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3D AND 4D PRINTING IN PHARMACEUTICAL TECHNOLOGY

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Abstract: 3D printing enables the creation of customized medication, tailored to an individual's specific requirements. This technology allows for precise dosage adjustments, combination therapies, and the incorporation of multiple active ingredients into a single tablet. 4D printing has emerged as a cutting-edge technology in the pharmaceutical field. 4D printing takes the concept of 3D printing a step further by incorporating materials that can change their shape or properties over time in response to external stimuli, such as temperature or moisture. This dynamic capability opens up endless possibilities in drug delivery and tissue engineering. The integration of 4D printing with drug delivery systems enables the development of smart drug carriers that can respond to specific stimuli in the body. For example, a 4D-printed capsule can release its contents at a predetermined location or time, optimizing drug efficacy. This technology has the potential to revolutionize the treatment of chronic diseases, where precise drug delivery is crucial. Furthermore, 4D printing holds great promise in tissue engineering, where the goal is to fabricate functional human tissues and organs. By utilizing materials that can transform their shape or properties, 4D printing allows for the creation of complex, self-assembling structures that mimic natural tissues. This advancement could transform the field of regenerative medicine, offering new possibilities for organ transplantation and personalized tissue implants.

***IndexTerms*– 3d&4d, Material, Techniques, Applications**

1. INTRODUCTION

In many industries, three-dimensional printing (3DP) is becoming the new standard for modern production tools. The way that products are laid out and manufactured is being drastically altered by this additive device. By using a 3-D computer model, customized products can be generated automatically layer by layer. 3DP seeks to offer customized tablets based on the needs of the patient. It considers the pharmacogenomics along with knowledge on their lifestyle, food, and environment. In 1986, Charles Hull became the first person to describe 3DP, a unique technology. Producing personalized pharmaceutical drug products is expedited by computer-based drug layout in conjunction with 3DP technology. The polypill idea in particular is a wonderful example of how 3DP technology has an embryonic in-person dose shape concept. The FDA in the United States approved Levetiracetam, or Spritam, as the main oral drug prescribed to treat epileptic seizures in 2015. Pharmaceutical manufacturing uses a variety of 3DP technologies, including Fused Deposition Modelling (FDM), Stereo lithography (SLA), Direct Energy Deposition (DED), Selective Laser Sintering (SLA), Thermal Injection Printing (TIP Printing), and Power Bed Injection Packaging. Growing interest in pharmaceutical preparation enhancement is being tapped into by 3DP as a potent way to address a few issues with traditional pharmaceutical unit operations. The standard operations of milling, coupling, granulation, and compression in a production unit may yield distinct characteristics for the end product when it comes to drug burdening, medicine delivery, drug stability, and pharmacological dosage form stability. Utilizing endure inject printing, the first wave of 3DP pharmaceuticals was created. Wu et al. developed the first drug delivery system with 3DP in 1996.[1]

Drug designers are constantly coming up with new concepts and refining their manufacturing techniques, materials knowledge, and manufacturing technology to provide superior dose patterns. When developing new drugs, active pharmaceutical ingredients (APIs) have a number of physicochemical and biological characteristics that must be considered and investigated. "Three-dimensional printing" is defined by the International Standard Organization (ISO) as "Fabrication of items through the deposition of a material utilizing a print head, nozzle, or other printer technology". Unlike the more widely used subtractive and formative manufacturing procedures, this approach is part of the additive manufacturing methodology. [2]

The creative process is endless. 4D printing is now a reality with the advent of the 3D printing era in medical and drug delivery. 4D printing adds a fourth dimension—time—to the 3D printing platform. In reaction to internal or external stimuli, products created via 4D printing frequently change their configuration over time (such as heat, p^H, temperature, or even water). The smart materials (feedstock) and the preplanned design of the good's fabrication process (referred to as smart design) may contribute to

conversion into this "fourth dimension". According to an analysis of the literature, 4D printing is a sophisticated form of 3D printing. Here, modifications to a 3D printed product's characteristics, functionality, and form are a result of moment. It appears to be capable of achieving self-assembly, self-repair, and multifunctionality. Thus, dynamic structures and movable shapes with various attributes or functions can be produced using 4D printing. To do this, the 3D printing process applies mathematical modelling to the construction of a building along with intelligent material. [3]

The technique used in 4D printing is comparable to that of 3D printing. It adds another level of transformation over time, where the printed object responds to environmental factors, such as humidity and temperature, to change form in accordance with specifications. This is a cutting-edge technology that is quickly making its way into a variety of fields, including computer science, engineering, medicine, chemistry, material science, and basic sciences. This method is based on the principles of stereolithography, a printing process that uses ultraviolet light (UV) to cure materials layer by layer. Implants are manufactured according to plan and grow as people do. It is a quick and precise way to manufacture soft structures that may be customized.[4]

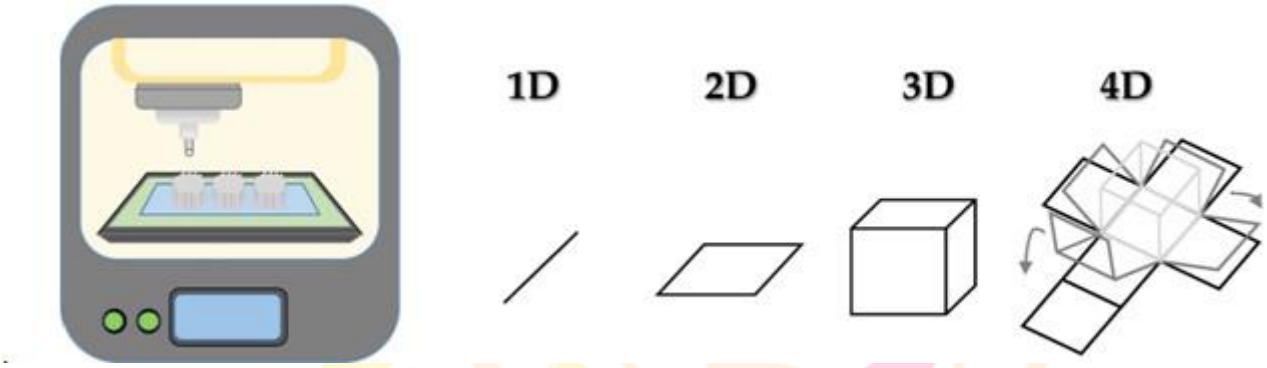

Figure -1: progress of 4D polymer printing Techniques.

2. HISTORY :

i. 3D PRINTING

The genesis of 3D printing may be traced back to Pierre A. L. Ciraud's description in the early 1970s of applying powdered material and then using a high-energy laser to solidify each layer. In this scenario, it is theoretically possible to prepare the object using meltable materials like metals or polymers. During the early 1980s, Carl Deckard developed a method of solidifying powdered bed by laser beam called selective laser sintering (SLS), and Ross Housholder described an idea of sand binding by different materials in a patent entitled: BA molding process for forming a three-dimensional article in layers. Stereolithography (SLA) was Chuck Hull's first commercially viable technology. This technique was based on the UV light-induced photopolymerization of liquid resin.With the use of 3DP technology, several drug delivery systems have been created, including fast-dissolving tablets, microchips, micropills, oral controlled release systems, and multiphase release dosage forms. [5]

ii. 4D PRINTING

Massachusetts Institute of Technology (MIT) introduced 4D printing to the public in 2012 during the TED Conference. Jerri Qi's study on form programming of thermally sensitive composites was a significant milestone in 4D printing technology. When subjected to the right temperature, these composites demonstrated shape memory, allowing them to create the correct 3D shapes. This approach is mostly used in bioprinting and requires a biodegradable base polymeric substance that degrades after tissue creation. Several ideas and techniques have also been developed to give an appropriate methodology for 4D printing. The 4DP (Four-dimensional plan) seeks to serve as a foundation for the design of 4D printed materials. The 4DP strategy mandates that smart materials be classified based on the responses they give when subjected to stimuli. .[6]

3. ADVANTAGES:

TABLE :1 Advantages of 3D and 4D printing

3D PRINTING	4D PRINTING
• Simple to use; no expertise is required. • The careful and accurate dosing of powerful medications at low dosages. • Lower production costs as a result of less material waste. • Appropriate medication delivery for active components that are challenging to manufacture, such as poorly soluble drugs. • Reduce the therapeutic window and make things more complicated. • Genetic variances, ethnic differences, age, gender, and environmental factors can all be taken into account when customizing medication for a patient. • When a patient is on various medications with different dosage regimens, the treatment can be	• The creation of programmable items with self-actuation and sensing capabilities is made possible by 4D printing. • It makes it possible to produce intelligent goods that may be activated without the need of any electromechanical systems or external devices. • Demands that a system or product be developed using the bare minimum of components. • Takes the least amount of time to assemble after manufacture. • Both time and money-efficient. • Decreases the quantity of products prone to errors • High level of sensitivity and productivity. • The design is easily produced, customized, and altered.
tailored to enhance patient compliance. • The versatile design and fabrication of this dosage form allows for the incorporation of immediate and CR layers, which aids in selecting the most appropriate therapeutic regimen for a certain patient. [7] • Prevent the variation in batches that occurs when manufacturing standard dosage forms in bulk. • 3D printers are reasonably priced and take up little room. • It is possible to manufacture small quantities and finish the procedure in a single run. • There is on-demand manufacturing. • Greater capacity to load drugs than with traditional dosage forms. [8]	• Completely personalized items featuring intricate geometric patterns. • Economical. [9]

