Section A-Research paper

3D PRINTING AS A NOVEL FORMULATION TOOL: A REGULATORY PERSPECTIVE

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Abstract:

A three-dimensional product may be created layer by layer from digital designs using three-dimensional printing (3DP). 3DP employs programming and computer-aided drafting technologies to produce three-dimensional objects by depositing material in layers onto a substrate one after another to reliably dispense modest amounts of medication along with fine spatial control for individualized drug administration. The 3DP technology is being extensively researched in the field of medicine delivery after the FDA approved the first 3D printed tablet of levetiracetam sold under the brand name Spritam. The pharmaceutical sector has used a variety of 3DP methodologies during the past 15 years including Inkjet printing systems, Nozzle-based deposition systems, and Laser writing systems. It has been utilized to develop novel and complex drug delivery systems that are almost impossible to produce by employing conventional formulation techniques providing alternatives to standard drug delivery systems. Regulatory control over the 3DP technique is in the nascent phase. Current requirements along with various regulatory challenges are the focus of the pharmaceutical community. The market is expected to grow to more than $1.3 billion per annum in the next few years. The article discusses the prospects and merits of various cutting-edge techniques and their regulatory perspective, making 3DP an exciting alternative technique.

Keywords: Three-dimensional printing, inkjet printing systems, nozzle-based deposition systems, laser writing systems, complex drug delivery systems.

Introduction

The construction of substantial things using a planned accumulation of polymers is known as 3D printing (3DP), a novel technique. [1] Rapid prototyping and digital fabrication are both possible with printing in layers, this is one of additive manufacturing's subtypes. The term "additive manufacturing" has been adopted as the standard by the American Society of Mechanical Engineers.[2] Making items of any size and shape is possible with the use of computer-aided design tools. However, this might be confusing for pharmaceutical manufacturing because additive processes like coating, capsule filling, and film lamination are all additive processes. Biomedical, pharmaceutical, construction, architectural, and aerospace are just a few of the many currents and future fields that make extensive use of 3D printing technology.[1, 3]

It may be effectively used while producing in modest quantities for things such as prototyping, customization, and manufacturing intricately crafted products, etc. It can also democratize design, which is sometimes challenging to produce using conventional techniques. Additionally, it delivers a decrease in energy use and material waste, speeds up the time to market, is environmentally benign, and ultimately lowers production costs.[4] the 3D printing process may be shown as figure 1.[5, 6, 7]

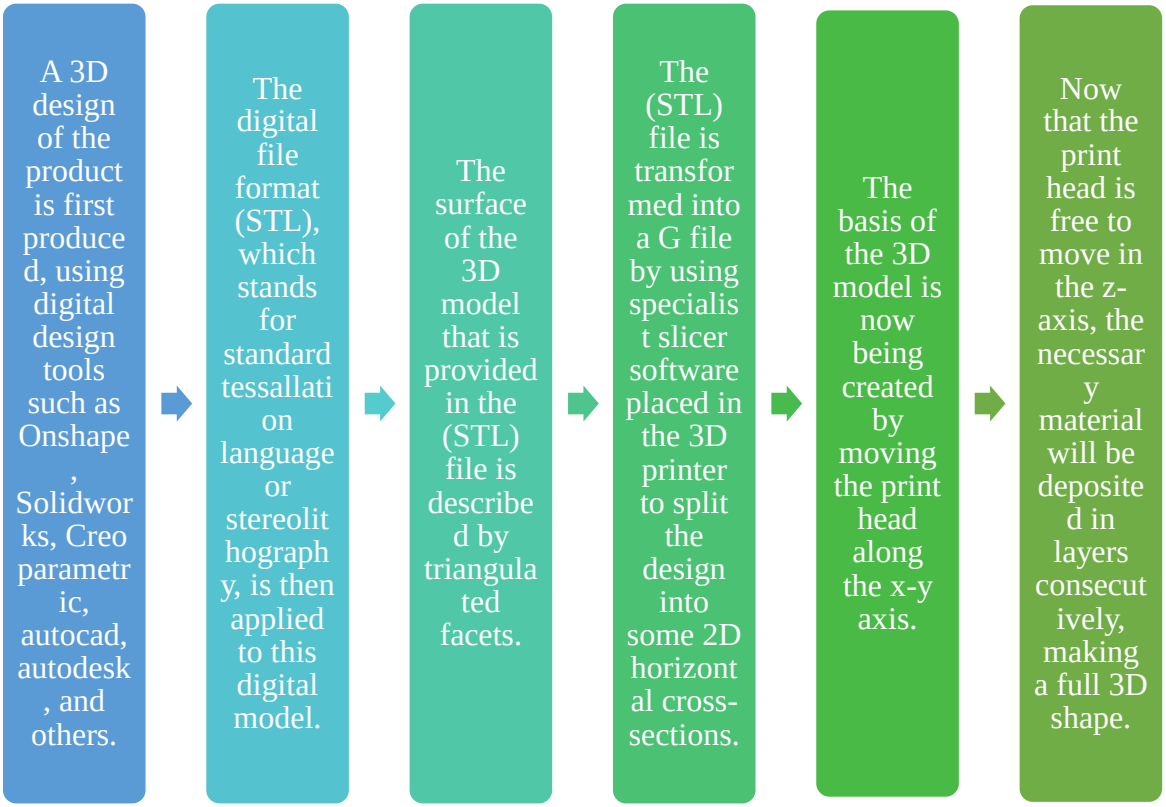

Figure 1. 3D Printing Process.

