Original Article

A Brief Technical Review On 4d Printing And Application In Medical And Pharmaceutical Sector

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Abstract

4D printing is an emerging and advanced technology of manufacturing and fabricating a smart complex structure which can change its own behavior while exposing to external environment. 4D printing helps to create a 3D physical object by adding smart material layer by layer through computer-operated computer-aided design (CAD) data. Here the 4th dimension “Time” is integrated to add a lot of advantages to the 3D (Lateral and Vertical movement) bio printed objects in both medical and pharmaceutical sector, make a microscopic change in its shape, size, pH, properties or function with respect to an applied external stimulus (such as heat, light, pressure or moisture). In this regard, the 4D printed structures draw a special attention in pharmaceutical and biomedical field to do the extensive research by exploring various dugs for a particular genetic or hereditary disease. This review highlights on how the 4D printing is the latest technology that creates innovation and addresses complex medical problems. Paper briefly describes the 4D printing and details its difference from 3D printing technology, the materials used and the transformation of preprogrammed dynamic polymer with their composites and the shape memory polymers used as the smart materials (stimulus responsive). After that the current progress and application of this updated technology is explored for the development of implantable biomedical devices and pharmaceutical medications are discussed.

Keywords: 4D Printing, Smart materials, Additive manufacturing, Implants

1. INTRODUCTION

The history of four-dimensional(4D) printing may be traced back to the improvements and advancements made in three-dimensional(3D) printing. Therefore, it is important to understand the history of 3D printing, which eventually gave way to the development of 4D printing. A basic understanding of 3D printing, including its background and printing methods which will assist the reader comprehend the idea of 4D printing and how it has changed. Using computer-aided design (CAD) and a computer's guidance, 3D printing is a method for producing simple or complicated structures using layer-by-layer deposition method. Hull and colleagues first proposed three-dimensional (3D) printing in the year 1986 (1). Then, it has received much interest in the disciplines of tissue engineering and bio medicine (2). Numerous sorts of biological structures have been created using various 3D bioprinting technologies (such as heart tissue, blood vessels, bone and liver tissue) (3). The 3D bioprinting method has a great limitation. 3D printing technology solely studies an object's initial state and assumes it to be motionless and static. Elegant 3D structures, microarchitectures, and extracellular matrix compositions are produced during natural tissue regeneration, along with tissue that has special functionalities made possible by dynamic changes in tissue conformation (4).

In 2014, Skylar Tibbits and the director of the self-assembly lab introduced four-dimensional (4D) printing for the first time at MIT (MIT). A tailored material system facilitates switching between configurations (5). This 4D printing technique involves multi-material prints (also known as smart material) that have the ability to revolutionize over time. The evolution of 4D printing from the starting of 3d printing is mentioned in Figure. 1.

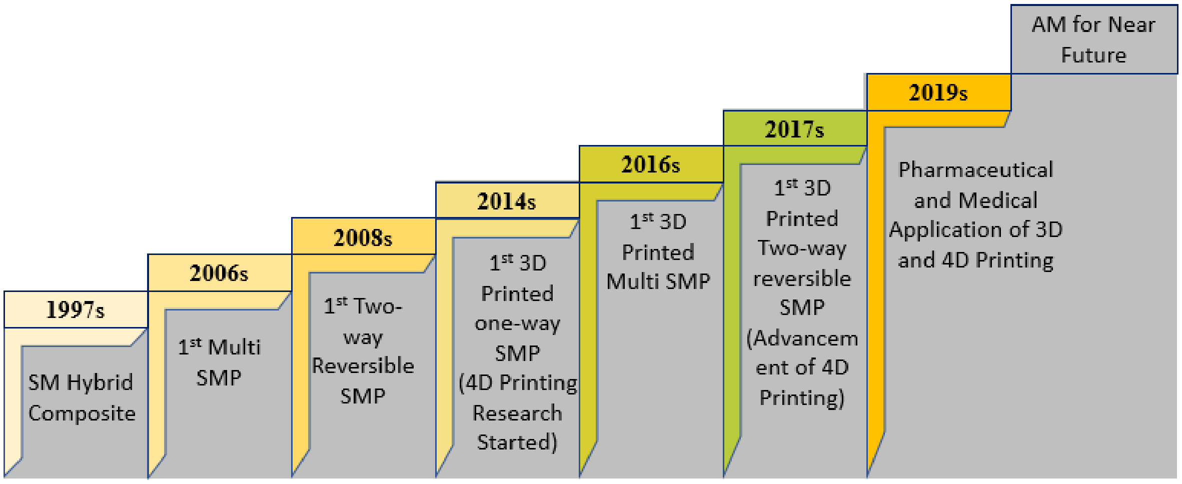

Figure 1: Evolution of 4D printing

Tissue engineering has quickly embraced in this technology. Incorporating the idea of time as a fourth dimension into 3D bioprinting can result in the creation of 4D bioprinting technology (6). By the application of stimuli-responsive materials (smart material), a variety of 3D-designed biologically active designs with the ability to dynamically modify their configuration over time in response to various needed stimuli can be created using 4D bioprinting. A variety of 3D-designed biologically active designs with the ability to dynamically modify their configuration over time in response to various needed stimuli can be created using 4D bioprinting (4). According to Gao et al, With the help of 4D bioprinting, 3D-printed constructions' cells or tissues can develop and become more useful over time, in addition to the growth of cells structure with 3D-printed can react to both internal and exterior stimuli. It implies that the printed structures' configuration remains unchanged (6). The two primary methods employed in 4D bioprinting are the printed structures' functional change and morphology over time. These characteristics are absolutely necessary for the rejuvenation and long-term equilibrium of biosynthetic frameworks, these qualities are completely essential. However, components in 3D-printed structures can completely vanish throughout the dynamic process and experience-controlled decay and should not be considered 4D printing. During structural or functional alteration, the majority of 3D-printed constructions maintain their integration (7). Therefore, the configuration or functionality of constructions created by 4D printing should be stable both before and after stimulation. Bone defects are induced by bone fractures and other destructive illnesses; thus, bone regeneration is essential to restore the tissues that have been destroyed (8). Over the past two decades, 3D bioprinting technology has advanced significantly for the purpose of building bone tissue constructs (9). Various types of studies have shown how to integrate biomaterials, smart materials, cells, and bioactive components. Through the use of biomimetic designs and regulated patterns, these technologies aid in the stimulation of bone regeneration. There are still a number of limitations for additional therapeutic applications of 3D printing in bone tissue engineering. Along with the mechanical property of structures with 3D printed, major bone defect healing involves neural reconstruction and biological processes in addition to reconstructing huge and uneven bone tissues for specific needs (10). The synthesis of bone tissue will be approached in unique ways thanks to the 4D-printed producers' ability to respond to the local microenvironments of problematic areas (11).

2. 4D printing vs 3D printing: A Comparative Analysis

The four fundamental forms of 3D printing are fused-deposition modeling, powder bed fusion, stereolithography and inkjet head, according to the literature. These technologies heavily rely on flexible materials with good mechanical and thermal properties (12) (13). The basic difference between the 3D printing and 4D printing is the outcome of the fabricated structure, which can be easily understandable from Figure. 2.

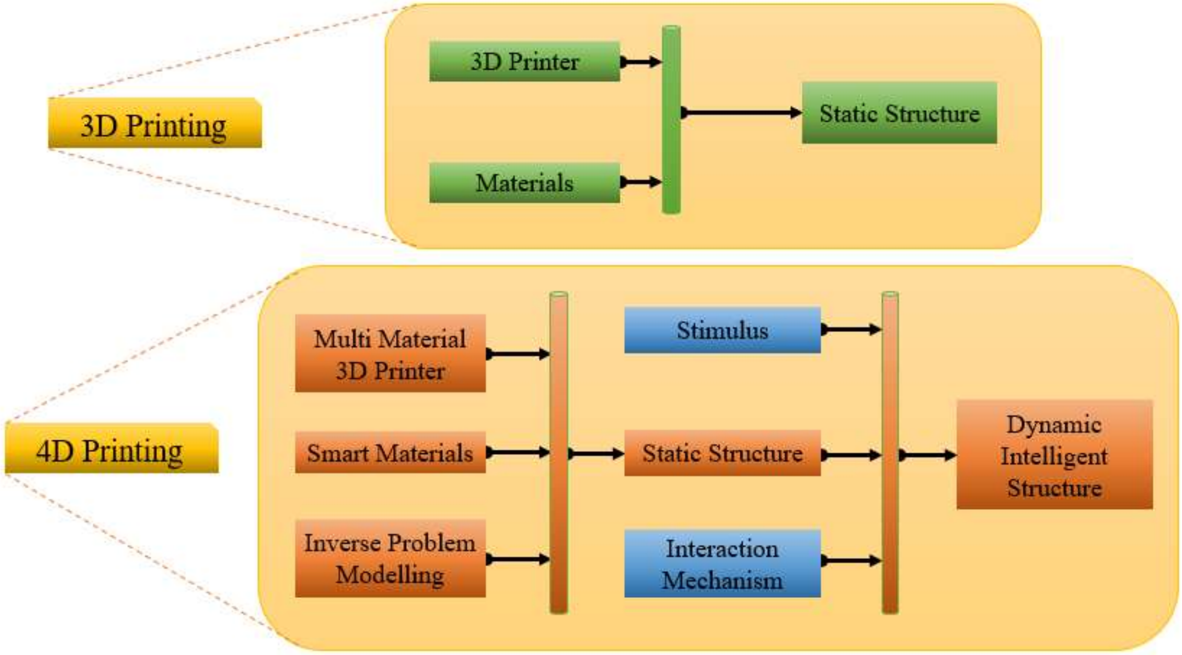

Figure 2: Basic structural difference between 3D and 4D printing

Reimagining manufacturing-related enterprises is necessary to fill in the gaps left by conventional production methods. Table 1 describes a comparison study between 3D printing and 4D printing method with respect to different characteristics.

Table 1: Comparison study of 3D and 4D printing method (14)

Sl. No	Characteristics	3D Printing method	4D Printing method
1	Development process	Using the method of 3D printing, a 4D structure is replicated from top to bottom in layers.	The evolution of 3D printing is 4D printing.
2	Utilised materials	Employs nanomaterials, biomaterials, ceramics, metals, and thermoplastics.	Uses intelligent, multiple-material, and self-assembling building materials. After being created, an item changes shape. To meet application requirements, new materials must be developed.
3	Flexibility	Rigidity and lack of flexibility.	Flexibility-related; flexible in nature.
4	Flexibility in object shape	The shape of the objects changed throughout this procedure.	The shape of an object changes over time and in response to temperature changes.