4. DISADVANTAGES:

TABLE:2 Disadvantages of 3D and 4D printing

3D PRINTING	4D PRINTING
• Nozzle issues pose a significant challenge since they might cause the print head to halt, which alters the structure of the finished product. • Another challenge is clogged powder printing. • The potential to alter the final structure in response to changes in storage conditions, mechanical stress, and ink composition. • Printer-related parameters and how they affect the cost and quality of printing. [10] • The exorbitant expense of the machinery needed makes it less practical. • Someone with training, professionalism, and skill is needed. • When 3D printers are used in enclosed spaces, like homes, they may release potentially harmful fumes and particles that cause cancer. [11]	• Living tissues have dynamic structures, they cannot be constructed. • A lengthy post-processing period. • Manual assembly that is limited to building static structures. • Despite all the progress made in this field, there are still a number of issues that fall into three main categories: material, design, and technology constraints. • Only a limited number of stimuli-responsive materials, typically triggered by a single unique stimulus, can be applied in a 4D process. • One such technique for fabrication is 4D printing. [12]

5. MATERIALS USED:

i. 3D PRINTING:

After going over the many kinds that are included in 3D printing, the next thing that crosses our minds is what are some of the materials that are used in these processes, how viable they are, what kinds of properties they offer, and which processes and applications we use them for. Material factors for each 3D printing technique have thus been explored in the parts that follow, taking these characteristics into consideration.

a) Materials used in stereolithography

As the name suggests, stereolithography is an optical manufacturing process in which liquid monomers, also known as photopolymer resin, are treated with UV light to bond them into polymers (allowing them to cross-link together). Then, in order to maintain the desired pattern, these polymers are layer by layer solidified. SL use a UV laser in a process known as photo polymerization to cure liquid resin into solid plastic. Additives used in stereolithography include solvent, photo-initiators, monomers/oligomers, stabilizers, binders, and reactive diluents, among others.

b) Materials used in fused deposition modeling

Among its many desirable qualities are their biocompatibility, hardness, transparency, and resistance to UV rays. This popular additive manufacturing technology requires a continuous filament and takes thermoplastic material as input.

c) Materials used in selective laser sintering

In this technology, granulated material (often nylon or polyamide) is sintered using a laser as the power source. The process is modeled in three dimensions, and the laser is automatically focused at certain locations in space to fuse the material together into a strong structure. Although it operates on a similar basis to selective laser melting (SLM), it necessitates different technical conditions. When using this laser on powders with lower melting or sintering temperatures, a liquid binder is typically utilized. SLM is typically used with specific metals, such as steel and aluminum, whereas SLS is utilized with a variety of polymers, alloys, and metal powders. provides a comparison analysis of the materials used in this process.

d) Materials used in powder bed fusion

The process involves evenly spaced, firmly bound powder particles in the form of fine layers on a platform.PBF is a type of rapid manufacturing method wherein a thermal source, such as a laser, is utilized to start the partial or total fusion of powder particles. The powder layer is then further smoothed by rolling the powder using a roller or blade re-coater. Melting and sintering are steps in the PBF method's combining process. Electron beam melting (EBM) and selective laser melting (SLM) are two examples of PBF processes. The components, attributes, and uses integrated.

e) Materials used in direct energy deposition

In a basic way, a DED process's working principle is different from a PBF process' in that it uses a high-density, powerful laser to focus on a continuous stream of powdered material that is applied directly to the substance rather than a layer of metallic powder that is pre-deposited.

f) Materials used in laminated object manufacturing

The terms "laminated object manufacturing" (LOM) and "ultrasonic additive manufacturing" (UAM) refer to the two main types of sheet lamination methods, which are as follows: the first uses a laser to cut the material sheets, and it is also known as "ultrasonic additive manufacturing." The second way uses ultrasound to join the sheets. [13]

ii. 4D PRINTING

More flexible and accurate material placement has been made possible by recent advancements in multi-material 3D printing, which are necessary for 4D printing of intelligent materials that react to various stimuli, such as heat, moisture, light, electricity, and magnetic fields.

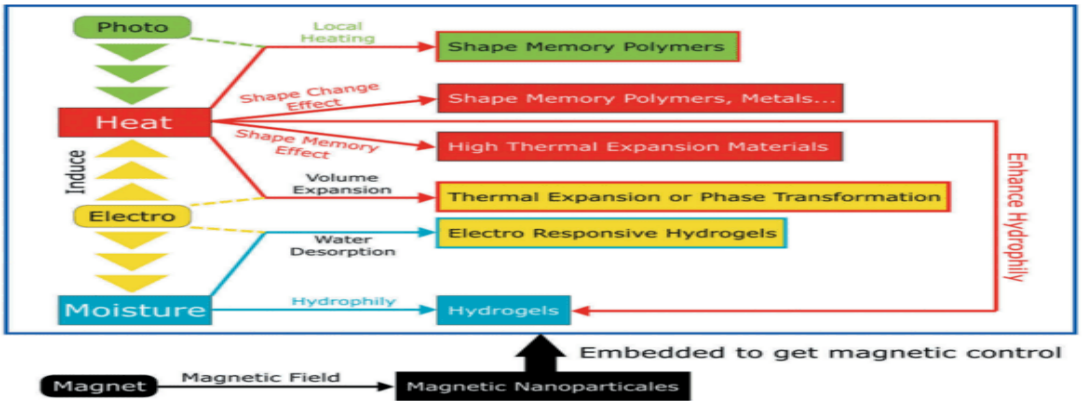

Figure -2: Classes of smart materials that can respond to different types of stimulus including heat, moisture, light, electricity, and magnetic fields

In this part, as seen in Figure we categorize 4D printing materials based on their temporal and/or environmental stimuli. We'll talk about a variety of stimuli, including as electricity, light, current, moisture, temperature, and magnetic fields.

a) Thermo-Responsive:

One of the two mechanisms that primarily drive the deformation of thermo-responsive materials is the shape memory effect (SME) or the shape change effect (SCE). Shape memory alloys (SMA), shape memory polymers (SMP), shape memory hybrids (SMH), shape memory ceramics (SMC), and shape memory gels (SMG) are subtypes of materials based on the SME that are referred to as Groups shape memory materials (SMM). Because they are the easiest to print, SMPs are the most preferred among researchers. Glass transition temperatures [Tg] for SMPs are often greater than operational temperatures. Above their glass transition temperatures, they are designed to undergo particular heat and mechanical treatments. After cooling, they are fixed at a temporary shape devoid of external loads.

b) Moisture-Responsive:

Due to their wide variety of uses and ubiquitous stimulation, materials that respond to water or moisture are much sought after. Since hydrogels can expand up to 200% of their original volume due to their hydrophilia, they are incredibly moisture-responsive materials. Hydrogels are a family of polymer materials that also has great printability. Hydrogels have the advantages of being biocompatible and being simple to print on using direct ink writing. But because of their sluggish reverse reaction, scientists have to wait hours for the hydrogels to dry and shrink. Hydrogel behaviour can only be programmed by giving the swelling anisotropy mixed cellulose fibrils with hydrogel ink so that the shear forces created by the ink's interaction with the print bed may align the fibrils. The programming of the 4D-printed structure is made possible by this alignment, which causes the transverse swelling strain to be four times greater than the longitudinal strain. In order to achieve anisotropically guided swelling. printed a structure in which the hydrogels are restricted in one direction by rigid materialsreport prompt reactions. Who created thin hydrophobic films with accurate and quicker reactions made of cellulose stearoyl esters (CSEs). Hydrogels are typically submerged in water, which causes them to absorb moisture up to the point of saturation. This restricts the hydrogels' potential to act as intermediate materials. However, the temperature of the aquatic environment can regulate how much a hydrogel swells. Gradient crosslinked microgripper joints were created using pNIPAM-AAc soft hydrogels. The saturation point can be changed to produce reversible actuation by heating or chilling the water in which the gripper is submerged. Additionally, unique hinge designs are used to prevent overswelling. Tibbits and colleagues showcased a mechanism wherein they self-assemble to offer resistance against extreme bending.

c) Photo-Responsive:

Materialabsorblightasheatwhenitstrikesanexposedarea,incontrastto other stimuli like heat and moisture.A sequentially controlled selfbfoldingstructure was demonstrated.