The (STL) file format is one of the most compatible format for 3D printing technology. A software program like Magic's (Materialise) may be used to rectify any conversion problems that can arise while converting a 3D model to an STL digital file. Other file types besides STL, such as the 3D manufacturing file format (3MF) and the additive manufacturing file format (AMF), are employed. The material type, colour, texture, qualities, and other characteristics are unknown to STL.[8]

History

Chale's Hull coined the phrase "stereo lithography" in 1984, a pioneer of 3D systems, and it was patented in 1987.[9] Hull came up with the notion of using UV light in a novel way to transform 2D computer-aided design software components into 3D things. Hull developed a device using a UV laser to cut the layers of acrylic into forms and stack the layers together to

construct an item using the photopolymers he had found. After years of study and testing, in 1988, Hull made $100,000 off the sale of his first 3D printer.[10]

In 1990s, 3D printing technology was mostly employed for medical tasks including creating personalized prostheses and dental implants. In due time, A 3D-printed scaffold enabled researchers to create organs from patient cells. As medical professionals continue to advance their technology, they seek to create fully functional organs without the need for a scaffold. In 2008, researchers were able to produce the first prosthetic leg. A 3D-printed jaw was manufactured in 2012 by a Dutch manufacturing company, layer by layer. Today, 3D printers are widely used in hospitals and are reasonably priced. Organs and other items that are essential to human life may now be created using 3D printers.[11] Types of 3D printing technology is given in figure 2.[12, 13]

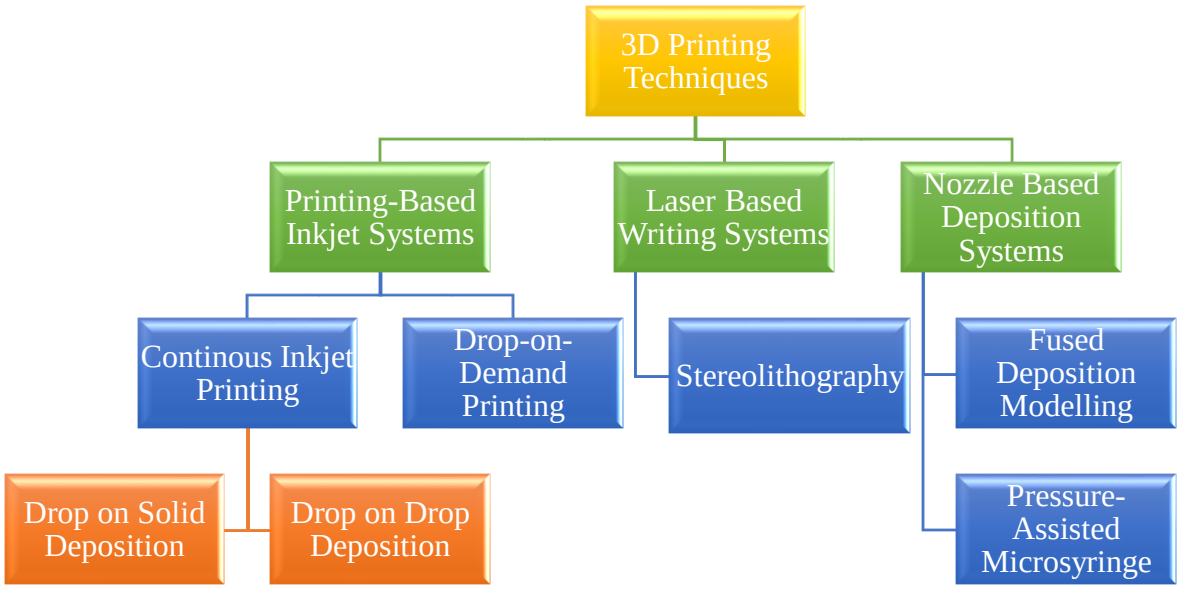

Figure 2. Types of 3D Printing Technology.