5	The scheduling of content	Not utilizing any programmable or sophisticated materials	Utilize programmable, cutting-edge, and frequently innovative materials that can perform a variety of functions.
6	Application	It has advantages in the medical, engineering, dental, automotive, jewelers, toy, fashion, entertainment, aerospace, and defense industries, among others.	Configuration that changes on demand for all applications through 3D printing.

3. Challenges of 3D printing

At this point, additive manufacturing (AM) has unquestionably proven to be a very effective strategy with many advantages. Nevertheless, there are many disadvantages of 3D printing that includes a lack of comprehension, a lack of materials, and improper design formulation. Also, in terms of governing standards and application process of the software this technology has significant limitations. An industrial robot of a sort is a 3D printer. AM will quickly revolutionize the entire creative manufacturing process, including the idea of consumed product. A content layer can be provided via 3D printing method through layer by layer deposition, due to taking actions to create the portion. After identifying difficulties in crucial 3D printing locations, this procedure would require converting input from the material to the final product. When it comes to computer-aided design (CAD), the challenging issues are present but have not been adequately handled (15). Figure. 3 shows the various challenges of 3D printing in Additive Manufacturing (16).

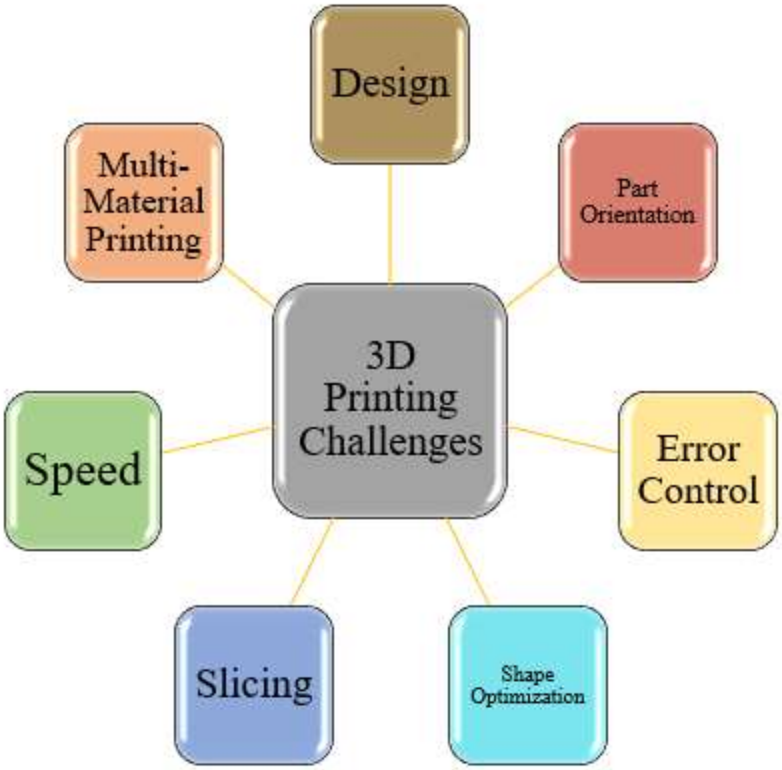

Figure 3: Challenges of 3D printing

Although there have been proven positive results in drug delivery, it is still in the developing stage. There are several obstacles to overcome in order to progress the improvement of 3D printed items and to broaden the application scope in innovative drug delivery systems, including adaptable use, acceptable excipient selections, and post treatment methods. When redesigning using 3D printing, the inherent flexibility may be the biggest source of liability from a safety standpoint. The main variables, such as rate of printing, velocity of print line heads, passes, time interval of printing layer, distance between powder layer and nozzle etc, need to be changed to improve the quality of 3D Printing (17).

4. Selection of Materials for 4D Printing Technique

The most recent advancements, which can meet the criteria for 4D printing, have made it possible to arrange materials more precisely and flexibly in multi-material 3D printing (18). 4D bioprinting materials have special capabilities as mentioned in Table 2 (19).

Table 2: Capabilities of the Materials used for 4D printing

Capability	**Description**
Self-shape change	Material responds to an external stimulus by changing shape.
Self-assembly	Permits assembly-line automation of folding
Self-actuating	Automated actuation that happens in reaction to an outside stimulus
Self-sensing	Enables automatic identification and occasionally quantification of environmental stimuli

4D-printing materials also can be classified according to the environmental or external stimuli, e.g., Thermo-responsive, Moisture-responsive, Photo-responsive, Electro-responsive, Magento-responsive. Different kind of stimulus like temperature, electricity, and moisture, current, light, and magnetic fields can also be applied to the 4D Printing materials. The classification of various external stimuli with responsive smart materials used for 4D printing are replicated in Figure. 4.

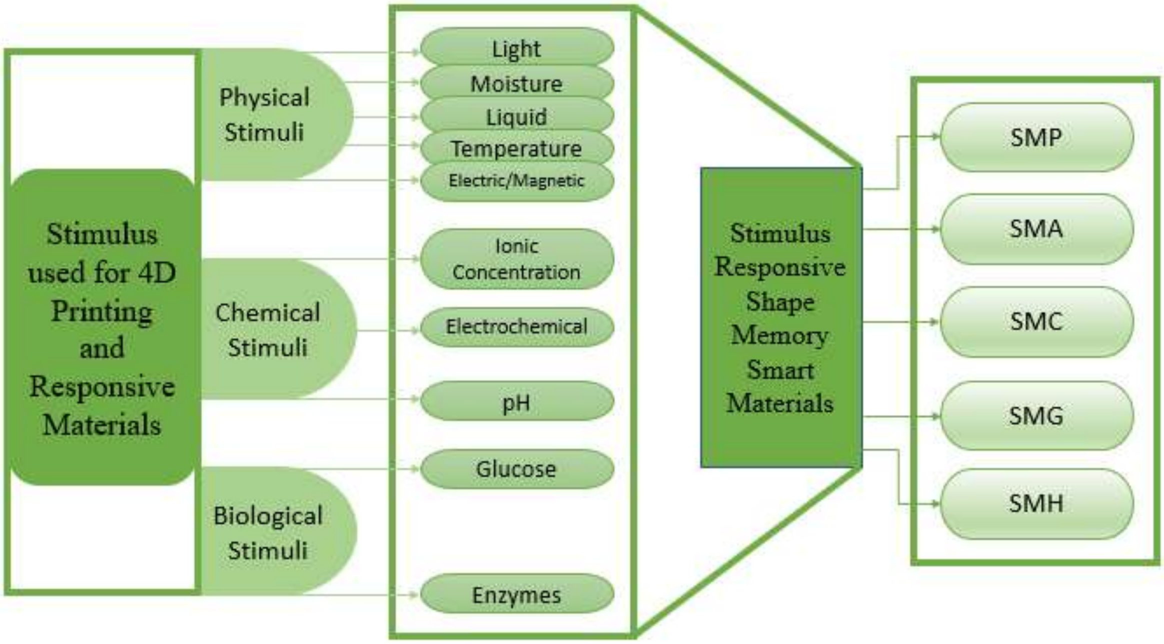

Figure 4: Classification of external stimuli with responsive smart materials used for 4D printing

4.1. Thermo-responsive

SCE (Shape Change Effect) (20) or SME (Shape Memory Effect) (12) characteristic damages the thermo responsive materials. Shape memory materials (SMM) are substances that are based on SME. Shape memory materials can be broken down into shape memory gels (SMG), shape memory alloys (SMA), shape memory ceramics (SMC), and shape memory hybrids (SMH) (21). Researchers primarily prefer SMPs for their printing work. Glass transition temperatures are higher than operation temperatures for SMPs. They are prepared utilizing mechanical treatments and precise heat over their glass transition temperatures. It is fixed in a transitory shape after cooling that is not affected by external loading. The specimen comes back to its original permanent shape, once after raising the temperature over its transition temperature (20) Researchers have changed a variety of SMP materials to take advantage of their printing features. Ying et al has described the creation of SMP ball by using the SLA method with the liquid resins which is polymerized under ultra violet light to get its permanent original shape. High-strength retractable cables on the ball can extend into a smooth plane (22). Ge & colleagues have created an SMP flower that, when heated, might bloom (23). This method is also used to create smart grippers without electromechanical parts or assembly. Bodaghi et al. have explained that preprogramming of the SMP structure can be done by using the FDM printers by using the heating process effectively (24), (25). SME mechanisms are followed by the SMPs. It is not possible to maintain the intermediate stable shape as SME is having only two or three different states. On the other hand, the SCE is dependent on the external stimulus and continuously changes between its extreme states(12). Mainly, SCE occurs for thermo responsive materials when the bilayer structures of the material have sufficient distinction in the coefficients of thermal expansion, because the regions at the contact between the layers are unaltered. The structure warps as a result of a stress field being trapped. Hu et al. have shown that whether heated or cooled, the grapheme-based bimorph structure can be rolled back to the cylinder. Either a rapid temperature shift or a mix of special materials are needed to achieve this kind of extreme deformation through SCE (26).

4.2. Moisture Responsive

The moisture responsive materials and water are most frequently used due to their pervasive stimulation and the extensive range of the applications. Because of the hydrophilic properties, hydrogel materials respond to the moisture. Since hydrogel materials are belonging from the group of polymers, so, it has a great printability character. In DIW (Direct Ink Writing) 3D Printing method, hydrogels are used due to its biocompatibility and ease of printing method (27). But in this case the researchers have to wait for a longer time till Hydrogels are getting dried and shrunk due to its slow reverse response. For this purpose, Anisotropy would be done towards Swelling to know the behavior of hydrogels. Gladman et al. figured out how to combine cellulose fibrils with hydrogel ink using shear pressures generated by the contact among print bed and the ink (28). This alignment causes the longitudinal strain to be four times greater than the transverse swelling strain, allowing the 4D-printed structure to be programmed. In order to create an anisotropic ally directed swelling, in a printing technique described by Mao et al., hard materials are used to confine the hydrogels in one direction (29). Zhang et al. described the rapid reactions and created thin hydrophobic films which are made up of cellulose stearoyl esters (CSEs) that reacts more quickly and precisely (30). The usual aquatic environment in which hydrogels are mixed causes them to absorb the water until they have reached their moisture saturation point, which restricts their ability to be controlled in the interim. Hydrogels' capacity to swell can be modified, though, by changing the temperature of the aquatic environment. Breger et al. created microgripper joints using gradient cross-linked pNIPAM-AAc soft hydrogels (31). By changing the saturation point, it is feasible to perform reversible actuation by heating or chilling method of the water in which the gripper is submerged. A self-folding bilayer structure made with Poly Jet printers was disclosed by Tibbits et al. (32). In the joints, rigid plates are printed to prevent folding past a predetermined angle. The plate tips will meet when this angle is reached to give the resistance to excessive bending.