Therate atwhich light power isabsorbed by joints as heat is influenced by both the color of the light source andthe joint itself employed a completely different method of usinlight as a trigger for deformation. Parts of a polymer gel block twell when exposed to light have a particular quantity of photoresponsive chromophores infiltrated into them. Furthermore, the patterning of the print demonstrates the flexibility of light as a trigger. A gradient crosslink in depth can be created by shining a little amount of UV light onto liquid resin

d) Electro-Responsive:

Current can also be employed as an indirect stimulus in 4D printing, similar to light. A printed soft artificial muscle composed of ethanol and silicone elastomer was showcased. Applying a current causes resistive heating, which produces heat and evaporates the ethanol. The entire matrix expands as a result of the ethanol's massive volume increase during this phase transition from liquid to gas. In order to regulate the water absorption or desorption, a current is also applied to polypyrrole (PPy) sheets. In order to reduce resistance while moving forward. Attached PPy sheets to an origami micro robot with unique foot shapes. The head is driven forward by a voltage in a humid atmosphere because of the moisture's absorption, and the tail occurs when desorption is because to a lack of electricity.

e) Magneto-Responsive:

Materials are those that can react to magnetic fields through 4D printing. Breger used magnetic fields to apply remote control after including magnetic nanoparticles into a hydrogel-printed micro gripper. During pre-processing, ferric oxide particles are combined with the material solution to complete the embedment process. Additionally, metal and polymer printing could benefit from

this technology. One disadvantage is that the print's size is limited because it needs to be light enough to be impacted by the magnetic field.

f) Smart Materials:

Smart materials have applications in tissue engineering, medication delivery, medical devices, immunological engineering. They promote tissue regeneration by distributing and directing stem cells. They can be used for controlled medicine administration and wound dressing to prevent infections.Smart biomaterials may be classified into two types:

1) Those that stimulate cells and tissues through stimuli-responsive materials.
2) Those with intelligent and regulated functionalities that play an active role in tissue regeneration.

6. TECHNIQUES USED

i. 3D PRINTING:

There are numerous processing steps involved in the formulation of a solid dosage form, including mixing, milling, granulating, etc. The likelihood of batch failure may rise with the number of preparation processes. Significantly fewer processes are needed with 3D printing, which means fewer quality control and regulatory concerns. The 3D printing methods utilized in manufacturing are as follows

a) Binder Jetting:

Two components are employed in the binder jetting process: a binder and a powder fused substance. Layers of powder are adhered to one another by the binder. Typically, the constructed material is in powder form and the binder is in liquid form. A print head deposits alternating layers of binding material and building material as it travels horizontally along the machine's x and y axes. The item being printed on its build platform comes after each layer.

Binder jetting steps -

- A roller is used to distribute the powder material across the build platform.
- Where necessary, the print head applies binder adhesive to the powder's top.
- The layer thickness of the model lowers the build platform.
- The top layer of powder is covered with another layer. Where the powder and liquid are joined together, the item is produced.
- The loose powder stays where it is around the object.
- Until the complete thing is produced, the process is repeated.

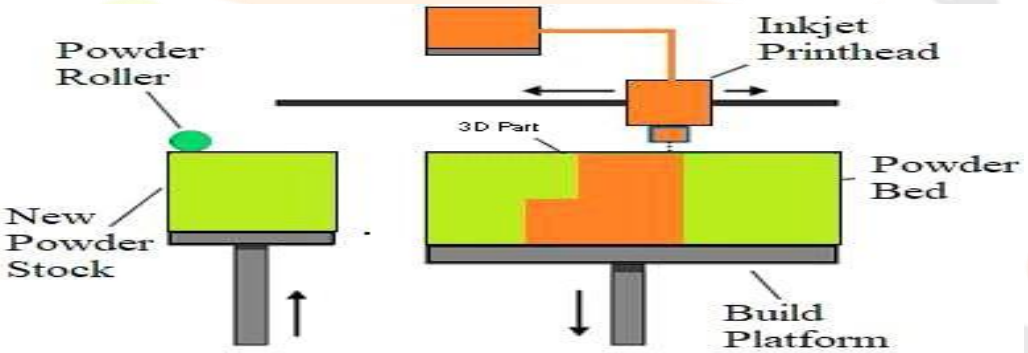

Figure: 3 Binder jetting

b) Stereo lithography (SLA) :

Using a light source to selectively cure photopolymer resin in a vat, stereo lithography is a type of vat polymerization 3D printing technology. An ultraviolet laser is used in stereo lithography to transform liquid plastic (photopolymer) into solid cross-section, allowing precise items to be built directly from 3D CAD data without the need for tooling. Each resin layer is formed on top of the one before it, forming the part layer by layer until it is finished. We refer to this process as photo polymerization. Upon completion of the SLA part, any residual wet resin is removed from the part surface by cleaning it in a solvent solution. Following this, the resin printing process is finished by curing the item in a UV oven. 3D system manufacturing (SLA) High throughput, build sizes up to 1524 mm, unparalleled part accuracy and resolution, and a variety of print materials are all provided by 3D printers. There are other uses for stereo lithography, including the most demanding fast manufacturing for extremely precise and long-lasting prototype shapes.

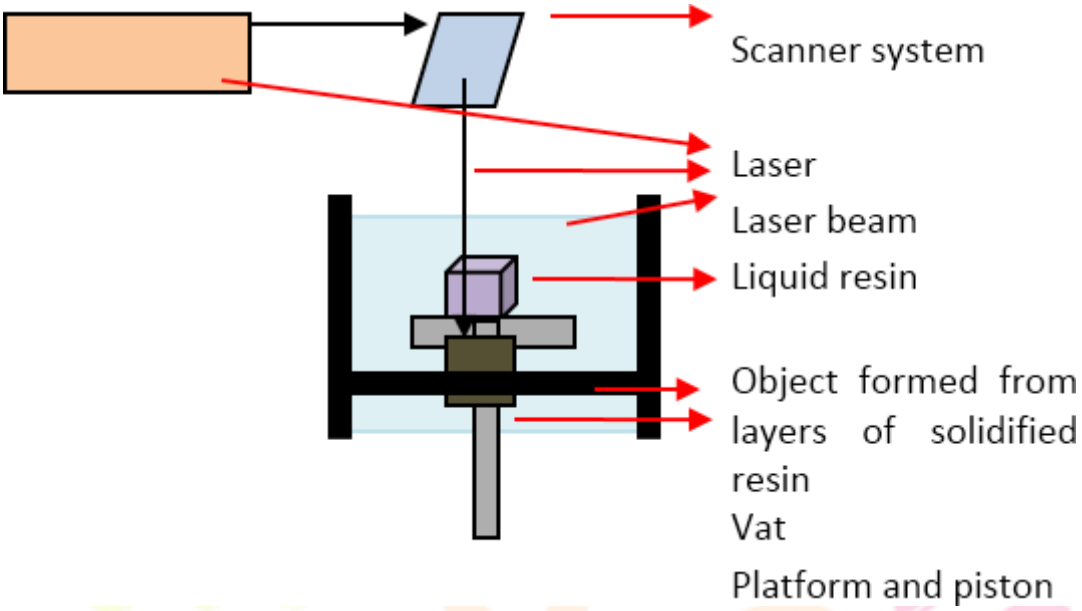

Figure:4 Stereo lithography (SLA)

c) Fused Deposition Modeling (FDM):

In fused deposition modeling, a solid thermoplastic filament is extruded through a heated nozzle, melting it as it goes through the process of material extraction 3D printing. Modeling via fused deposition, or FDM. They are also known by the acronym FFF, or fused filament fabrication. The 3D printer is used to load a spool of filament, which is then passed through to an extrusion head printer nozzle. After the printer nozzle reaches the required temperature, a motor forces the filament through the heated nozzle, melting it. Subsequently, the printer advances the extrusion head in accordance with designated coordinates, depositing the liquid material onto the build plate, where it cools and hardens. When a layer is finished, the printer moves on to the next layer. Printing cross-sections repeatedly allows the thing to be assembled layer by layer until it is complete

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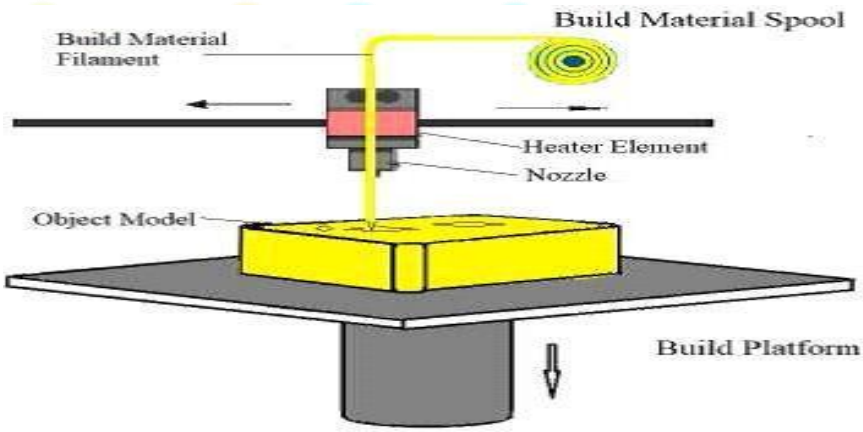


Figure: 5 Fused Deposition Modeling (FDM)

d) Selective Laser Sintering (SLS):

By selectively inducing fusion between powder particles inside a build region, a thermal energy source selectively fuses powder beds to generate solid objects in the process of selective laser sintering. A temperature that is slightly below the melting point of the polymer is first applied to a bin containing powdered polymer. Subsequently, the powdered material is applied extremely thinly on a build platform using a recoating blade or wiper, usually 0.1 mm thick. I then start scanning the surface with a CO2 laser beam. An object's cross-section will solidify when the laser sinters the powder in a targeted manner. The laser is concentrated at the precise spot by two galvos, same like in SLA. The build platform will descend one layer thickness in height after scanning the complete cross-

section. The laser will sinter the subsequent item cross-section onto the previously solidified cross-sections after the recoating blade applies a new layer of powder on top of the most recent scanned layer. Until every product is finished being made, these stages are repeated.