1. **Printing-Based Inkjet Systems:**

   The two technologies that makeup inkjet systems are continuous inkjet printing (CIJ) and drop-on-demand printing (DOD). Employing a high-pressure pump, CIJ technology generates a constant flow of ink via an aperture that is 50–80 mm in diameter, as opposed

to DOD technology generates drop that are 10–50 mm in diameter and 1-70 pL in volume.[14] A printing head is included in both IJ systems and must control fluid viscosity as well as droplet speed, size, and duration. A piezoelectric crystal or a thermal head are two the types of printer heads that may be used with the DOD system.[15] The ink is heated on-site and creates droplets that expel ink in thermal DOD, also known as bubble jet printing. In piezoelectric DOD, a quick volume shift due to crystal shape creates an acoustic pulse strong enough to propel ink. The thermal DOD method restricted with relation to volatile liquids, but this piezoelectric DOD approach may be used with a diverse range of liquids. Additionally, the piezoelectric DOD approach is capable to operate at ambient temperature with less volatile and more biocompatible liquids. The thermal technique can reach temperatures of up to 300 degrees Celsius, adversely affective drugs. As a result, the piezoelectric DOD mechanism conceivably more appropriate for pharmaceutical applications.[16]

The drop-on-drop deposition and drop-on-solid deposition variants of DOD technology may be further classified into two categories. A high-resolution 3D structure is produced through drop-on-drop deposition, in which the droplets are ejected onto one another by the printer head to form a solid layer. When using this direct writing IJ-printing technique, it is possible to create microscopic drug delivery systems with a variety of geometries. The droplet size used is approximately 100 microns, and smaller layer thicknesses may be caused by surface wetting, solvent evaporation, or shrinkage. The entire composition should be appropriate for jetting and quick solidification in the printed fluid.[17] the viscosity and volatility of the printed fluid, among other physical characteristics, are crucial in avoiding the coffee ring effect, fluid leakage, and nozzle blockage. According to reports, the ideal viscosity is between 8 and 14 cps. The product's loading capacity and stability are also impacted by the physicochemical and therapeutic qualities of the integrated medicines.

Drop-on-solid deposition appears to be more appropriate as the pharm printing of a variety of medications, from chemical entities to biomolecules, as compared to drop-on-drop deposition. Since the solid components (powder) are spread out on top of a platform and the binder (a liquid ink) is selectively sprayed on the powders, drop-on-solid deposition is also

known as drop-on-powder or drop-on-bed deposition, plaster printing, or powder bed 3DP.[18] A fresh coating of powder is distributed once the platform is lowered, and the cycle is continued until a 3D structure is created. The binder ink binds the powder bed, which typically has a height of 200 µm and particle sizes between 50 and 100 µm, together to produce a three-dimensional object. Layer thickness and interlayer distance should be regulated for better adhesion between layers. The quality of the finished goods is greatly influenced by reactivity of the powder bed with the binder ink and topological characteristics.

2. **Laser-based writing systems:**

The first commercially viable solid freeform manufacturing technology was stereo lithography (SLA), a laser-based printing process. A 3D item is created with SLA by carefully controlling the photo-polymerization of a liquid resin. The tank containing the liquid photopolymer contains a moveable platform.[19] after the appropriate laser is applied, the lifting platform is first lowered into a vessel to a depth corresponding to the thickness of the newly polymerized layer. The lifting platform first starts near the liquid photopolymer's surface. Repetition of this procedure results in a stable 3D object. SLA is extremely relevant to thermo-labile pharmaceuticals because of its high resolution, which enables the creation of complex structures, it also limits heating during the printing process. It is crucial to select a photopolymer that is both suitable for human use and a liquid that swiftly hardens when exposed to ultraviolet (UV) radiation. Consequently, even though SLA is widely employed in tissue engineering, the pharmaceutical uses of SLA are severely constrained by the absence of Food and Drug Administration (FDA)-approved photosensitive polymers and the low drug loading. A new 3DP method called digital light projection (DLP) combines liquid photopolymer resins and a laser beam to solidify and construct objects, just as SLA.[20] Utilizing a digital mirror device, which enables the simultaneous curing of a single layer, distinguishes DLP from SLA. The layer manufacturing time is significantly decreased due to the ability to cure a complete layer at once due to the simultaneous management of millions of mirrors. DLP provides a somewhat quicker construction process and simple layer thickness control as a result.