4.3. Photo Responsive

Light, which is an indirect stimulus as opposed to heat and moisture, causes a photo responsive material's exposed area to warm up. A self-folding structure that is controlled in a sequential way has been shown by Liu et al (33). The varying colors of the joint and the light source affect how quickly light power is absorbed as heat by the joints. Kuksenok et al. used light as a catalyst for the distortion process in a different way. Some areas of a polymer gel block are infiltrated with photo responsive chromophores so that these regions only inflate when exposed to light (34). The print's patterning also illustrates how flexible light works as a trigger. In order to establish gradient crosslinks, weak UV light is directed across liquid resin, allowing the 4D-printed structure to bend due to its anisotropy (35).

4.4. Electro Responsive

Miriyev et al. have shown that light and current can be used as an indirect stimulus in the case of 4D printing. This indirect stimulation can be observed by printing a soft artificial muscle consisting of silicone elastomer and ethanol. When electricity is delivered, heat is produced by resistive heating, which could result in ethanol evaporation. This transition from liquid to gas helps to raise the volume of the ethanol, which then causes the entire matrix to expand (36). Polypyrrole (PPy) films' water absorption or desorption can also be regulated by applying a current. Okuzaki et al. have proved that origami micro robot having unique foot geometry uses PPy films to experience less resistance as it advances. In a humid environment, a voltage causes moisture to be absorbed, which causes the head to move forward, and the lack of a voltage causes moisture to be absorbed, which causes the tail to follow (37).

4.5. Magento-responsive

4D printed items made of magneto-responsive materials react to magnetic fields. Breger et al. coupled a hydrogel-printed micro-gripper with magnetic nanoparticles so that it could be controlled remotely by magnetic fields (31). The embedding takes place during pre-processing, when the material solution is combined with ferric oxide particles. Printing on metal and polymers is possible with this technology. The print size is the main constraint, which must be suitably light weight and susceptible to the magnetic field, is a major drawback.

5. Smart Materials for 4D printing

In addition to the above 4D printing various stimuli responsive materials, different kind of Smart materials (SMP, SMA, SMC, SMG and SMH) are also investigated below. The pros, cons and different actuation methods of these smart materials are introduced in Table 3.

5.1. Shape Memory Polymers (SMP)

SMPs have attracted more interest, because of stimuli-triggered dynamic processes that shows the same properties but change the shape of the 4D material with respect to time (38), (39), (40). Heat-activated SMPs are the most widely used types of shape memory polymers because to their extensive range of thermal, optical and mechanical characteristics (41), (42). A melting temperature (Tm), often known as a glass transition temperature (Tg) or a transition temperature (Ttrans), is used to manage the molecular switching segments that set the temporary shape, while the physical or chemical crosslinks in the thermally started SMPs are typically used to fix the permanent shape. The switching parts of molecules are "soft" as the SMPs are heated over their Ttrans, allowing a distortion to be used to fix the temporary shape. When the temperature is decreased below the Ttrans, the molecular switching segments will ‘‘freeze’’ to immobilize the predetermined momentary form. The molecular switching segments become soft once more because the SMPs will regain their enduring shape near to a temperature exceeding Ttrans, allowing the crosslink networks to restore the structure to its original shape (43). Direct heating is one type of actuation. The form recovery process, for instance, is again triggered by temperature changes brought on by electronic triggers and near-infrared light (44), (45). Direct heat activated SMPs are the significant variety in 3D printed inks and will be the main topic of this presentation.

5.2. Shape Memory Alloys (SMAs)

SMAs are engineering materials used in a variety of physical applications. These applications were first widely calculated in the late 1960s. SMAs were invented by Ullakko in 1996 at MIT (46). It is also known as ferromagnetic shape memory alloys or magnet-responsive material while changing the measurement and configuration. This alloy displays an unusual form of memory behavior because of the austenite-to-martensite phase shift that takes place at atomic temperature. This behavior is known as change of thermoelastic martensitic. When temperatures are high, austenite turns into martensitic, and when temperatures are low, martensitic turns into austenite. A high-temperature substance in the alloys is cooled to produce a martensitic segment. Thermo responsive and magneto responsive are two group of alloys can be classified here with respect to the stimulus. The NiTi-based SMA is a very useful material frameworks for enabling fabrics that offers the most promising results. This merges a range of thickenings with high vitality and offers a lot of actuation and displacement options.

5.3. Shape Memory Composite/ Ceramics (SMC)

The shape memory effect (SME) is shown by ceramics., and along with MIT in 2013, shape memory ingestions led the ceramics announcement pack production (47). Shape memory ceramics (SMC) have a comparable martensitic development that affects the tetragonal system's mono clinical structure. Lead zirconate titanate (Pb (ZR, Ti) O3, PZT) ceramic manufacture shown significant isotropic volumetric shape memory performance as an antiferroelectric shape memory (AFE) composite gesture.

5.4. Shape Memory Gels (SMG)

One of the most extraordinary soft material kinds, Shape Memory Gel (SMG), has some distinctive qualities. SMG exhibit Constriction and expansion to modify the polymer's overall, physical, macromolecular or artificially coupled system structure. The gel is probably suitable for both medical purposes and other uses, such as 3D bioprinting and novel reactions, utilities, and water-based upgrades (48). Electroactive hydrogels, made by Lee et al., exhibit the bow that favors the electric field. This gel is printed using the small-scale stereolithography (PSL) technique after being cross-linked by PAA bile DA (Mn = 700 g mol-1). Small-scale stereolithography (PSL) is used to print this gel after it has been cross-linked by PAA bile DA (Mn = 700 g mol-1) (49).

5.5. Shape Memory Hybrid (SMH)

SMH can be made for cupric sulphate pentahydrate and the elastic wipe. It can demonstrate an individual reservoir's quick water responsive method of acquiring a good shape. A shape memory hybrid can currently be exported using the SMP, which is still meant to be the most recent literature of natural, metal, and anonymous procedures (50). SMH and SMPS, although it appears that many things, including forgeries and protections, are being disputed by the composition. In contrast to shape memory alloys, which demand solid aptitudes and chemical data, they also provide chemical data and solid aptitudes.

Table 3: Merits, Demerits, and actuation methods of the Smart materials used for 4D printing

Available Smart Materials	**Merits**	**Demerits**	**Different Methods of Actuation**
Shape Memory Polymers (SMP)	Programming is simple (51)	Tensile strength is low (52)	Light, Ultrasound, Metallic ions, Heat, pH (51)
	Density is low (53)	Thermal conductivity is low (52)	
	Self-healing capability (51)	Shows Slow shape-memory action (51)	
	Biodegradability and Biocompatibility (52)	Susceptible to degradation (54)	
Shape Memory Alloy (SMA)	Can be used for large-scale Fabrication (55)	More expensive than the SMPs (55)	Electricity, Heat, Magnetism (51)
	Tensile strength is high (55)	Density is high (53)	
	Can be operated in wide temp. range (55)	Programming is more complicated as compared to SMP (56)	
	Modulus is high (55)	Available options for biodegradable and biocompatible are less (55), (51)	
Shape Memory Composites/Ceramics	Strain recovery is good (57)	It is not developed well till date (58)	

(SMC)	Lower density and tensile strength can be achieved as compared to SMA (57)		Electricity, Ultraviolet, Light, Magnetism, Water, Microwave (51)
Shape Memory Gel (SMG)	Effect of shape memory (59)	Availability of very limited Raw materials for the fabrication (59)	Water (60), Electric/ Magnetic Field (2), pH (61), Temperature (62), Light
	Self-healing capability and Sol-gel transformation with control (59)	Properties used for triggering shape morphing characteristics are very limited (59)	
	Self Fold or Self unfold Capability (59)	Might not be suitable for 3D Scaffold used for living body repairing (63), (64)	

6. Additive Manufacturing Methods used in 4D Printing

Additive manufacturing (AM) is another name for the 3D printing process. It is used to create 3D specimens by continuously adding layers of material under the guidance of a computer program to create an actual item. The different software and geometry used for AM design is explained in Figure 5.

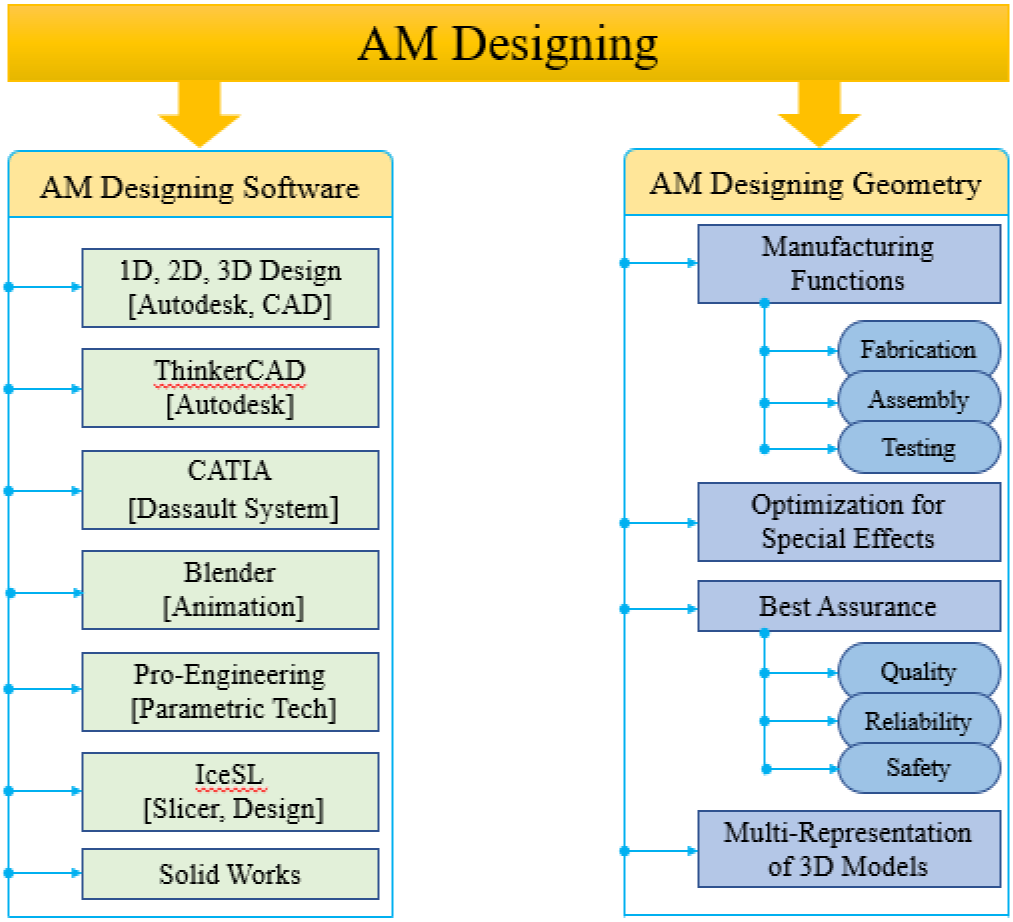

Figure 5: Software and Geometry used for AM design

There are 7 types of AM (Additive Manufacturing) techniques available in ISO/ASTM 52900-15 standard. E.g., Vat Photopolymerization, Material Extrusion, Powder Bed Fusion, Sheet Lamination, Material Jetting, Binder Jetting, Directed Energy Deposition. Out of these available printing methods, mainly three printing mechanisms are widely used for 4D additive manufacturing. Those techniques are Liquid Solidification, Direct Material Extrusion and Powder Solidification (65). The AM systems which are involved with these AM techniques can be studied in the Table. 4.