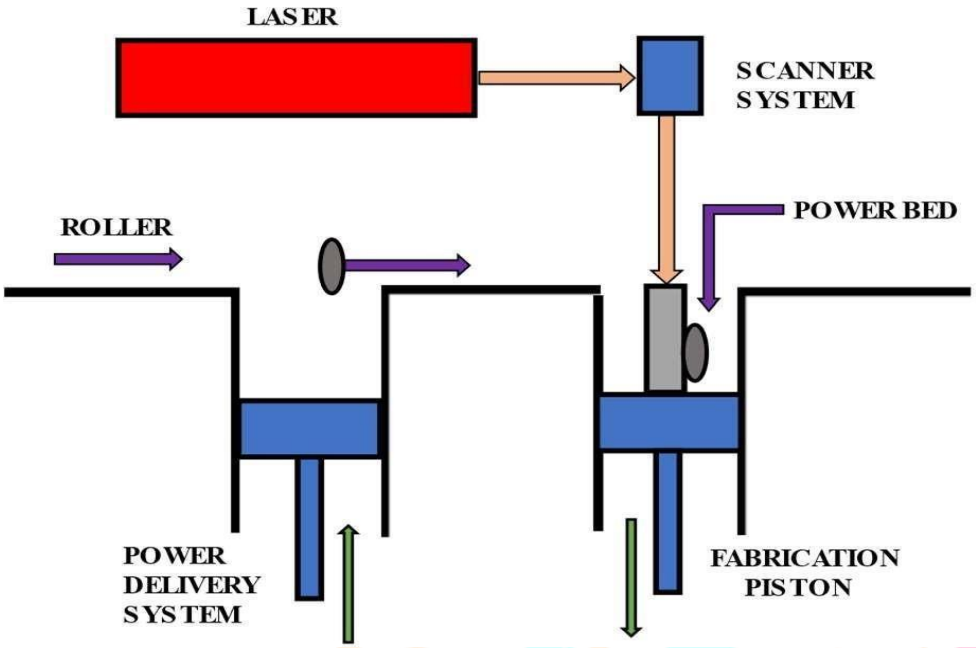


Figure: 6 Selective laser sintering (SLS)

e) Material Jetting (MJ):

A 3D printing technique called material jetting involves depositing material droplets on the build plate in a targeted manner. Objects are built up layer by layer using photopolymer or wax droplets that cure when exposed to light. The operation of material jetting is comparable to that of a typical inkjet printer. The print head sprays hundreds of microscopic photopolymer droplets, which are subsequently cured or solidified by an ultraviolet (UV) light. The construction platform is lowered to the one-layer thickness once the first layer has been applied and cured, and the procedure is then repeated to create a three-dimensional item. Material jetting is not the same as other 3D printing technologies that use a point-wise deposition to deposit, sinter, or cure build material. Material Jetting machines deposit construction material quickly and line-by-line, as opposed to utilizing a single point to delineate the cross-sectional area of a layer. Material Jetting printers may produce many items in a single line with line-wise deposition, which has the benefit of not affecting build speed. Material Jetting is capable of producing parts more quickly than other kinds of 3D printers, provided that the models are placed correctly and the area inside each build line is maximized. Support is needed for objects created with substance Jetting, and it is printed concurrently with the build from a dissolveable substance that is eliminated during post-processing. One of the few applications of 3D printing technology that allows for the production of items built frommulti-material printing and full-color.

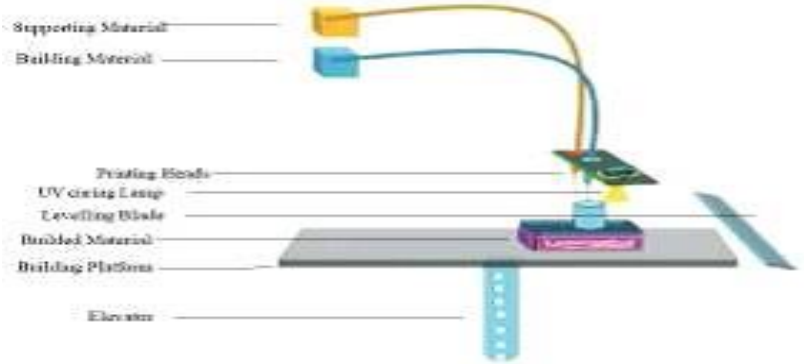


Figure: 7 Material Jetting (MJ)

f) Powder Bed Fusion:

By applying heat to separate the metal powder particles one layer at a time, Powder Bed Fusion is a type of 3D printing that creates solid things. By applying heat to separate the metal powder particles one layer at a time, Powder Bed Fusion is a type of 3D printing that creates solid things. The final component is coated in the metal powder via most Powder Bed Fusion systems, which use machinery to add powder while the thing is being created.[15].

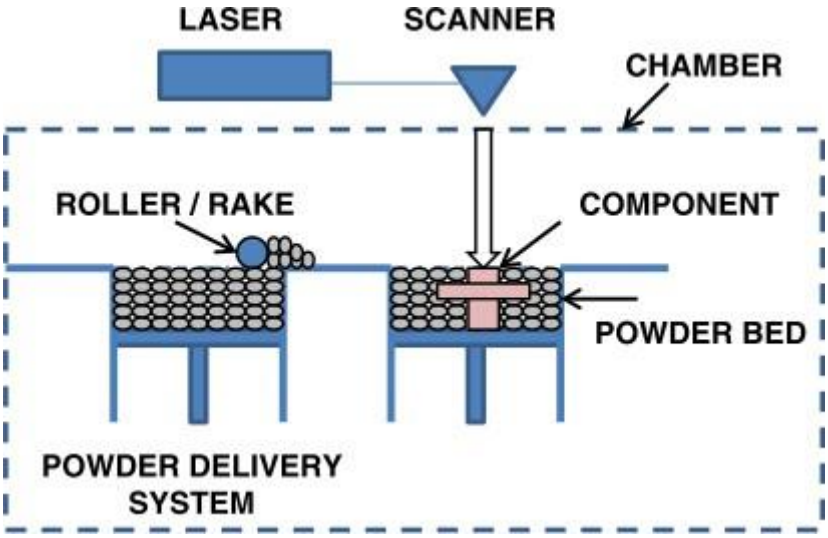


Figure: 8 Powder Bed Fusion

ii. 4D PRINTING:

Materials including ceramics, metal, and plastic are frequently utilized as 3D printing materials to create 3D structures. Unfortunately, due to their inability to respond to outside stimuli, the majority of these materials are not suitable for 4D printing. By altering or changing process factors like nozzle characteristics, temperature, and printing environment, more materials with functional qualities have recently been created using 3D printers. Consequently, selecting the appropriate materials is of 4D printing technology. Smart materials for functional 3D printing or 4D printing have been made possible by recent breakthroughs. These materials include those that self-assemble in reaction to water absorption, temperature, UV light, or self-degradation. One newly developed 4D printing material creates a 4D printed structure by using its ability to absorb water. Underwater, multimaterials manufactured by a Massachusetts Institute of Technology (MIT) research team can change their shape. The team printed material structures using two distinct materials with varying porosities and capacity for absorbing water. On one side of these structures is a stiff waterproof substance, and on the other is a porous material that absorbs water. After printing, the building was immersed in a water bath, allowing water to absorb on both sides. As seen in Figure 9, water absorption led the freshwater-absorbing side to expand in volume while the opposite side remained constant, causing bending to the stiff side. A linear structure with preprogrammed hinges could slowly shrink into a three-dimensional shape in water bath. This method is derived from the multimaterial printing process and incorporates materials with different porosities or architectures into a single printed structure. Oxman developed software for modeling variable properties, as well as a multimaterial printing device that employs concrete foam and cement. Porosity was controlled by altering the cement-to-aluminium ratio. This method can produce functional components with continuous gradients by dynamically grading, mixing, and altering material ratios. These components can have highly customizable features and additional functionalities, as well as be highly optimized for performance, material efficiency, and waste elimination. Shape memory alloys and other temperature-responsive materials are well-known examples of 4D materials because of their ability to expand or contract in response to temperature changes. When the temperature of a shape memory polymer rises over the critical temperature for shape change, the deformed structure returns to its normal state. Figure 9 shows how shape memory polymers can be employed as filamentous material in the material extrusion (ME) process to print temperature-sensitive artificial structures that can be folded back into their unfolded states. Figure 10c shows a functional 3D robotic system that can self-fold from a single flat material into a three-dimensional structure. Six These devices can perform a range of functions, such as degradation in liquids like acetone or water, temperature-activated self-folding, and actuation controlled by an external magnetic field. Materials that react to light or photos can also be used for 4D printing, Sunlight or UV rays can activate 3D printed things. Figure 9 illustrates how UVresponsive polymer strands containing azo chemicals can deform. The polymer-chain structure deforms due to UV light radiation, changing its colour from white to purple. The polymeric chain shifts from the ordered to the disordered pneumatic phase, which results in this colour change. The printed object's colour returns to its natural white when kept in a dark setting. Similar methods have also been reported to change the forms or surface patterns of some light-responsive materials instead of their hue. Photovoltaics, medicinal gadgets, aeronautical structures, and shopping bag packaging are just a few applications for these light-responsive materials. Materials that react to UV light can be found as ME filaments.