High-power laser such as, selective laser sintering (SLS) fuses a powder photopolymer. The platform supporting polymer lowers to refill with powder after the laser selectively fuses the powder photopolymer.[21]

SLS technology has the benefits of speed, chemical resistance, and high strength. Direct metal laser sintering is a comparable technique to SLS (DMLS). While SLS is used on a variety of materials, including polymers, metals, and ceramics, DMLS is only used on metal alloys. SLS is also comparable to selective laser melting (SLM) and electron beam melting (EBM). However, EBM and SLM melt metal powders throughout the layer-by-layer procedure, in contrast to the sintering technique. While EBM employs a high-power electron beam in a vacuum, SLM uses energy from a laser beam to heat the powder particles over the melting point to fuse them. Though EBM's precision and surface quality are poorer than SLS's, it can offer better throughput and more uniform dispersion of heat fields. Drug-loaded implants frequently employ EBM and SLM.[22]

There are other additional 3DP technologies available in addition to those already mentioned, including multi-jetting modelling, selective heat sintering, and laminated item manufacture. Some of those 3DP technologies have a significant potential for pharmaceutical applications in the future even if they are not currently employed for pharmaceutical manufacture. As a result, significant progress in material sciences and the development of new suitable materials will enable more widespread uses of different 3DP technologies (Table 1).[23, 24]

3. Nozzle-based deposition systems:

In light of the fact that popular IJ printing-based approach has the problems of having Low drug loadings, an unsatisfactory surface, and nozzle-based deposition devices that would be good substitute to get over those restrictions.[25] Nozzle-based deposition methods mix the binder with the solid parts before 3D printing and immediately the mixture is deposited through a nozzle to create a 3D object rather than dumping the binder solution on a powder bed. Fused deposition modelling (FDM) (Table 2) and pressure-assisted micro syringes (PAM), which refer to the processes whether or if the substance melts, respectively, are two subtypes of this technique.[26]

One of the most widely used 3DP processes is FDM, which has undergone extensive research in several industries, including biotechnology, food, and pharmaceuticals. The term "Fused Deposition Modelling," or "FDM," refers to a method. It involves layering a plate with molten thermoplastic polymer filament that is extruded via a high-temperature nozzle with instantaneous solidification.[27] the thermoplastic polymer and active pharmaceutical ingredient (API) are combined in pharmaceutical goods by melting them together at the proper temperature or incubating them in a certain solvent before to being incorporated into the filament. An affordable manufacturing method, FDM has certain benefits including the ability to produce difficult medications that are exceedingly complicated geometries, high mechanical endurance, and the capacity for alter release properties of drugs. Although there are also significant drawback that restrict its use in the pharmaceutical industry, include high operating conditions and a lack of thermoplastic materials that degrade naturally favourable extrusion fluidity of a melt qualities.[28]

One more nozzle-based deposition technique is PAM. PAM involves the extrusion of a micro syringe of viscous and semi-liquid materials. Like an IJ printer head, this syringe can move, and compressed air is used to release the semi-liquid substance. Microstructures of 5 to 10 µm or less may be produced using PAM technology. It has an advantage versus other approaches as it is possible used in a steady stream at the room temperature and can also accustomed to develop sophisticated medication delivery mechanisms. However, using solvents during the production and drying processes may result in stability and safety problems. Similar to PAM, micro syringe with piston assistance (PAM2) is a fast prototyping method, however, instead of compressed air, PAM2 uses the printing ingredients are released by a stepper motor.[29, 30]

Table 1. Examples of Medicines Prepared with Various 3D Printing Techniques

Techniques used	API	Remarks
Fused deposition modelling (FDM)	a. Paracetamol	Anti-pyretic, enteric release tablet[31]

	b. Ibuprofen	NSAID, sustained release tablet
	c. Prednisolone	Anti-inflammatory, ellipse-shaped tablets
	d. Budesonide	Inflammatory, enteric-coated tablet
	d. Dipyridamole	Anti-coagulant, sustained release gastro floating tablet[32]
Hot melt extrusion (HME)	a. Indomethacin	NSAID, controlled-release IUDs, and subcutaneous rods[33]
Stereo lithography (SLA)	a. Ibuprofen	Network polymer matrices hydrogel
	b. Insulin	Insulin skin delivery micro needles[34]
Semi-solid extrusion (SSE)	a. Aspirin	Cardiovascular disease polypill
	b. Nifedipine	Complex tablet with sustained release polypill
	c. Captopril	Osmotic, glipizide, and nifidepine polypill
	d. Glipizide	For captopril, a pump /polypill
	e.Hydrochlorothe azide	tablet with several uses for polypill[35]
Inkjet printing	a. Acetaminophen	Antipyretic, doughnut-shaped, multiple-layered tablets
	b. Loperamide	NSAID, sustained release print lets

	c. Theophylline	Hyper spectral imaging using a CNS stimulant in QC printlets
	d. Captopril	Anti-hypertensive, rapid distributing a tablet[36]
	e. Levetiracetam	Antiepileptic, rapid dissolving solid tablet

Table 2. A few instances of 3D-printed products that the FDA has authorized.