Table 4: Merits, Demerits and Materials used for various AM methods (66)

Manufacturing methods	**Materials used**	**Merits**
Vat Photopolymerization	Polymers that UV-cure Photographic resin Visijet line of resins (3D systems)	High degree of accuracy and strong completion Process was relatively quick. Object 1000 has a typical huge build area of 1000 x 800 x 500 and a maximum model weight of 200 kg.
Material Extrusion	Plastics and polymers are used throughout the material extrusion process.	widespread and affordable technique It is possible to use ABS plastic, which has high structural qualities and is widely available.

	Nylon, PC, PC, ABS, and PC polymers are used.	
Powder Bed Fusion	Uses any powder-based materials, but common metals and polymers are used Stainless Steel, Titanium, Aluminum, Cobalt Chrome	Reasonably affordable Suitable for prototypes and visual models Powder serves as a seamless support system. A wide variety of material choices
Sheet Lamination	Anything that can be rolled into a sheet. Paper, plastic, and a few types of sheet metal. A4 paper is the substance that is most frequently used.	Speed, low cost, and convenience of material handling are advantages; however, the strength and integrity of the models depend on the glue employed. Due to the cutting approach only using the shape's contour and not the complete cross-sectional region.
Material Jetting	Polymers and plastics are used Polymers: HDPE, PS, PMMA, PC, ABS, HIPS, and EDP are among them.	A high degree of precision in droplet deposition and little waste Multiple material pieces and colors can be used in that process.
Binder Jetting	Stainless steel is used as metal Polymers: PA, PC, ABS Glass Ceramics is used	Parts can be produced in a variety of colors. Uses a variety of materials, including ceramic, metal, and polymers. The procedure typically moves more quickly than others
Direct Energy Deposition (DED)	Metals, rather than polymers or ceramics, are used in the DED in Electron Beam Melting method. Like Metals: Cobalt Chrome, and Titanium	High degree of control over the grain structure makes it possible for the method to repair high-quality, functional pieces. Although speed can frequently be given up for high accuracy and a pre-determined microstructure in repair applications, a balance between surface quality and speed is still necessary.

The printing method is selected based on the essential characteristics of smart or intelligent materials to be printed and the functions of the finished product. The accuracy of the fabrication is directly influenced by the various factors including speed of the printer, frequency of the laser, and temperature of the nozzle. In order to expand the industrial manufacturing process, these factors must be analyzed and optimized. In order to improve and facilitate the object's shape-memory capability, the printing method can also be selected. To create a 3D structure, a comprehensive Computer Aided Design (CAD) model of the physical structure is necessary, which is not dependent on the AM technique (66). The CAD design model is typically separated into thin horizontal layers, which are then printed one at a time by the printer to create the 3D structure (67).

6.1. Vat Photopolymerization

To create the solid 3D structure, this type of AM technology uses a liquid photopolymerizable resin. Light source is applied to the fabricated solid 3D structure in layer by layer to make it hard. Vat photopolymerization and photo jetting are the main 4D printing methods which are based on applied light source. The process is illustrated in Figure 6.

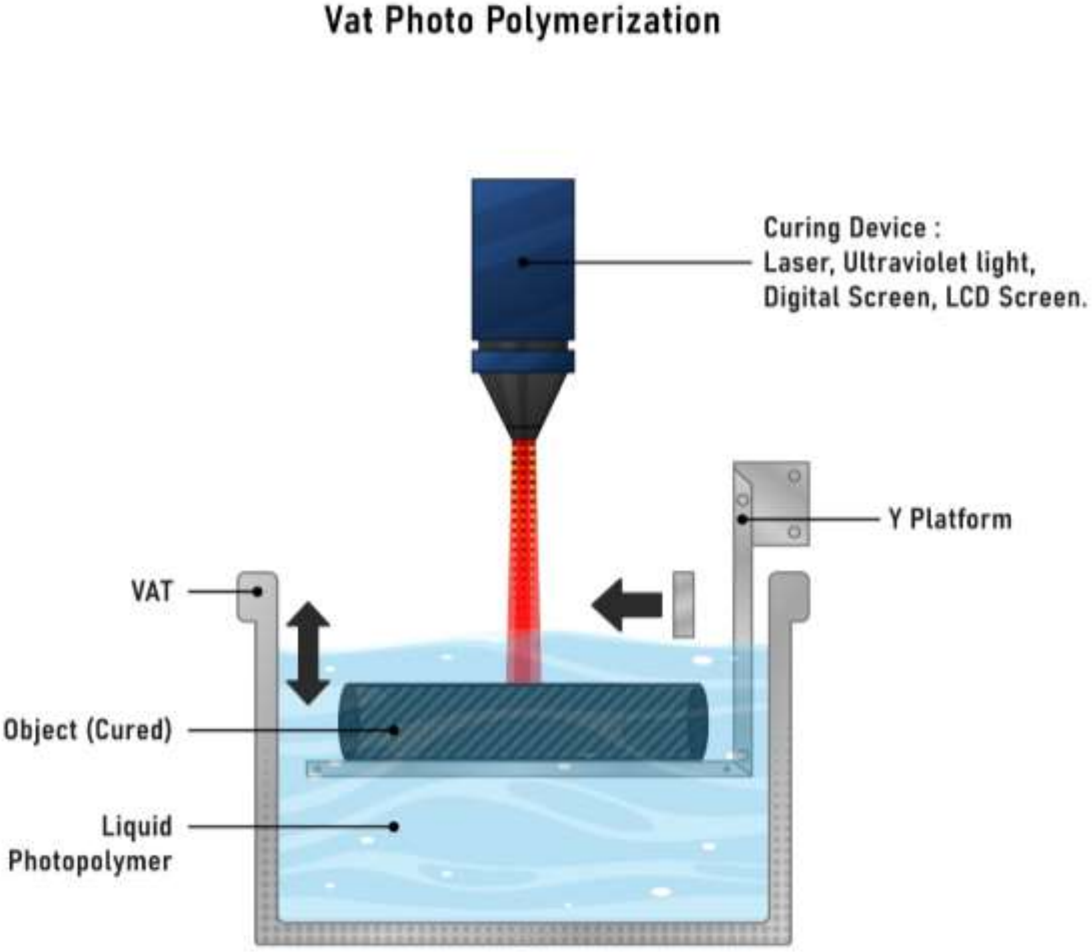

Figure 6: Process of Vat photopolymerization

The involved processes of vat photopolymerization are Direct Energy Deposition (DED) and Digital Light Processing (DLP).

6.1.1. Stereolithography (SLA)

In the stereolithography procedure, a resin monomer contained in a vat is exposed to a UV light source, which initiates a localized polymerization reaction that causes the resin to harden. Once a layer has dried, the build-platform shifts the structure to expose a fresh resin layer to the UV light (68). The solid 3D structure is created by repeating these procedures up until the last layer is curing (69), (70). Stereolithographic equipment (SLA) was initially utilized as a quick and affordable method of producing prototypes and adaptable designs (5), (71). One of the most popular methods for solid free form production now a days is SLA (69), (22), (72). Materials that can achieve quick cure times and pinpoint depositions when printed are advantageous for this AM method. Resins that can be cross-linked and photopolymerized in liquid form must be used (22), (73). These material limitations and the labor-intensive nature of the vertical layer build-up remain SLA's main disadvantages as a 3D printing technique. The ability to construct high-resolution objects of different sizes using SLA is one of its main advantages; things from submicron to decimeter size have been created using this technique (69). This demonstrates the appropriateness of stereolithography for the creation of complex biological devices where the deployment of small, precise structures is necessary. Since so few liquid photopolymerizable smart materials are now on the market that are biocompatible and hence appropriate for application in biomedicine, the field is still in its infancy. Research is being done to improve the qualities of those that are already available and to find new ones. For instance, Melchels et al's review includes several biomaterials that can be used with SLA to create porous structures that can be used for tissue engineering applications (69). SLA is suitable for multi-material applications and creation of shape-memory composites (SMCs) as demonstrated by Arcaute et al. (73). SLA and other light photopolymerization-based techniques provide an accurate and uncomplicated way for creating dynamic structures. This approach has promise as a way to mass-manufacture complex 4D structures for use in biomedicine, if additional advancements can be made to speed up printing.

6.1.2 Digital Light Processing (DLP)

Digital light processing (DLP) is another AM technique which is based on light source, used to manufacture the biomedical devices. This technology makes use of a digital mirror device (DMD) made up of many mirrors. There is a pixel of 2D pattern that is focused towards that mirror and allowing the instant polymerization of whole resin. The device can be turn on/off by the rotation of the digital mirror device (DMD) and disconnect from the light source. Since the entire layer is cured at once, the print time is not independent of exposure time and layer thickness (69).

Invernizzi et al. have demonstrated that DLP is an acceptable method for creating SMPs. Additionally, he created a new thermo-responsive SMP material's 4D structure. That is composed of monomers like 2-ureido-4 [1H]-pyrimidinone (UPy) which crosslinked with polycaprolactone (PCL) chains. DLP was selected as a low-cost fabrication method. and the researchers were able to create a structure with self-healing capabilities suitable for biomedical application (56).

6.2. Material Extrusion

Fused Filament Fabrication (FFF), commonly known as material extrusion, is one of the most widely utilized techniques for 3D printing at the hobbyist level. Extrusion of materials A thermoplastic continuous filament is used as the basic material in 3D printing. A moving heated printer extruder head, frequently referred to as an extruder, is used to feed filament into the machine from a coil. The deposition of second layer can be directly develops on the workpiece when the first layer is finished, at which point the extruder and platform are separated in a single motion. The molten material is deposited on the base, which can be heated for improved adherence, after it has been forced out from nozzle of extruder. Computer control is used to move the extruder head. Cartesian topologies require at least three axes for the extruder to move, however delta and polar systems are also gaining popularity. Until the thing is finished being made, one layer is added on top of the previous one (32). The whole process is shown in Figure 7.