UV-responsive materials have promising uses in the entertainment and fashion industries, for example, One important category of intelligent materials for 4D printing is biomaterials. Using 3D printing technology, functional materials that might break down on their own within the body were investigated in late 1990s. The human body is made up of dynamic, constantly moving systems, thus every part is exposed to a different environment and has to adjust over time to variations in circumstances like body fluid or temperature. Consequently, for invivo application, printed body parts or structures ought to exhibit dynamic functioning behaviours. In this sense,

biocompatible materials ought to break down in the bodily milieu over time. In the body, the aforementioned materials undergo water or UV-responsive processes between seconds to days, but biomaterials may take years to fully decompose in a fluid environment. Polylactic acid (PLA) and poly-caprolactone(PCL) are two well-known examples of self-degrading materials. The primary material used in the ME method is PLA, while the primary material used in the selective lasersintering methods is PCL. It has been observed that both materials deteriorate over a number of years, eventually dissolving the polymer chain entirely in bodily fluid. Except for degradation, these methods did not take into account any time-dependent changes used stereolithography to design a supporting structure.

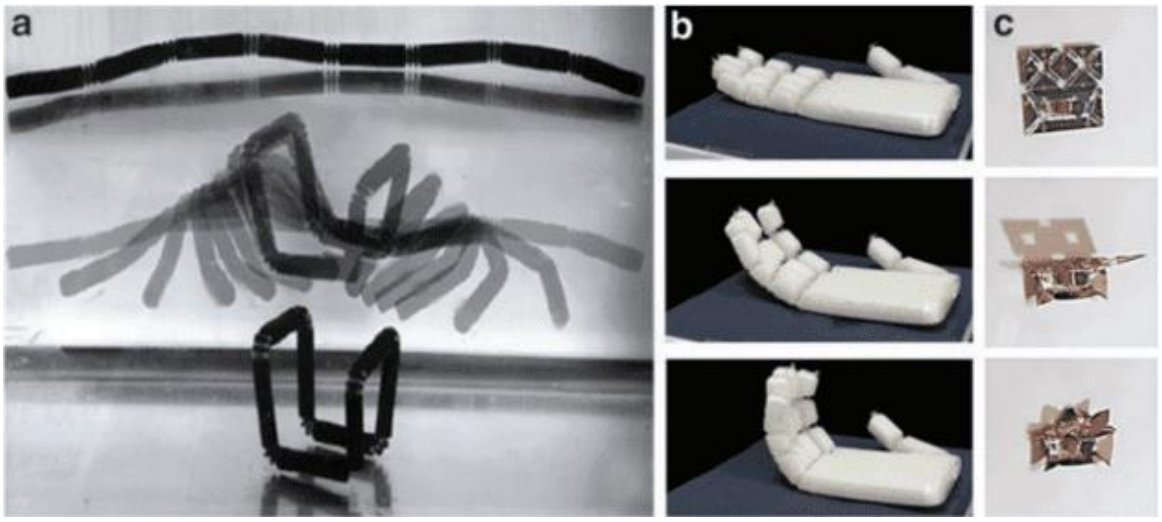


Figure -9: Technology examples for 4D printing. (a) Massachusetts Institute of Technology (MIT) prints a building that is transformed from a 1D to a 3D using materials that absorb water. Reprinted from Tibbits with permission.14Authorized by John Wiley & Sons, Ltd. In 2014. (b) Korea Institute of Science and Technology's artificial hands with temperature-responsive design. (c) A working 3D gadget made by MIT. Reprinted from Miyashita et al. With permission. Six IEEE Copyright © 2015.

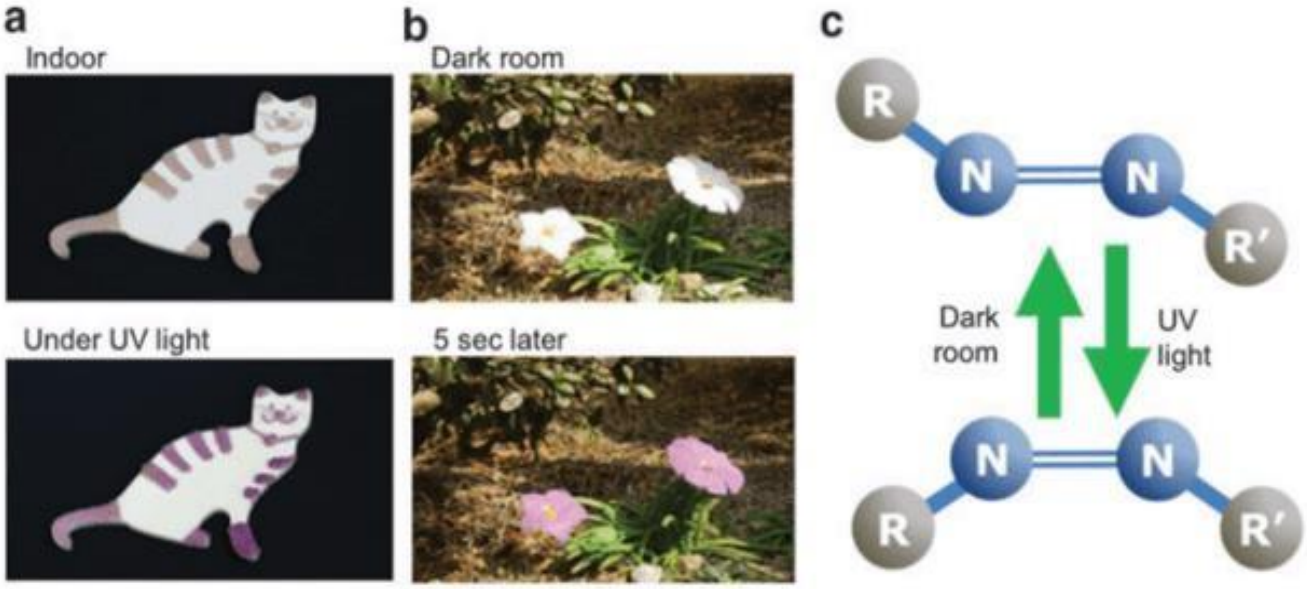


Figure-10: Printing examples of objects made with a photoresponsive material: a flower, a cat, and a schematic depicting how the microstructure of a polymer changes in response to light.

For newborns with severe trachea bronchomalacia, the stereo lithography (SL) apparatus approach with liquid PCL is used to avoid airway collapse during normal breathing.As a biocompatible and biodegradable material, PCL substance printed the supporting structure with a specific design for patients under a year old, but as in figure11 illustrates, the splint expanded to meet the patient's changing airway size over the course of three years. The materials were totally eliminated from the body after three years, at which point the fully developed airways could operate on their own. This illustration shows how plans for modifications in shape and material properties, when combined with 3D printing technology, can be achieved.

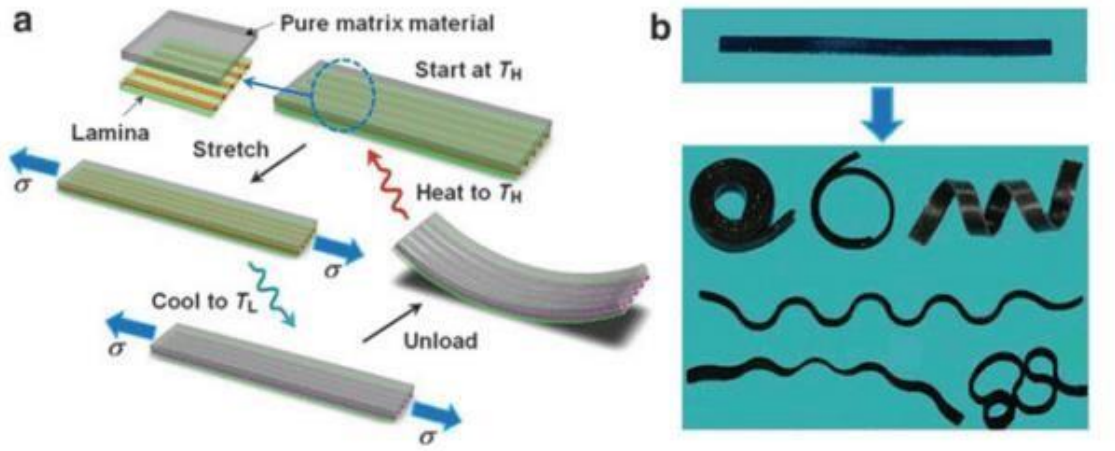


Figure-11:Using shape memory polymers in 4D printing. Diagram showing the folding process in (a) and sample photos showing folding by heat in (b). Reprinted from with permission. AIP Publishing LLC, 2013. All rights reserved.