Name	Year of approval
The first-ever material in the world for 3D-printed denture bases has been approved by the FDA for DENTCA.	Aug 10, 2015
Customized sports mouth guards are being made by GRiTT 3D using 3D printing.	Feb23, 2015
OssDsign AB	Jan27, 2017
E-Denture	Jul4, 2017

The benefits of 3d printing for the pharmaceutical industry:

1. **Increased productivity:** 3D printing produces therapeutic goods more quickly than conventional techniques, notably when fabricating implants and prosthetics. It also has the advantages of higher resolution, repeatability, precision, and dependability.[37]
2. **Personalization and customization:** One of the ground breaking advantages of this technology is the freedom to manufacture personalized medical items and equipment. Custom implants, prostheses, surgical instruments, and fixtures may greatly help patients and doctors.[38]
3. **Enhanced cost-effectiveness:** The cost of 3D printed things is low. Since practically all elements are cheap, it is beneficial for businesses that make complicated goods, parts, or small-scale manufacturing units. Costs associated with production can be decreased by

eliminating the usage of superfluous resources. For instance, depending on the situation, 1-mg pills may theoretically be made from 20-mg tablets.[39]

4. Controlled droplet size, intricate drug release patterns, dose strength, and multiple dosing are all made possible by 3DP.

Drawbacks of 3d printing:

1. Only ink with a specific viscosity will allow for the appropriate ink flow in inkjet printing.
2. The substance used to create ink should have the ability to bind to itself but not to other printer components. When the ink in a formulation is lacking such ability or it binds with additional printer parts, the resultant composition lacks the necessary hardness.
3. The bands of ink which may be using additional printing supplies, may have adverse effect on the release rate of the drugs.[40]

Legislative bodies

1. Pharmaceuticals subject to FDA's centre for the drug assessment and analysis regulation (drugs/UCM2018538) (USFDA)

2. The FDA's Centre for Devices and Radiological Health (CDRH), (Medical devices/UCM2005076) regulates medical devices (USFDA)

3. The FDA's Centre for Biologics Evaluation and Research (UCM2018586) regulates blood vaccinations (USFDA)

4. American society of the international association for testing and materials (ASTM) committee F42 formed an Additive manufacturing technology

5. The International organization for standardization / technical committee 261 (ISO/TC 261)

6. The American National Standards Institute (ANSI) (US)

DESCRIPTION OF THE DEVICE REGULATION

The fundamental legal criteria that producers of medical devices sold in the US must follow are shown in (Table 3).

Table 3. Legal criteria for medical devices Sold in US.

Regulation	Requirement
21 CFR Part 807	Establishment registration
21 CFR Part 807	Listing medical equipment
21 CFR Part 807 Subpart E	Premarket Notice 510 (k)
21 CFR Part 814	Prior Market Approval (PMA)
21 CFR Part 812	Clinical Study Exemption from Investigational Device (IDE)
21 CFR Part 820	QS (Quality System) guidelines
21 CFR Part 801	Labelling requisite
21 CFR Part 803	Medical Device Reporting (MDR)

3D PRINTING AND THE FDA

Manufacturers, repackages, re-labellers, and importers of medical devices for sale in the US are all subject to regulation by The CDRH is a division of the FDA's Centre for Devices and Radiological Health. The production procedure and governing procedures for receiving approval are the same for 3D-printed medical equipment as they are for conventional medical equipment. Some regulatory requirements (referred to as "pre-marketed requirements") before they are commercialised, apply to medical devices, while other requisite (referred to as "post-market requirements") apply to medical devices after they are sold. There are three classes of medical devices: I, II, and III. In addition to defining the categorization of rules about the legal criteria for a broad category of devices, regulatory jurisdiction grows from class I to class III. Pre-market Notification 510(k) is not necessary for class I gadgets, however, it is for class III devices.[41]

The manufacturing facility will be inspected within 2 months of the date when the regulatory bodies submitted their marketing application to confirm conformance with before the regulatory body issues a licence to produce or market a medical device that falls under class C or D, the quality management system. The inspection crew will then finish writing an inspection

report. After receiving the inspection report, the government has 45 days to approve or deny the request to manufacture or sell a medical device.[42]

3D-PRINTED DRUGS AND MEDICAL DEVICES: FDA'S PERSPECTIVE

The FDA has used conventional medicine and device review processes to approve 3D-printed goods. A New Medicine Application (NDA) will be approved by the FDA according to its appropriate and carefully monitored interventional studies and if it finds that the new medicine is secure and efficient when used by the suggested labelling. Similarly, if a medical device is essentially identical to (safe and effective) a lawfully marketed or predicated product, the FDA will "clear" the clearance outlet for that device based on its risk categorization for marketing. The new device must serve the same purpose as the predicate device and may also have a similar technical feature or one that is different as long as it doesn't raise any new concerns about safety or efficacy.