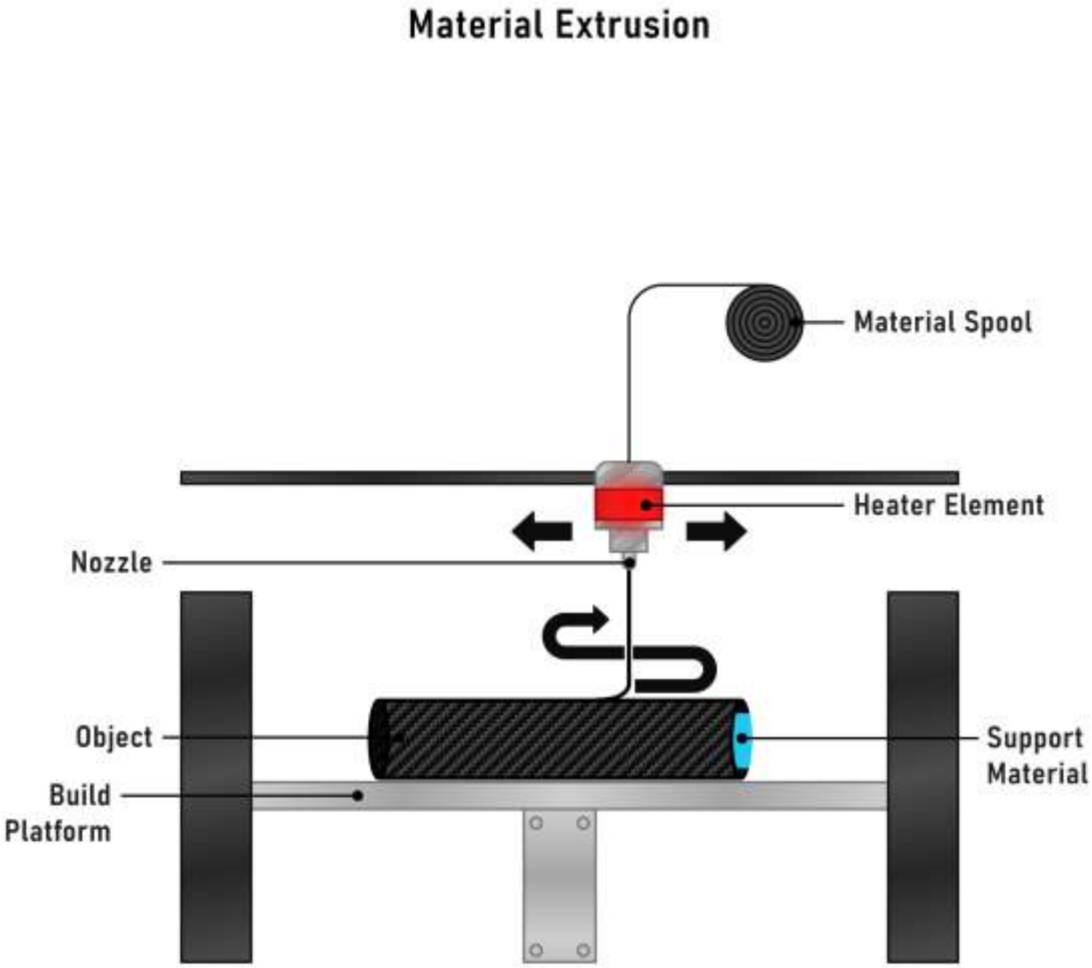

Figure 7: Process of Material extrusion

There are two techniques are included in the material extrusion method, these are Direct Ink Writing and Fused Deposition Modeling

6.2.1 Direct Ink Writing (DIW)

An anisotropic filler's control and orientation inside a polymer matrix is a crucial procedure, which is part of DIW. Through the use of ink writing, this results in pressures that are gradually varied for particular pixels. Long manufacturing times nevertheless result from the change of individual pixels even though labor-intensive material layering and light-based process curing are omitted (74).

The main limitation is the slow printing, and There is therefore a lot of research being done in this area for both 3D and 4D printing. The possibility for mass production is hampered by the lengthy and layer by layer fabrication process. Huang et al. described a potential rapid 4D printing approach that eliminates the requirement for sequential layer by layer deposition or pixel alteration by momentarily exposing light-curable monomers to digital light. A 2D monomer film's pixels polymerized to variable degrees as a result of brief light exposure, resulting in different crosslinking densities throughout the substance. Due to this, the printed structure experienced differential tension and swelling that could be controlled. It will produce morphing in 3D shape. The smart material cross-linking densities can be customized by managing the exposure to digital light. According to Huang et al., this straightforward method can create complicated geometries in less time due to the adjustable tensions and brief light exposure (74).

6.2.2 Fused-Deposition Modelling (FDM)

The other name of Fused-deposition modelling is fused filament fabrication (FFF) or melt material extrusion (MME). It is coming under AM technique, this is based on thermoplastic filaments extrusion (68). Polymer filament is extruded through a heated nozzle after being melted to a semi-liquid state. placing the partially-melted filaments on the building platform, it will get solidify and give a 3D structure that can be created by layer by layer deposition of the extruded filaments(75). FDM utilizes the filaments, that can be produce from various thermoplastics like Polycarbonate (PC), Acrylonitrile Butadiene Styrene Copolymer, Polyurethane, and Polylactic Acid , they all have different stiffness, toughness and elasticity. FDM printers can produce a variety of medical equipment which are easy to use, affordable, and dependable. Bodaghi et al. develop a triple-SME structure by mixing the cold and hot programming of an SMP in FDM method.

Heat-resistant materials can only use in the FDM because a high temperature is needed for printing process. For printing of hydrogel and cell-laden bio inks this method is not applicable, these materials can be denatured when a high temperature will be applied (76). FDM is an intriguing fabrication method for tissue engineering because it can produce porous polymer scaffold (53). Polymers having low glass transition temperatures (T_g) cannot use for fabrication in FDM . At room temperature, low Tg polymer filaments become less stiff and are almost impossible to extrude through the printing nozzle (76). Use of materials with higher Tg or operation at temperatures considerably below the glass transition temperature can prevent this (76). The approach of combining FDM with salt leaching to make porous SMP structure, a radiopaque with high ability to use in interventional radiology, was explored in a study by Kashyap et al (76). The presence of fillers in the printing filament raised the polymer's viscosity, which helps to decrease its capacity to be printed and led to nozzle blockage. The inclusion of fillers in the filament printing help to increase the viscosity of the polymer, which decrease the polymer capacity to be printed and led to nozzle blockage. To prevent obstruction, the researchers advised using a printing nozzle with a wider diameter, although this will decrease precision and accuracy of printed structures . The team believed that by applying the filaments with high stiffness under ambient conditions, and consequently polymers with high glass transition temperature (Tg), the pushing force and blockage may be increased (76). Getting the appropriate materials to construct biomedical equipment with built-in shape-memory behavior is the main aim of extensive research. The price of FDM printers has significantly dropped due to developments over the past ten years. This is in favor of the hypothesis that FDM might be a low-cost substitute for producing personalized medical devices, such as drug delivery systems.

6.3. Powder Bed Fusion

A material is melted or fused together by applying heat, which is the basic concept of powder bed fusion AM (68). The important techniques coming under powder bed fusion are selective laser melting (SLM) and selective laser sintering (SLS) (77). These processes don't require any supports because the un-sintered powder is compacted around the structure. The powder bed Fusion method is described in Figure. 8.

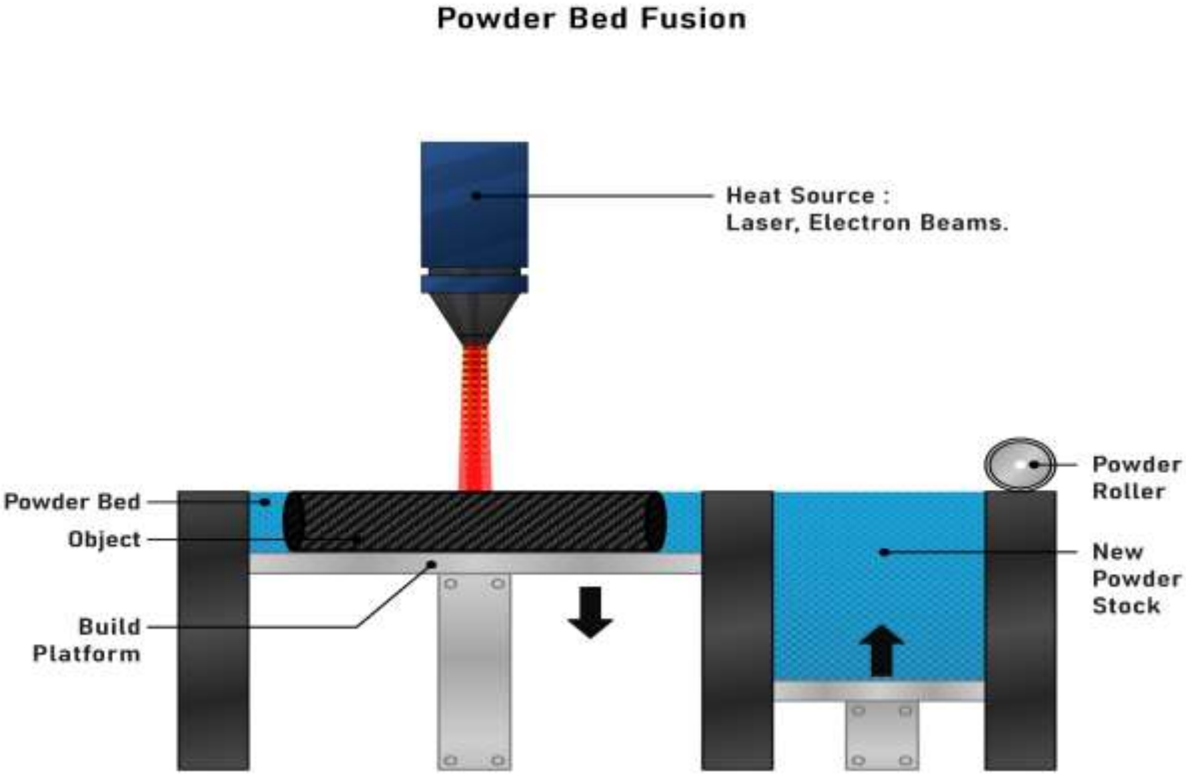

Figure 8: The powder bed Fusion method

6.3.1 Selective Laser Melting (SLM)

SLM is a layer-by-layer method that utilizes a laser light for melting of metallic powders by curing each stage with a high-intensity laser beam in between (78). By doing this, a uniform and dense metallic 3D framework is produced, negating the need for binders or structural supports (68). Metallic compounds need an inert atmosphere to be reactive, where the printing setup is contained inside a chamber. With the aid of this technique, single metallic smart materials and shape-memory alloys (SMAs) can be created. For instance, Shishkoysky uses SLM to create various structures using the shape memory alloys like Nitinol (Ni-Ti) and Cu-Ni-Al (78).