4D biomaterials have great potential and are very helpful in medical. Numerous healthcare applications, including the creation of self-assembling humanscale biomaterials, tissue engineering, and nanoparticle design, can benefit from the usage of 4D printing. The development of functional human tissues has been the focus of multiple bioprinting efforts undertaken by Organovo Holdings Inc., U.S.A. This startup is employing 4D printing technology to create an artificial human liver. Smart pharmacolog y, personalized medicine, and programmable cells and tissues that can precisely target therapies for diseases can all be made possible by the technology's potential to develop programmable biological materials with changeable shapes and properties. Using a ME 3D printer and Thermal Polyurethane (TPU), a shape memory polymer filament, we were able to build a hexahedral planar structure. Although TPU may be used to print every part, we created hinges with varying thicknesses to enable the correct bending and deformation of every arm, as seen in Figure12b and c. Additionally, in order to enhance shrinkage strain as temperature increased, we joined the six faces by introducing TPU lines through holes that were predesigned.

7. PRINTERS FOR 4D PRINTING

Standard 3D printing materials, such as PLA or acrylonitrile butadiene styrene (ABS), are designed to print at pre-determined temperatures and nozzle diameters in each 3D printer. Current 3D printers may experience problems with smart materials that perform specific roles or multicomponent materials since they have the potential to agglomerate, clog, or resolve during printing. As a result, several different ways have been used with 4D printers. We used a printer with a coated nozzle tip that was modified to print TPU consistently using the ME method. This printer includes a heated bed to ensure proper heat circulation while printing. The printing nozzle easily clogs because TPU has a high thermal expansion coefficient and compresses in the nozzle when heated. In addition, there's a potential that the molten TPU may flow over the cold end sections, that might lead the printed lines, layers or pores to adhere badly. The TPU printer nozzle is coated in polytetraflouroethylene and has a barrel that is 1.2-1.5 times longer than normal PLA nozzles to avoid molten material overflow and friction. To reduce heat loss, the heating device is also placed near the nozzle. Printing multimaterial components is an important step in the 4D printing of structures with the required functionalities and adaptability. With the use of multi material printers, printed structures could be able to alter colour, shape, or electrical characteristics in reaction to heat, water, light, or UV radiation. By combining two or three distinct materials into a single printed structure, multimaterial printers can create biomaterial structures or functionally graded structures. Multiple material printing printers have already been produced. Using nonheated me created functional electroactive polymer actuators by discrete multimaterial manufacturing. Using a hybrid manufacturing system that combined direct print (DP) and SL technologies, Lopes et al. Also created biomedical scaffolds and 3D structural electronics. This allowed them to create 3D constructs with embedded electronic circuits. An nScrypt micro dispensing device and a 3D SystemsSL 250/50 machine were used in the design and development of a hybrid SL/DP system. dispensing pump connected to the SL machine by linear translation stages that are orthogonally aligned. This method was also used to build a comparable manufacturing process for the fabrication of 2D and 3D monolithic structures with embedded electrical circuits. Part design, process planning, integrated manufacturing (which included several SL and DP starts and pauses as well as numerous intermediate processes), and postprocessing were all engaged in the process. Substratum/mechanical structure production was handled by SL, while DP conductive inks were used to create connections. Basic functional demonstrations using both two- and three-dimensional circuit designs were completed. Professional-grade ME systems were first used for discrete multimaterial manufactured. The development and construction of a multimaterial, multitechnology ME system allowed for the fabrication of parts employing diverse build process variants (changing layer thickness and road width). In order to enable the strategic, spatially controlled thermoplastic deposition of several materials with multiple extrusion nozzles during the same build, two old ME machines were upgraded and integrated onto a single manufacturing system. An overall control system, a central PC, a bespoke application (FDMotion), a graphical user interface, a build platform attached to a pneumatic slide that moved the platform between the two ME systems, and an overall control system enabled the automated process. The ME machine controls contour and raster road widths during the manufacturing process by feeding more or less material through the nozzle for a specific extrusion head speed. These parameters can be chosen from a range using the ME part preparation software. [16]

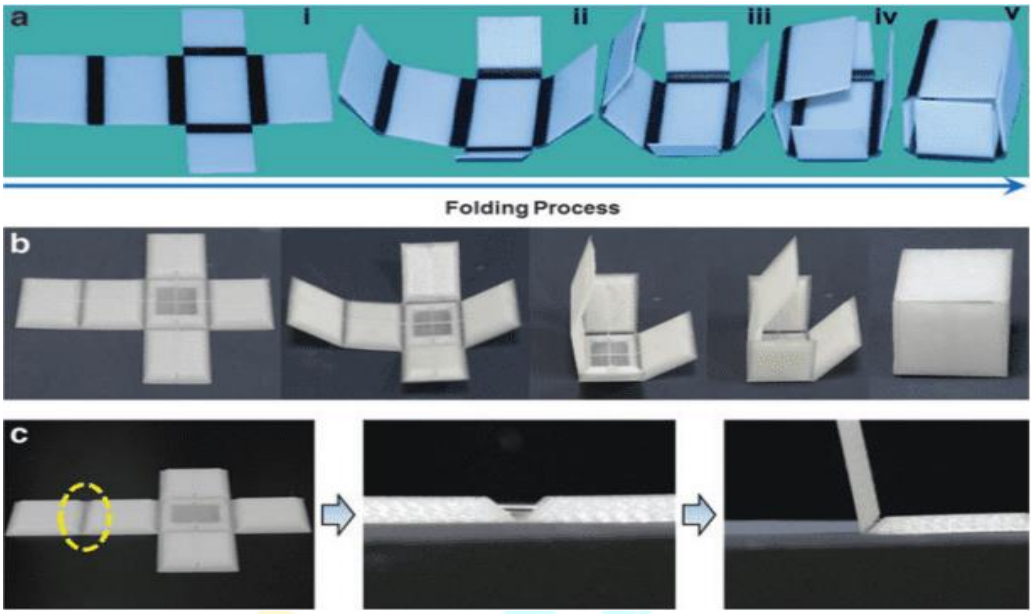
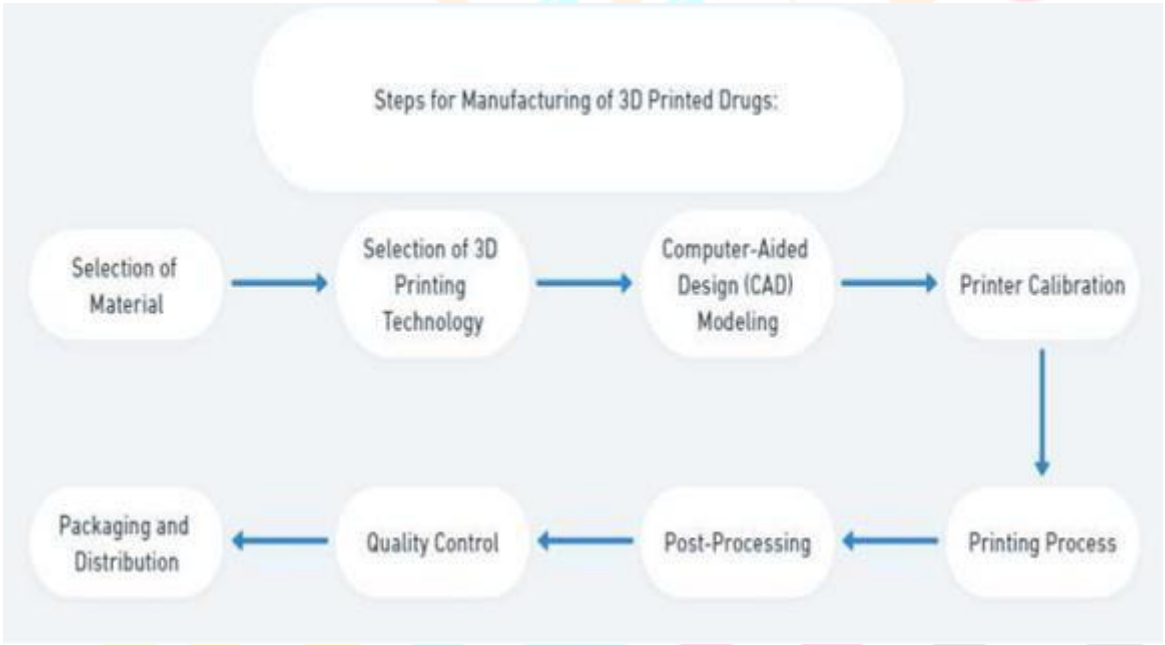


Figure-12:(a) The procedure of folding cubes produced in a composite material with a shape-memory polymer hinge. Reprinted from with permission. AIP Publishing LLC, 2013. All rights reserved.
(b) The cubes printed with a single shape memory substance are folded. (c) One-material hinge concept for a heat-induced folding cube.