FDA currently assessed applications for 3D printed medical equipment have increased to more than 100 from the 85 that were reviewed at the time the draft was posted. These, Therefore, in this situation, sustaining the drug's efficacy depends significantly on both the chemical makeup and the production method. Active components such as cells are governed as biologics due to their biologically based action mechanism. Applications include knee replacements and implants used for facial reconstruction. Spritam, a 3D drug used to treat epilepsy, received FDA clearance in 2015 after going through the approval procedure. It was discovered that 3D printing enables the fabrication of tiny layers of medication, aiding in the pill's quicker disintegration. It only melts once a sip of water is taken. As a result, because of the drug's composition, which ultimately produces the desired effect, the drug's efficacy and chemical reaction are improved. For manufacturers that are enhancing or creating devices using 3D printing processes, the US FDA provided a draft guideline paper on the "technical consideration for additive manufactured devices" in 2017. The FDA refers to the guidelines as "leap-frog" recommendations.[43]

ASTM Guidelines

The ASTM Committee F42 was established on Additive Manufacturing Technologies in 2009. The committee comprises eight technical subcommittees, which now have more than 725

members. The Annual Book of ASTM Standards, vol. 10.04, contains all of the standards developed by F42.

The creation of a single collection of 3D printing requirements and testing procedures is beneficial because it maintains consistency and guarantees that the devices are secure, dependable, and of high quality. These standards may be used for 3D-printed medical devices everywhere in the globe. These standards are divided into numerous areas, including general standards (such as nomenclature, test procedures, and safety), standards pertaining to feedstock and applications (consisting of in medicine), standards for processes and tools, and completed components standards.[44]

In 2011, the International Organization for Standardization (ISO) established Group 261 Additive Manufacturing (ISO/TC261) as a committee dedicated to 3D printing. Nine nation's watch the developments while 22 countries, participated in this program. To eventually create a single set of global standards, ISO and ASTM collaborated to build a shared plan and organizational structure for 3D printing standards. The development of the nation's overall 3D printing industry standards is being coordinated by the American National Standards Institute (ANSI), the United States' representative of the ISO. The ISO standards' development will benefit from this data. ISO/IEC 23510:2021 is a standard in the field of information technology that pertains to 3D printing and scanning. Specifically, it outlines a framework for an Additive Manufacturing Service Platform (AMSP). This document establishes the guidelines for an Additive Manufacturing Service Platform (AMSP). It covers the following components: An introduction that provides an overview of the stakeholders and the workflow involved in an AMSP. Requirements that outline the necessary conditions from various perspectives. A framework that defines a general functional architecture based on the identified requirements. Use cases that illustrate typical work modes of an AMSP. The scope of this document is applicable to 3D printing and other services related to the submission, design, and production of additive manufacturing parts.[45, 46]

BASIC MATERIALS FOR 3D PRINTING

Similar to different manufacturing processes, 3D printing needs superior components that adhere to strict requirements to produce dependable, high-quality products. Procedures, Specifications, and material control of suppliers, buyers, likewise, the material's final consumers are validated for each batch to assure quality. It can print items in the different colours in glass, plastic, rubber-like material, transparency, and opacity, and metallurgic forms. The final qualities of the intended product determine the material to use. E.g., Poly-lactic acid (PLA) is a good option for a biodegradable material, whereas thermoplastic polyamide and Acrylonitrile-Butadiene-Styrene (ABS) is used for strength, flexibility, and durability.[47, 48, 49] the utilized substance is categorized as:

1. **Thermoplastic resin**: It is the material that is most frequently utilized in a variety of combinations. In the FFF/FDM process, it is employed in filament form and as a powder for sintering. The most frequently Nylon, polyamide, and ABS are materials that are utilised, which is utilize its warmth resistance qualities; PLA, a substance that degrades naturally that is acrylic and SLA utilise it as a resin, also known as PMMA; Poly-ether-ether-ketone (PEEK); Polyethersulfone; Polycarbonate; Polyethylene (PE), particularly ultrahigh molecular weight PE; Polyetherimide; Polybenzimidazole; Polyphenylene oxide; Polyphenylene sulphide, Polystyrene; Polypropylene and Polyvinyl chloride.[50]
2. **Ceramics**: Ceramics are vitality used more often, even firing and glazing processes must come first. Gypsum is regularly utilized.[51]
3. **Sheet**: The proprietary SDL process uses standard A4 paper, which is widely available.[52]
4. **Wood**: this is frequently utilize in the wood/polymer composite known as WPC in filament form[53]
5. **Glass**: soda lime and borosilicate have been utilized in 3D printing, due to the MIT-mediated matter group and Micron 3DP.
6. **Metal:** Aluminium and cobalt are the most utilized metals. Additionally stainless steel, brass, gold, and silver, powdered titanium is also utilized.
7. **Food:** Chocolate is frequently utilized to create culinary products using 3D printing. Along with beef, pasta, and sugar.

