; mainly, the biocompatible, powder-based binder system for 3-D printing is a key threat. Apart from 3-D printing, the biodegradability is also a prominent factor of biosafety. For example, after the regeneration of cells, tissue, or any other organ, the remains of synthetic body implant can start affecting the new growth formation by partial degradation. This phenomenon can be checked via phase composition and material porosity.

prosthetics, Bio-synthetic organs, and personalized drug delivery systems. All these novel inventions are in the infancy stage of production. They are limited due to various restraints, such as the lack of biomaterial, compatibility with current 3-D manufacturing

techniques, the biocompatibility of materials with organisms. Even the compatible materials with recent techniques suffer some dimensional non-uniformity, defeating the whole purpose of this novel technique, making the object short-lived. Other than the physical features, the composition, cellular structure, and the natural material also affect the overall printing technique. The application of 3-Dimensional printing along with biological

characteristics of a person is a distinct feature. However, at the same time, it possesses threats such as identity theft and access to one's anatomical data such as their DNA, retinal id, fingerprint which might be used for unauthorized cloning. Despite these limitations, this novel technique offers n number of applications in each field, which promises to change the humans' live.

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