8. STEPS FOR MANUFACTURING 3D PRINTED DRUGS:



a) Material Selection:

Choose the drug's active pharmaceutical ingredient (API). Choose the right excipients, or inert substances, such as fillers, binders, and disintegrants. To obtain the required qualities, formulate the medication by mixing the API and excipients in precise proportions.

b) Technology Selection for 3D Printing:

Assess various technologies for 3D printing, including extrusion-based printing, stereolithography, and powder bed fusion. Picking the best technology requires taking into account a number of aspects, including the drug's properties, the appropriate dose form, printing speed, and resolution.

c) CADmodeling—Computer-Aided Design

Using CAD software, create a digital model of the intended medication dose form. Give the medication product's measurements, form, and geometry in the CAD model (Rhinoceros 3d, Free CAD, Fusion 360).

d) Printer Calibration

Set the 3D printer's calibration in accordance with the manufacturer's guidelines. To guarantee precise and accurate printing, modify settings like temperature, speed, and resolution.

e) Material Preparation

Get the medicine formulation ready for 3D printing. Make a customized ink, filament, or powder mixture with the medicine

formulation and any additional additives needed, depending on the 3D printing technology that is used.

f) Printing Process

- Insert the ready-made medication composition into the 3D printer.
- Launch the printing procedure, which entails layer-by-layer material deposition or fusion using the CAD model.
- If needed, the printer may precisely put the material and harden it using a laser or nozzle.

g) Post-Processing.

- Following printing, apply post-processing techniques to improve the qualities of the drug product 3D produced.
- These techniques can include curing, drying, or further treatments like exposure to heat or light.

h) Quality Control

- Perform thorough quality control testing on the manufactured pharmaceutical items to guarantee that the requirements for safety, effectiveness, and quality are met.
- Conduct analytical testing to confirm the identity, potency, and purity of the substance.
- Perform dissolution testing to evaluate the drug's absorption and release throughout the body.
- Carry out stability tests to assess the medicines' shelf life and storage circumstances.

i) Packaging and Distribution

- Ensure that the 3D printed medication goods are packaged in appropriate containers with clear usage instructions and labeling.
- Observe legal rules regarding distribution and packaging.
- Give the medications to hospitals, pharmacies, and other medical facilities[17].

9. DIFFERENCES BETWEEN 3D AND 4D PRINTING:

Table:3. Differences between 3D printing & 4D printing.[4]

CHARACTERISTICS	3D PRINTING	4D PRINTING
Built Process	3D printing replicates a 2D structure layer by layer, from bottom to top.	4D printing is an advancement of 3D printing.
Material Used	Utilizes thermoplastics, ceramics, metals, biomaterials, or nanomaterials	Uses smart, multi-material, and self-assembling materials to produce an item that changes shape after manufacturing. There is a need to design new materials according to the needs of the applications.
Object shape flexibility	Rigidity, lack of flexibility	Object form changes over time and with temperature changes.
Programming of material	Not utilize any programmed or sophisticated material.	Use programmable and modern (mainly new) materials that can give a variety of functions.
Applications	Its applications include medicine, engineering, dentistry, automobiles, jewelry, toys, fashion, entertainment, aerospace, and defense. Industry sectors include industrial art, toys, robotics, entertainment, automotive, aerospace, fashion, and bio/medical gadgets.	3D printing enables dynamically changing configurations for all applications 3D printing enables dynamic form altering for many purposes, including self-repairing and regeneration.

10. APPLICATION OF 3DP TECHNOLOGY TO PHARMACEUTICAL DOSAGE FORMS:

3D printing has a wide range of uses in the production of various pharmaceutical dosage forms and delivery methods. This method has been applied in the past 20 years to create a variety of one-of-a-kind implants, tablets, capsules, transdermal drug delivery patches, and self-emulsifying drug delivery systems with the singular goal of creating a customized medication. Following the US revolution in precision medicine in 2015, more research has been done on customizing medicines, which has led to the use of 3D printing. The FDA released guidelines for additive manufacturing methods in 2017. To the best of the regulatory agencies' knowledge, 3D printing can now formally expedite this procedure by creating customized formulation in small quantities for more accurate application. provides an overview of several dose forms made with different 3D printing processes.

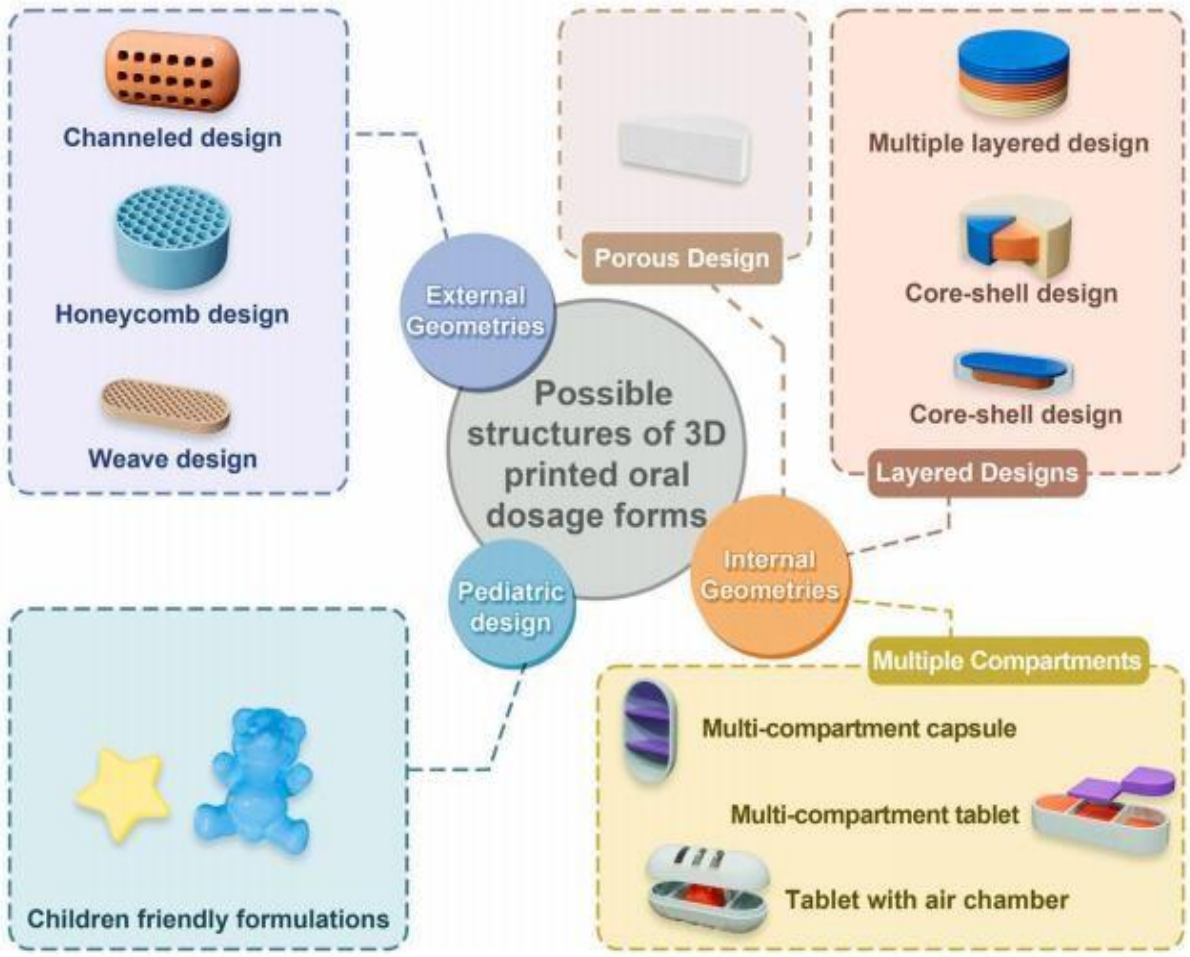


Figure: 13. Possible structures of 3D printed oral dosage forms

- It may also be used for medication delivery with a modest level of patient compliance.
- Potential applications include process optimization and performance modification for industrial design, aircraft, medical, tissue, and architectural engineering, among other fields.
- It primarily focuses on the two possible locations for pharmaceutical product development to advance into uncharted territory, producing advanced delivery systems, and customized medicine.
- In Healthcare industry to create dental implants.
- On fabricating an organized release multi-drug implant for bone tuberculosis remedy.
- Helps in Organ printing, biomaterials and cell-laden materials.[18]

4D PRINTING:

- Hydrogels can be combined with various cells, such as mesenchymal stem cells, fibroblasts, and endothelial cells, to create tubular constructs that are 4D printed to resemble vasculature.
- Following several weeks in culture, the cells spread, multiply, and mature throughout the constructions, resulting in the formation of vascularized structures that express classical adhesion proteins and genes specific to endothelium.
- However, a significant obstacle in the sector is the approach's poor resolution, which prevents the creation ofsmall-scale vascular structures.
- In fact, the finest resolution on hand forCompared to non-tailored scaffolds, ornamented constructions demonstrated increased in vivo bone formation, enhanced cell differentiation and calcium deposition, and higher expression of RUNX2, ALP, osteocalcin, and osteopontin genes.[19]
- The capacity of medications to release pharmaceuticals at the ideal time and anatomical place has been a primary focus of the drug development business.
- Authority overcardiac microtissues, hydrogels loaded with cells for three-dimensional human cancer spheroids or structures, or stents with shape memory for the trachea and bronchi. It's important to note that these tiny implants for the trachea and bronchi can adjust physiologically to the surrounding tissue by changing their form and arrangement in response to various microenvironmental conditions.
- In fact, when these implants were put, a newborn with trachea bronchomalacia did not require artificial ventilation three weeks after surgery.
- One of the main goals of the drug research industry has been the ability of medicines to release active ingredients at the appropriate anatomical location and timing.[20]
-