8. **Combinations:** Combinations of thermoplastic polyurethane, elastomeric polyurethane, and carbon fibers have been employed. With the help of combining common materials, Stratasys has developed a proprietary (Object Convex) synthesis 140 and above different various materials.
9. **Printing:** file coding based design may be printed.
10. **Post-Process:** A single or several post-processing stages perhaps carried out on the apparatus or component after the printing is finished. Cleaning is necessary for this procedure to remove any remaining debris, controlled cooling (called "annealing"), and/or other processes including cutting, drilling, polishing, and sterilizing may be necessary.
11. **Verification and Validation of Processes:** verify the device and product for design qualification (DQ) and mechanical toughness. This method is specifically designed to verify precise geometric characteristics rapidly, accurately, and non-descriptive. Confirming procedures, Process validation guarantees that an assembly line will result in a product that is within the specifications and that the limitation are managed and monitored.
12. **Testing:** Each apparatus may have a unique a series of tests procedures it could be based on advice manuals, global guidelines, or international standards process. Medical apparatus produced using 3D printing technology must often comply with a similar regulatory criteria further conventionally produced medical apparatus. The FDA receives device testing procedures and their findings, which demonstrate that the device complies with legal standards and is safe and effective for the purpose for which it is designed. Figure 1 shows a straightforward illustration of one potential 3D printing production process.

MATERIALS FOR 3D-PRINTED DEVICES

Usually, the FDA only authorises or clears final medical equipment, not the materials or the components that may be utilized to make 3D-printed medical devices. For instance, the FDA has authorized titanium alloy-made spinal implants[54], but it does not assess or give general permission in support of using titanium in medical equipment. The FDA assesses the safety and efficacy of medical goods for their intended uses while evaluating the materials used in their formulation.

The FDA assesses a substance as a component of the finished product's function. Additionally, it determines whether the device's technological capabilities, including its materials, are reassuringly secure and effective for a product that is sold legally. The FDA, therefore, grants approval or removal for each specific the device's intended purpose. However, do not in any way let the manufacturer to utilise the same materials in other goods. Devices made of new materials can be approved using the 510(k) Premarket Notification process should indicates that the new substance is at least as secure and efficient as a device that has been legally marketed.

Components of 3D-Printed Dental Devices

The FDA approves some specially designed materials, deliberate application as a machine for producing 3D dental equipment. These particular components are regarded as finished products that may be used by medical practitioners and are customized or fitted to the patient at the moment of treatment. There are several dental prosthetics and restorative materials namely inlays, crowns, night guards, dental cement, orthodontic retainers, and direct filling resins. The FDA often demands performance evaluation of the material in its completed state before clearing or approving these devices in order to show that the content has the necessary actual and tangible qualities when used as intended purpose.

It's important to keep in mind that the FDA has approved certain supplies for devices used in situations like "to build a denture foundation" or "to correct a structural deficiency in teeth." Neither the FDA certify or authorize substances for unrestricted purposeful uses. Every manufactured substance is approved to make a certain device with a specific set of physical characteristics and its intended function. For instance, a component of a device that has been approved by the FDA for one purpose may not automatically be used for another, such as an "Endosseous dental implant abutment." Manufacturers may want to intentionally employ the same material for a different purpose.[55] The FDA would assess data on material characteristics and for the new intended use. The maker could be obligated to meet any legal requirements for that classification rule if the new purposeful use comes according to a distinct categorization law.

Cranial Implants

OsteoFabTM, an additively manufactured polymer (Table 4) from Oxford Performance Materials (OPM), is used to create patient-specific cranial devices received the FDA's first 510(k) approval (OPSCD). The plastic PEKK material was utilized to create the adaptable implant, which is intended to fill up holes in the skull brought on by disease or damage. It is produced by EOS in only a few hours using additive technology, both its usage was seen only recently after a patient's insertion of the device proved successful who had lost a sizable amount of a skull bone. Yet, in contrast to other polymers, PEKK has a high melting point. The first industrial 3D printer 'EOSINT P 800' that uses additive layer manufacturing to generate high-temperature polymers.[56, 57]

Table 4. The 3DP technique uses polymers and their physicochemical characteristics.

Polymers	**Daily maximum dosage (as per the USFDA IIG database)**	**Physiochemical characteristics**
Polyethylene glycol 1000	1000mg/5ml	• M.P- 37-40°C • Unable to be used with colouring chemicals.
Pectin	5.45mg	• Used in food items and oral medicinal preparations.
Alginic acid	400mg	• Unsuitable for a strong oxidizer. • Precipitate when aluminized earth metals are present.
Carrageenan	15mg	• can engage cationic materials
Gelatine	756mg	• Easily hydrolysed
Polypropylene glycol	1000mg/ 5ml	• B.P- 188°C • M.P- 59°C