6.3.2 Selective Laser Sintering (SLS)

SLS is similar to SLA, employs a powerful laser to sinter a photopolymer powder rather than a liquid resin. An incident laser beam sinters the powder to create the freshly created layer. The previously created layer is covered with fresh powder using a levelling roller; the un sintered powder serves as support for the overlapping layers. Iteratively rolling and sintering powder is used to create the final 3D structure. This technique's drawback is that due to the high temperatures involved and the need for meticulous washing to remove extra powder, it is currently unsuitable for bioprinting (79). Shells for hearing aids can currently be printed using this technique in 3D. Its capability to print biomaterials suggests that it has the ability to create a variety of custom medical devices (73), (75).

6.4. Sheet lamination

Sheet lamination, a technique of 3D printing that involves stacking, laminating, and layering sheets of incredibly thin material, produces 3D objects. There are several ways to combine the material layers, but the two that are most usually employed are heat and sound. The best technique can be chosen based on the material being utilized, the materials like metals, polymers, and paper are all employed in sheet lamination. One of the less precise 3D printing processes, the technology produces products that need extensive post-production polishing. As the print develops, CNC routers and laser cutter are utilized to mold the print into the required shape. In this method more waste occurs than other 3D printing technologies. Sheet lamination is a technique used by manufacturers to produce non-operational prototypes quickly which is affordable. It should be mentioned that many items made in this technique are too weak to be used as functioning parts and work best as decorative items(5). The process of Sheet Lamination is explained in Figure 9.

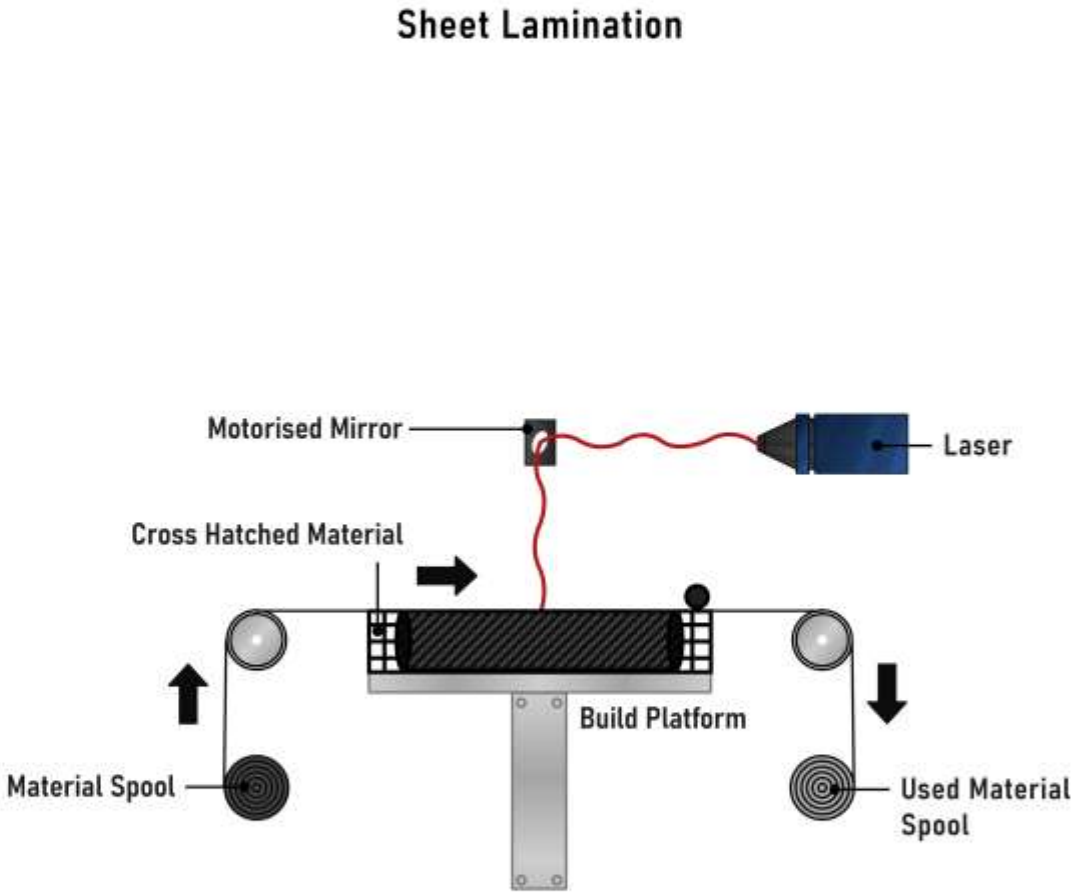

Figure 9: Process of Sheet Lamination

6.5. Material Jetting

The printer that uses photo jetting principle is known as photopolymer Inkjet (poly jet), that made significant advancements in 4D printing technology in recent years. In 4D printing process photo jetting is a method where the microscopic resins are jetted layer by layer to create a platform. Poly Jet technology has recently been enhanced to enable printing on several materials (80), (68). This method operates by simultaneously extruding of various materials through several nozzles of the apparatus. Ge et al. claim that it is possible to print both inactive and active materials in different areas of a structure, such as hinges and joints, leading to the fabrication of structures with an origami-inspired shape that can curl, twist and self-fold in response to external influences (40). SLA, DLP, and Poly jet are light based printing methods where because they can create intricate structural designs, photopolymerizable inks, which are cured by light, are appealing. Finding liquid photopolymerizable compounds that are biocompatible has received significant effort. However, more study is necessary before this technique may be used extensively in the production of biomedical equipment. The material jetting technique is explained in Figure 10.

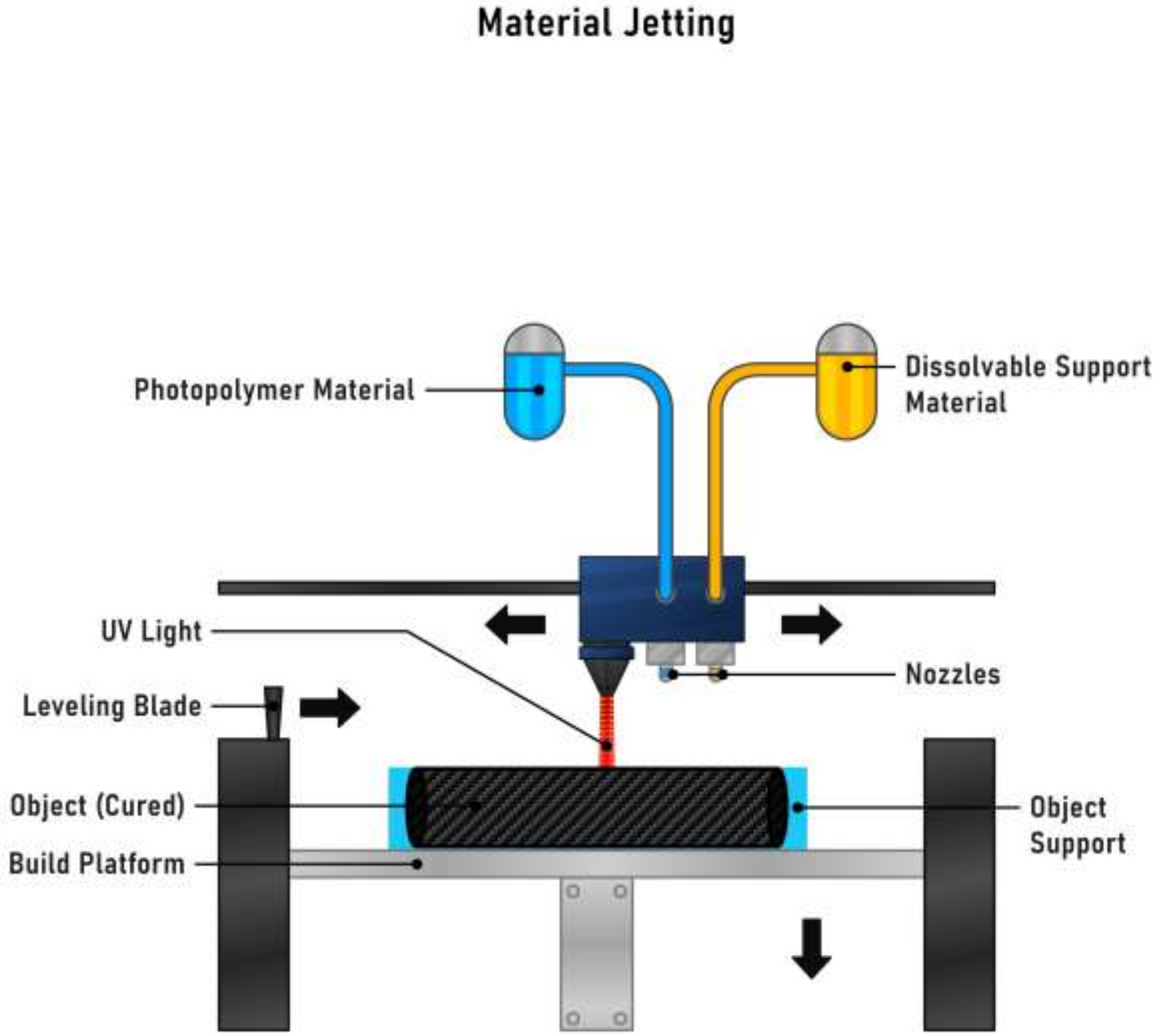

Figure 10: Material jetting technology

6.6. Binder jetting

This 3D printing technique selectively binds a powder bed using a liquid bonding agent. Like SLS, Binder jetting is a 3D printing method that uses powder as the foundation layer and to build a platform. But in SLS, there is a laser light or energy are used to sinter powder but here in binder jetting heat helps to move the printer head over the powder surface and will deposit the binder droplets, whose diameter is 80 microns. Each object layer is created by these droplets, which join the powder particles. After printing of one layer, the powder bed is lowered and a fresh layer of powder is put over the previously printed layer. That process will continue till the finished object is created. The item is then left to cure and become stronger in the powder. The item is then taken out of the powder bed, and any loose powder is taken out with compressed air (5). The Binder jetting process can be demonstrated in Figure 11.