11. USA-FDA APPROVED 3D PRINTED DRUG PRODUCTS WORLDWIDE:

In August 2015, Aprecia Pharmaceuticals unveiled the first medication that treats epilepsy with the ZipDose method. For the treatment of partial seizures, primary generalized tonic clonic seizures, and myoclonic seizures in adults and children, the FDA approved the medication product SPRITAM levetiracetam for oral use. Spritam's porous, quickly disintegrating formulation was created using ZipDose technology. Spritam was created to meet the needs of people experiencing issues with their prescribed pharmaceutical regimen. Large doses up to 1000 mg can be incorporated into a single dosage form thanks to ZipDose technology. This technology made it easier for patients to comply with their medication regimen. With ZipDose technology, the special manufacturing capabilities of 3D printing are combined with the science of medicine formulation. Aprecia Pharmaceuticals holds a license approved by the FDA to develop pharmaceutical dose from all over the world. [21]

Table: 4. Fabrication of dosageforms by 3D printing technology

3D Printing	Dosage Form	Drug
FDM	Catheter	Nitrofurantoin
FDM	Implant CR	Dye
FDM	General Device	Gentamicinsulphate, Methotrexate
FDM	Implant	Nitrofurantoin, Hydroxyapatite
Thermalink jet printer	Tablet	Prednisolone
Inkjet Printing	Implant	Levofloxacin
Thermalinkjetprinter	Solution	Salbutamol
Inkjetprinting	nanoparticles	Rifampicin
Thermalink jet printer	Solid dispersion	Felodipine
Thermalink jet printer	Nano suspension	Folicacid
Desktop 3D printer	Tablet	Guaifenesin
Alab-scale 3D Pmachine	Capsule	PseudoephedrineHCl
3DP	Tablet	Acetaminophen
3DP	Multi-drug implant	Rifampicin,Isoniazid
Extrusion printing	Tablet	Captopril,Nifedipine, Glipizide
3Dprinter	Microfluidic Pump	Saline solution
3Dprinter	Fast-disintegrating	Paracetamol
Stereolithography 3DP	Tablets(MR)	Paracetamol
3Dprinter	Biodegradable patch	5-Fluorouracil
Stereolithography printer	Anti-acnepatch	Salicylic acid
3Dprinter	Tablets	Paracetamol

12. AVENUES OF 4D PRINTING FUTURE RESEARCH:

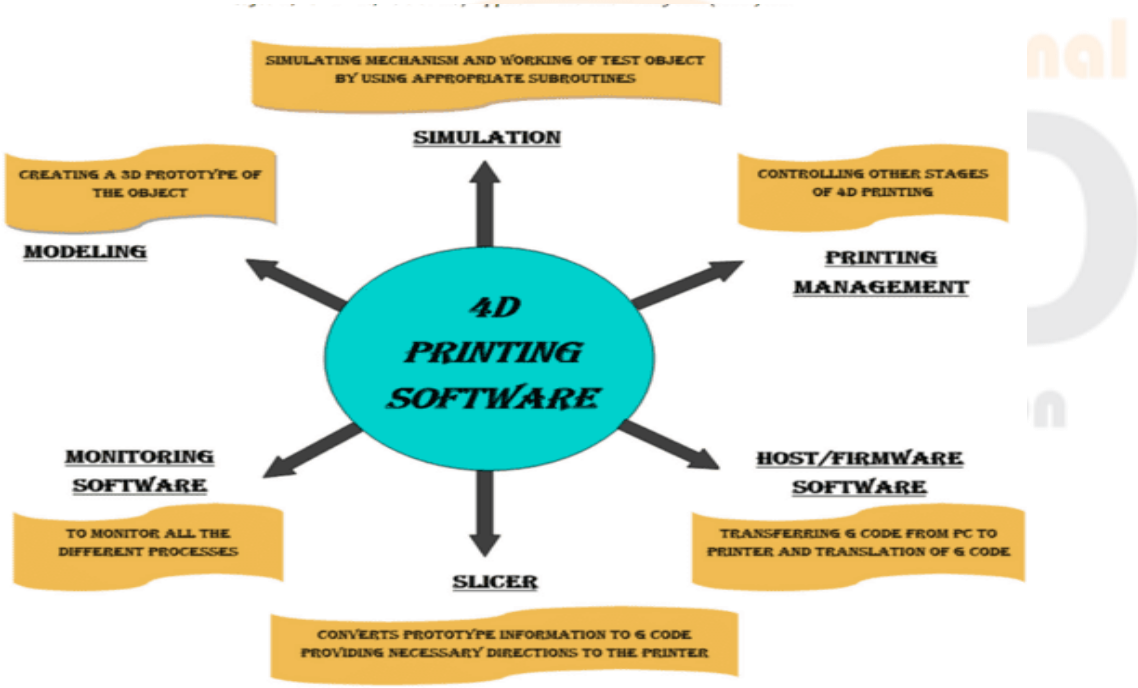


Figure-14: 4D Printing Software

The numerous developments in 4D printing portend a bright future in which the method will find use in every industrial and manufacturing domain. The development of novel, highly adaptable materials that can change their structure in response to various environmental stimuli is necessary to usher in a prosperous future for cellular printing. For the many kinds of 4D printing procedures,

new software needs to be developed. The base smart material, the printing method, the product's structural and geometric requirements, and the 4D printing technique's shape-changing mechanism must all be taken into account while developing software in this field. The development of 4D printing procedures that are not limited to a single material and can adapt to several materials is imperative. In the numerous biomedical engineering subfields, 4D printing has a lot of promise. Nonetheless, considerable work is required to create bioprinting methods that are quicker and more affordable.[22]

13. CONSTRAINTS :

3D PRINTING

- The majority of 3D printing methods use nozzle technology to build layers upon layers to create solid objects. This makes it difficult to maintain a steady flow when the print head breaks off. Inadequate feeding, binder migration, and nozzle head blockage are additional risks that could influence the formulation's properties.
- Choosing the raw materials is the initial stage in the printing of pharmaceuticals. We must choose carefully, taking into account factors like melting point, thermal conductivity, physical and chemical characteristics, and printableness. Thus, selection of content is crucial.
- Several equipment operate at high temperatures, which causes materials to disintegrate even before they are manufactured. Many formulations exhibit surface defects as a result of the deposition of plastic beads and powder layer over other .
- Post processing operations that alter the final properties and look of the product, such as brushing off excess powder and unsticking things from the construction platform, can incur waste.
- Since these procedures are entirely computer-designed, there is a chance that they will be hacked online. There will be a significant leakage of phony production, and the CAD data and blueprints are accessible. The situation will pose a threat to manufacturers as well as consumers. [23]

4D PRINTING

- A lot of intricate production procedures that would otherwise need a lot of labour could be replaced by 4D printing technolog y. Therefore, there won't be a need for such labour, which would cause joblessness and a financial catastrophe.
- As of right now, this technology might only be permitted for usage in a select few specialized settings, such military facilities, space stations, hospitals, and conflict zones. It can take decades before 4D technology is widely used.
- In the field of bioprinting, 4D printing might have advanced bioprinting. However, research on unidentified side effects of 4D bioprinting of organs and tissues is lacking.
- The high initial cost of 4D printing is another significant barrier, partly because so few companies are currently developing the necessary technologies , methods that facilitate 4D.
- Following commercialization, 4D printing prices might go down.

14. CHALLENGES:

In medication delivery applications, it has encouraging outcomes. Numerous obstacles must be overcome in order to increase the performance of 3D printed items and broaden the variety of applications in innovative drug delivery systems. These include optimizing the process, enhancing device performance for varied usage, choosing suitable excipients, post-treatment methods, etc.

Achieving high-quality 3D items requires optimizing some key parameters, such as printing rate, printing passes, print head line velocity, time gap between two printing layers, distance between nozzles and powder layer, etc. It also plays a significant role in post-prototyping processes like drying (using hot air heat, microwaves, or infrared radiation) since it affects the quality of the final 3D printed goods. Uniaxial compression and suspension dispersal techniques are used to boost the drug loading capacity in 3D printed tablets; nevertheless, this methodology has the drawbacks of increased complexity and spray nozzle clogging[24].

15. CONCLUSION:

The environmentally friendly technology of 3D printing has the potential to displace more established ones. The environmental effects of industrialization can be lessened by 3D printing since it is not only economical but also environmentally benign. Conclusion: Several 3D printing technologies with varying materials compatible with them have developed as a result of the literature review. There are various benefits and drawbacks connected to each 3D printing method. Three-dimensional printed parts require very little post-processing, aside from their capacity to handle complicated and elaborate forms. Although it works better with polymeric materials, FDM is the most widely used 3D printing technology. Various challenges, including transportation difficulties, plague powder-based technologies like SLS.

The impact of 4D printing has increased. The development of printable smart materials, printing methods, and mathematical models will make it possible for 4D printing to improve surgical procedures, targeted drug delivery, soft robotics, and other hitherto unimagined engineering domains. In the medical field, where patient-specific medical device designs are essential, 4D-printed devices hold great promise. The extent to which 4D-printed surgical procedures have previously been successfully implemented in clinical settings is demonstrated by their success.

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