Polyethylene oxide 7,000,000	393.46mg	• M.P- 65- 70℃ • Strong oxidizing agents and Polyethylene oxide cannot coexist. • Low toxicity and weak GIT absorption.
Polyvinyl alcohol	79.4mg	• M.P- 228℃ • It is incompatible with inorganic salt especially sulphate and phosphates.
Hydroxypropyl cellulose	0.54%w/w	• M.P- 130℃ • Unable to be used with phenol derivatives that have been replaced, such as methylparaben. • Utilized in formulation for topical and oral usage.
Eudragit L 30 D	100.69mg	• For solid dosage forms, it serves as an enteric coating film forming. • Although the covering is impervious to stomach acid, it melt easily at pH levels above 5.5.
Polyacrylic acid	0.01mg	• Resorcinol stains carbopol and Strong acids, cationic polymers, phenol, high electrolyte concentrations, and cationic polymers are incompatible with them. • Additionally, carbomers and certain polymeric excipients can create pH-dependent interactions.
Microcrystalline cellulose	1553mg	• M.P chars at 260-270℃ • Unsuitable for use with a strong oxidizer.

Carbomer homopolymer	175mg	• It carry carboxylic acid [-COOH] groups to a maximum of 68.0 percent and a minimum of 56.0 percent. • In 3D printing, carbomer polymers [like carbopol] with one to one hundred Pascal of yield stresses are used.
Povidones	240mg	• Spray-drying is used to create povidones that have k-values of 30 or less and exist as spheres. • K-value of 90 and above Polyvidones are produced by tumble drying in the form of plates.
Hypermellose	480mg	• The hydroxypropyl methylcellulose has the appearance of white powder and is flavorless and odorless. • The pH level has no impact on how easily hydroxypropyl methylcellulose dissolves in water.
Methacrylic acid	180.05mg	• Used as leather treatment agents, adhesives, and paints. • For producing Ion exchange resins.

Dental 3D Printing Technology From Envision Tec

1. **E-Guard**: E-Guard is perfect option since it is translucent, biomass material that can be used to create precise snout guards, night guards and bite guards in the Prefatory® range of 3DPrinters. E-Guard and Envision TEC technology work together to produce outcomes that are superior to those obtained with guards against built-up bites and night guards. The material is transparent and permits the greatest visibility.

2. **E-Dent**: An FDA-accepted option for precise 3D printing of dentures both long-term and transitory crowns and bridges is E-Dent 400 MFH printing material.
3. **E-IDB:** A material for 3D printing that enables creation of indirectly bonded trays to precisely position and release dental orthopaedics.
4. **E-Guide Tint:** To synthesize high-precision surgical drills guidance used in implant operations. It is an approved Class I biomass material. When E-Guide Tint and Envision TEC are used together, the outcomes are better than those from using conventional techniques to make implant placement guides.
5. **E-Denture:** The FDA-approved, biomass Class II A material E-Denture 3D Plus is appropriate for 3D printing of varieties of false teeth bases.[58,59]

Materials for Bio printing

The initial 3D-Bioplotter materials weren't available until 2017, although Envision TEC has been offering the largest bio printer in the world since its foundation in 2002. The Envision TEC is the only open-source material printer for the 3D-Bioplotter. Using silicones, ceramics, metal pastes, thermoplastics[60], hydrogels, and increasingly commonly living cells to print.

With more than 200 citations in peer-reviewed publications, 3D-Bioplotter has grown in popularity, and demand for standard printing materials has also been rising. That has shown to be particularly precise for typical tasks like printing structures for soft implants or supports for tissue engineering applications. Currently, Envision TEC provides bio printing materials that are cell-friendly and biocompatible for a range of different purposes. Three grades of materials are currently available, listed in order of purity.[61]

1. Scientific Grade (TG)
2. Analysis Grade (RG)
3. Clinical Grade (MG)

To accommodate various printing requirements, several of Envision TEC's conventional bioprinting materials have been given classifications for low temperature (LT) or high temperature (HT). For instance, the support RG material from Envision TEC is available in LT and HT variants. When the support is no longer required, it can be made from this research-

grade substance and then dissolved in distilled water. The cellulose-based LT version can be processed at 23℃ or 73℉, whereas the sugar-based HT version may be processed at 150℃ or 302℉.[62]

CONCLUSION

Applications of 3D printing technique in pharmaceutical segment have resulted in selection of appropriate medications which specifically caters to the needs of patients thus promoting individualized therapy. It offers several benefits like increasing the pace of manufacturing, modification of complex dosage forms, betterment in medical outcome and patient compliance, reducing adverse effects, effective utilization of expenses thus resulting in safe and effective treatment, minimizing the requirement for post manufacturing testing and quality assurance. However, despite offering following advantages there are various challenges associated with 3D printing which has prohibited its widespread application in commercialization of product. These include limited availability of regulatory provisions, nascent stage of robust quality control procedures, biocompatible materials, technical issues which have influence on stability of material and process parameters which ultimately affect the quality of final product. Constant improvement in 3D printing technique may help in overcoming the regulatory and technical problems and further result in evolution of this technology for making it universally applicable to various drug delivery systems and thus pave the way for effective dosing and personal medication.

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