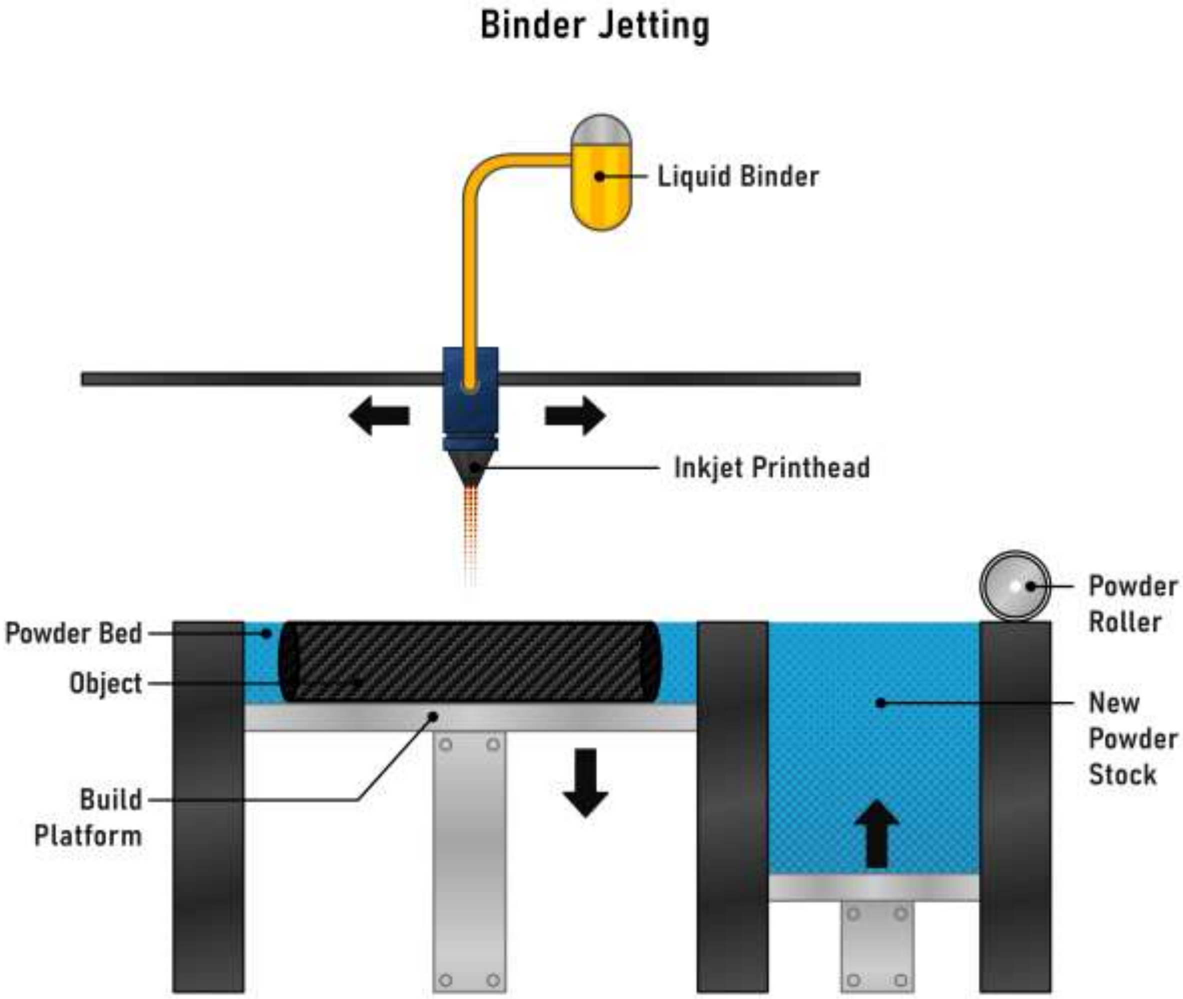

Figure 11: Binder jetting process

6.7. Direct Energy Deposition (DED)

The material is melted and fed by powerful thermal energy simultaneously in the DED process of 3D printing. Three energy sources are frequently used: an electron beam, a laser, or plasma. The heat source melts the material as it exits the nozzle in either powder or wire form, creating intricate designs. This technology can be used to patch up damaged objects as well as to build up prints layer by layer. DED is therefore frequently utilized for maintenance rather than possibly for the production of brand-new printed materials. The use of several powders to combine components and produce various outputs is also a possibility when employing powder feedstock. The major drawback of DED may be that not all of the material is utilized during the process, even if the requirement for a sizable supply of inert gas could be considered a drawback. There will inevitably be some powder that misses its mark and does not melt. DED also has the drawback that parts made in this way frequently need substantial post-processing (5). The DED method can be shown in Figure 12.

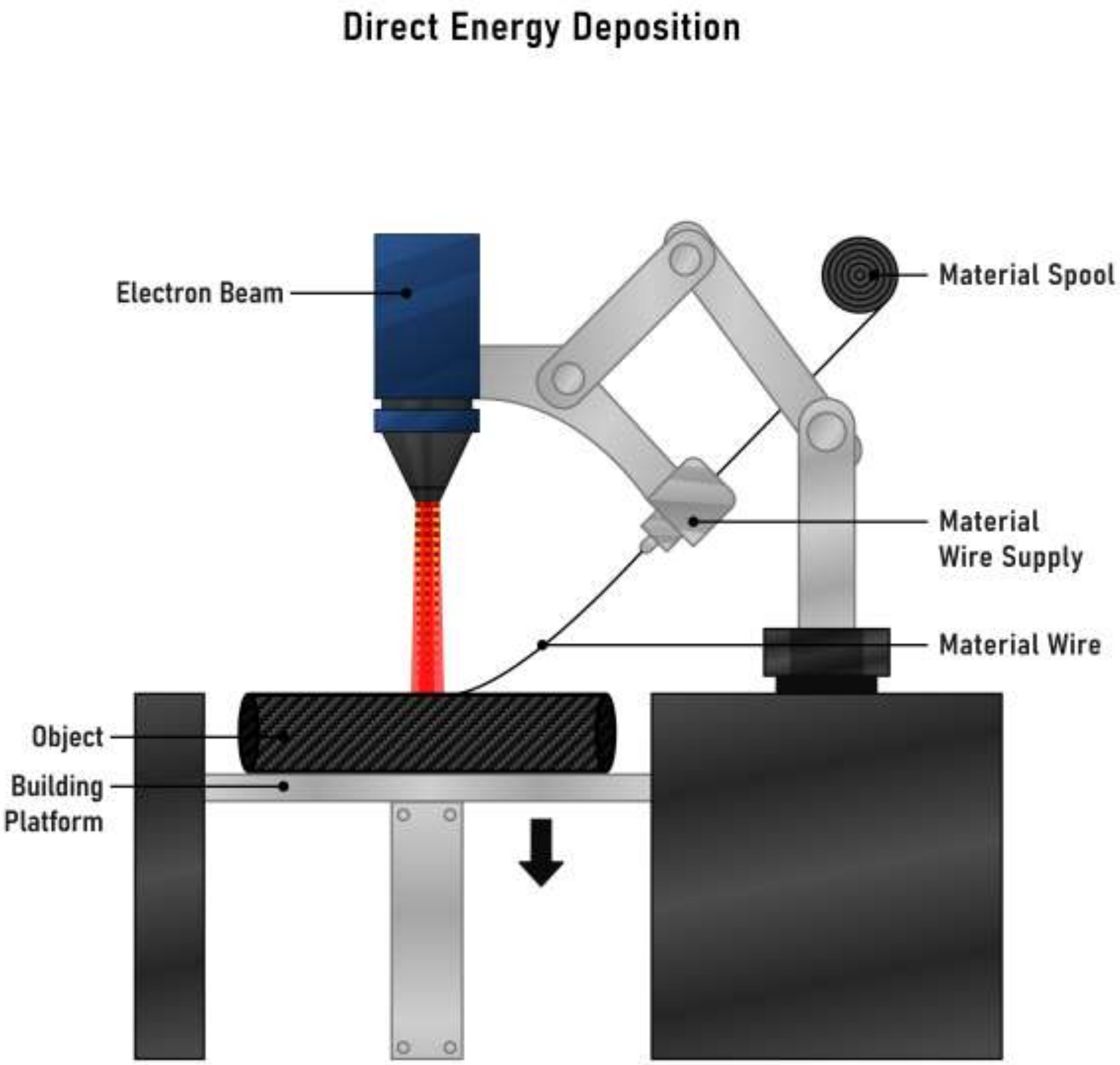

Figure 12: The Direct Enegy Deposition method

7. Applications of 4D Printing in Medical Sector

7.1. Smart Stent

By using the patient's body heat, 4D printed stents will be able to expand and take on the correct shape. With respect to time and temperature, shape of the stent changes. This newest treatment saves a patient's life quickly during a challenging operation (81), (82).

7.2. Organ Printing

Complex 3D body parts are produced by using this cutting-edge method. In order to save the lives of the patient, this method is utilized to create organs from the patient's own cells. It offers possible remedy for the lack of organs (7).

7.3. Smart Multi Material Printing

This method utilizes the layer-by-layer approach with UV curable polymer. It is a new method for printing customizable, intelligent, multi material implants for the human body. By using this method, multi part of the body can be fabricated which can be seen in a 3D-printed body (83), (83).

7.4. In Dyspnea (Respiration/breathing Problem)

Dyspneic infants are saved by the use of 4D printing technology. It quickly produces a medical implant that can adapt to a baby's growth and help them to breathe.

7.5. Tissue Engineering and Intelligent Medical Implants

The shape-shifting material's amazing potential is made possible via 4D printing. Its possible applications include tissue engineering and medical implants that can alter shape inside the body. Scaffold preparing and utilizing for tissue engineering or bone reconstruction is the best example of this. It can be defined as three-dimensional biomaterial structure which is used for bone wound healing/regeneration/ repairing. Scaffolds are often used to regenerate tissues like muscle, bone, and cardiovascular tissues where mechanical characteristics change dynamically with physical activity. The scaffold provides physical support for the growth and development of new tissues(84), (85).

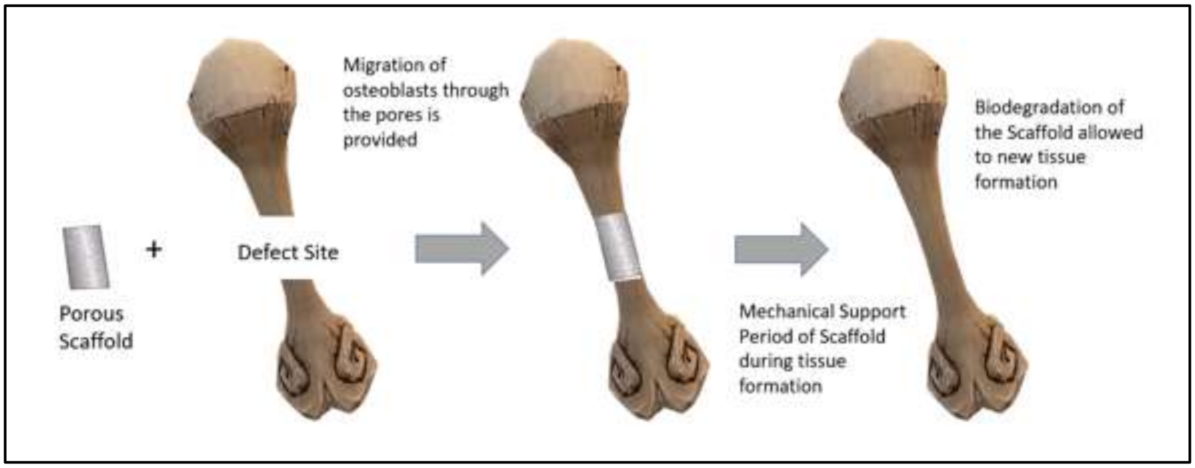

Figure 13: Scaffold is used for tissue regeneration to repair the Bone Defect

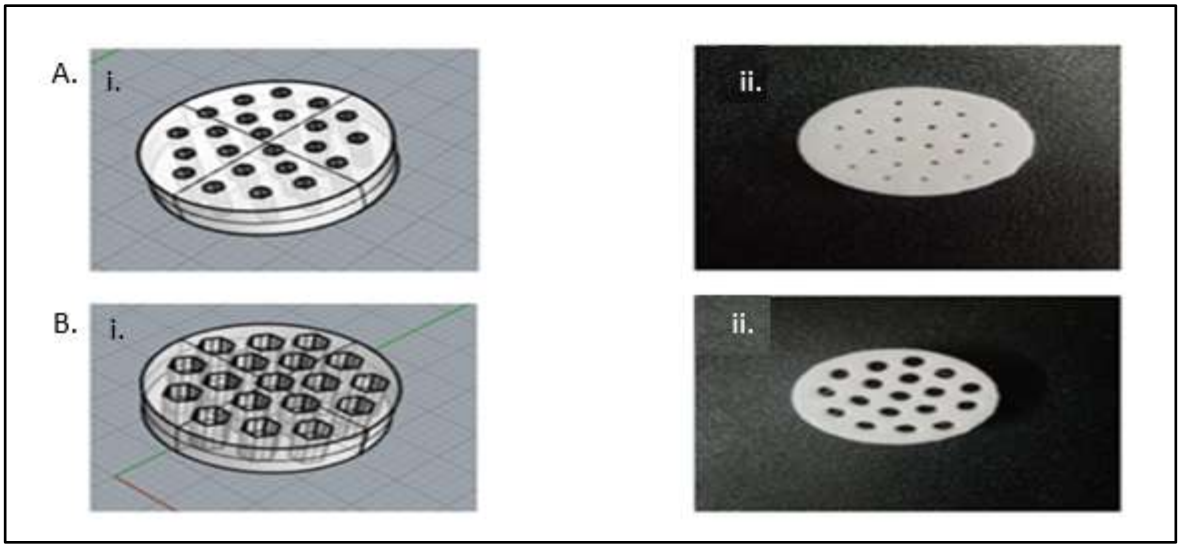

Figure 14: PLA Polymer Coated Scaffolds used for Bone defect repairing A-(i) Scaffold developed in CAD with Pore Size 300µm, A-(ii) Fabricated Scaffold using 3D Printing with Pore Size 300µm, B-(i) Scaffold developed in CAD with Pore Size 800µm, B-(ii)) Fabricated Scaffold using 3D Printing with Pore Size 800µm

7.6. Liver, Kidney, And Heart Prints

By utilizing the smart material, 4D printing method will eventually be capable of manufacture the heart, liver, and kidney. The 4D printing having the capability to print parts with excellent flexibility, accurate fit, and ideal genetic compatibility (86), (87).

7.7. Grafted Skin

There are many opportunities to print skin grafts in the patient's natural color. Additionally, this is helpful for burn patients because it quickly implants in the body and develops just like an original skin (64), (88).

7.8. Creation of Smart Medical Equipment

With the help of this technology, sophisticated, highly functional medical gadgets can be 3D printed. Time has been adjusted in accordance with the needs of the surgery (89), (90), (91), (92).

7.9. Intricate Surgery

To represent the body's appearance and motion, it might develop a haptic model. It may eventually be used for rather complex surgeries that are not compatible with other manufacturing processes. It may eventually be used for rather complex surgeries that are not compatible with other manufacturing processes. With the use of CT and MRI scans, it is possible to create a model using smart material that precisely replicates hand or other body action. It may accurately and precisely depict anatomical details (93), (94), (95), (96).

7.10. Nerves

The peripheral nervous system (PNS) is made up of nerves that composed of bundle of nerve fibers which is known as axons. The basic unit of PNS is nerve, and the function of nerve is to send the electrical impulses. By using the 4D bioprinting the damaged nerves can be repaired. The 4D printed conduits provide good chemical signals and physical signals for regeneration of nerves, and the human mesenchymal stem cells can differentiate into neural cells (97). It is possible to demonstrate the potential for self-enturbulation for dynamic and seamless integration using the way neural conduits work (98). Now-a-days Clinical application of nerve guides is possible, and various research projects are ongoing in this area, highlighting the pressing need for more effective PNS nerve regeneration methods(99).

7.11. Drug Delivery Systems (DDS)

Another important use of 4D printing technology is drug delivery, which has attracted more interest. By setting the SME transition point of thermo responsive materials close to physiological temperature and achieving a wide transition temperature range, localized drug release can be achieved within the body (100). Due to low weight and large surface area of porous polymers it is used as drug carriers (101). Mirani et al. use 4D bioprinting to create a directly activated medication delivery device (102). PCL is a preferred SMP because it is having low melting point, slow in vivo degradation rate and high drug permeability, so it has long been employed in biomedical applications(55). Since hydrogels can include pharmaceuticals, antibodies, and other biological components embedded inside them, their potential as drug delivery vehicles has been extensively reported.

7.12. Implantable Organs

In 1954, there was a successful transplant of a human organ. Because of the development and growth of the industry, there is a greater demand for implantable organs (64). The potential of additive AM for many applications could be drastically changed by the time-dependent aspect of 4D printing(103). In addition to the potential use of printed tissues for transplants and repairs to aid in the fight against a lack of available organs nationwide. For testing medications and doing physiological research, artificial organs may also be employed (104). Before the technology is used clinically, more study is necessary to understand how to use 4D printing to create human organs.

8. Conclusion

Many 3D printing-specific additive manufacturing processes have been updated for usage with smart materials. The high-resolution structures that may be created on the micro and nanoscale make the light-based stereolithography and Poly Jet techniques appealing for biomedical applications. These methods contain photopolymerizable liquid resin layers that are sequentially UV-cured. Further study is necessary to increase the range of material alternatives because there are just a few biocompatible materials that can be used with these approaches. All the materials are not applicable for bioprinting method Shape-memory alloys (SMAs), which are more mechanically resilient, and shape-memory polymers (SMPs), which are low density, biocompatible, and biodegradable using hydrogel and cell laden materials due to the high-temperature processes needed by selective laser melting, fused deposition modelling and selective laser sintering. In other sectors, such as aerospace, defense, and manufacturing, these approaches, nevertheless, demonstrate intriguing capabilities. The usage of smart materials and AM methods affects the shape-memory response, to fully grasp this technology and realize its potential, additional advancements are necessary. Shape-memory materials have undergone many advancements since the advent of 4D printing in 2013. The shape memory materials include SMAs which are more mechanically resilient, and SMPs which are low density, biocompatible, and biodegradable. These can be used to create massive structures, and hydrogels that enable the printing of biomimetic structures. SMPs and SMAs are single materials that can be printed, but they have intrinsic limits that have prompted the implementation of adaptable SMCs. By overcoming the limitations imposed by the physical properties of individual materials, these composite materials can expand the potential of 3D printed objects. 4D printing technology will have a disruptive impact in the medical, engineering, and other industries in the future years. It is a more effective technique in terms of quality, effectiveness, and performance. Every medical model is unique and varies from patient to patient; these models are sourced from specific patients and can be quickly and easily printed, which is extremely beneficial to humanity. On this revolutionary technology, research is increasing now-a-days. It significantly aided the medical industry's ability to produce customized smart implants, instruments, and equipment with greater accuracy. The main goal of this technology, which substitutes traditional scaffold manufacturing techniques, is to create implants with distinctive geometrical properties and features that allow for greater model shape freedom. Organ printing, self-assembling human scale biomaterials and tissue engineering are example of how 4D printing technology has significantly changed the healthcare industry. According to human growth, it leads to the development of biomedical splints, stents, bioprinting, and orthodontic devices. Future advancements in this technology will make it more useful and open up countless opportunities in the medical field.

9. Outlook

Applications for 4D printing in the medical sector will grow in the future to meet the demands for innovation. The ability to create intelligent, personalized implantable medical devices with high output will become a commonplace and crucial technology for surgeons. It delivers details on bleeding, chest wound infection, blood clots are respiratory problems applying a sophisticated multi-print paradigm. The surgeon can now manufacture smart anatomy models of each patient at any point, which was previously impossible due to the increased flexibility in the creation of medical models. Due to the creation of intelligent materials, future 4D printing technology will considerably advance the fields of engineering, medicine, and other relevant fields. Using this technique, huge, adjustable automotive parts that can be modified for the environment and power needed could be useful in engineering. These items enable the plumbing system to alter pipe diameter in response to flow rate and water demand. When there is a break or crack, pipes may have the ability to repair themselves naturally. This cutting-edge technology may also offer the best alternative for smart structure like Buildings and bridges that can adapt to the weather.

Abbreviations

4D	Four dimensional
3D	Three dimensional
CAD	Computer Aided Design
AM	Additive Manufacturing
SCE	Shape Change Effect
SME	Shape Memory Effect
SMM	Shape Memory Materials
SMG	Shape Memory Gels
SMA	Shape Memory Alloys
SMC	Shape Memory Ceramics
SMH	Shape Memory Hybrids
DIW	Direct Ink Writing
CSEs	Cellulose Stearoyl Esters
PPy	Polypyrrole
Tg	Glass Transition Temperature
DED	Direct Energy Deposition
DLP	Digital Light Processing
SLA	Stereolithography
DMD	Digital Mirror Device
PCL	Polycaprolactone
FFF	Fused Filament Fabrication
FDM	Fused Deposition Modelling
MME	Melt Material Extrusion
SLS	Selective Laser Sintering
SLM	Selective Laser Melting
PNS	Peripheral Nervous System
DDS	Drug delivery System

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