3D PRINTING TECHNOLOGY FOR PHARMACEUTICALS:A PUBLIC REVIEW

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ABSTRACT: Three-dimensional printing is an ultra-modern technique that allows three-dimensional objects with various geometrics in a layer-by-layer process by depositing the material on a substrate. The 3D printing technique was granted in 1986. This technique provides various solid dosage forms containing multiple drugs with excipients to obtain immediate (or) delayed- release i.e., enteric-coated, buccal tablets, sublingual tablets, orodispersible, and so on. It has become one of the most additive manufacturing processes based on computer-aided design software. To change the form and dosage of products, the 3D printing techniques permit extensive acceptance of customized medicines due to contrast and modesty. The obvious benefits of 3D printing are emphasized and have become an effective instrument presenting as a technology of accurate manufacturing of individually developed dosage forms, tissue engineering, and modeling of disease. The numerous 3D printing technologies that can be accepted in various personalized and selectable medicines are selective laser sintering, fused deposition modeling, semi-solid extrusion and stereolithography, thermal inkjet printing, inkjet printing, zip dose, laser-based writing system, continuous layer interface production, power-based 3D printing, 3D technology for creating biological tissues (3D bioprinting).3D technology is designed one of the assuring areas of the medicine. This system has the prospect to open up new probabilities that are ambitious to elaborate. The allowances of 3D printing technology in compounding pharmacies include the capacity to build tablets of any shape and size, capacity to arrange the dosage individually for each patient, and the capacity to determine the number of active substances in the creation of the tablet, remove (or) replace the individual component. The risks and undesirable consequences of 3D printing technology include high energy consumption, 3D printing equipment, and materials charge make the technology overprice, the materials that can be used are finite and some are still under development, 3D printers operate high-voltage power supplies, technical equipment, and parts which cause them hard to apply and handle. 3D printers are time-consuming when it comes to manufacturing many objects. 3D printing technology could reconstitute and reshape the world. Advances in 30 printing technology can change and enhance the way we manufacture products and produce goods. Worldwide and many companies are already using the technology to consistently produce complex components. E.g., In automotive and aerospace manufacturing.

KEYWORDS: Three-dimensional printing, Ultra-modern technique, Delayed-release, Computer-aided design software, Personalized medicines, Stereolithography.

INTRODUCTION:

Gaining immense interest both in the academic and industrial sectors is the concept of three-dimensional (3D) printing technologies. Domains like aerospace, engineering, FMCG, architecture, military, fashion industry, chemical industry, and medical field are by no way untouched by this technology **[1,2].** 3DP has a wide range of applications including tissue design, the printing of organs, diagnostics, the manufacture of biomedical devices, and the design of drug and delivery systems in the medical field **[3,4].** From the data originated by various techniques like computed tomography (CT) scan and magnetic resonance imaging (MRI), complex anatomical and medical structures according to the need of the patient can be fabricated **[5,6].** Replacing and repairing defective organs like kidneys, hearts, etc., or all together creating a new organ that mimics the same functions as that of the original are some additional uses of this technology **[7]**. This technology is so widespread that its applications include things that are an integral part of human life like clothing, eyeglasses, jewellery, parts of cars, and drugs that can be printed in almost any geometry and shape as per the requirement of the user **[8].** In this technology, a concept is transformed into a prototype by taking help from 3D computer-aided design (CAD) files, hence digitally controlled and customized products can be fabricated **[9].** This technology utilizes a bottom-up approach in which layers of materials like living cells, wood, alloy, thermoplastic, metals etc., are placed on top of each other to make the required 3D object **[10].** Therefore, 3D printing is also known by other terminologies such as layered manufacturing, additive manufacturing, computer-automated manufacturing, and rapid prototyping (or) solid freeform technology (SFF) **[9].** In subtractive methodology or conventional method, the product is designed from the bulk substance, and due to non-advanced tools used non-standard geometries and objects made from many materials cannot be made with high quality **[11,12].** In contrast to the conventional method, 3DP technology is more automated, rapid and easy to use, customized and sophisticated, and cost-effective **[13-15].**

HISTORY:

3D Printing posed as a possible platform for personalized medicine in the 1990s. There are major achievements in 3D printed medical devices, FDA's Centre for Device and Radiological Health (CDRH) has reviewed and cleared 3DP medical devices **[16].** The first 3D printing t16echnique used in pharmaceutics was achieved by inkjet printing a binder solution onto a powder bed,

binding, therefore, the particles together. The process was repeated until the final desired structure was obtained. This first happened in the early '90s at the Massachusetts Institute of Technology invented and patented by Sachs et al **[17].** [In 1989, Scott Crump, filed a patent on another 3D printing technology: fused deposition modeling, where extruded polymer filaments heated into a semi-liquid state were extruded through a heated nozzle and deposited onto a build platform layer by layer to harden **[18,19].** Inkjet printing was the method used to manufacture Spritam (levetiracetam) tablets for oral use, the first 3D printed drug approved by the Food and Drug Administration (FDA) in 2016 by Aprecia Pharmaceuticals **[18].**3D printing is more advanced in the fields of automobile, aerospace, biomedical and tissue engineering than in the pharmaceutical industry where it is in its initial phase. FDA encourages the development of advanced manufacturing technologies, including 3Dprinting, using risk-based approaches.

APPLICATIONS OF 3D PRINTING TECHNOLOGY:

- 3DP technologies such as IJ, FDM, and SLS, are currently available for manufacturing adequate pharmaceutical dosage forms. In this review, the pharmaceutical applications of 3DP technology are focused on the oral solid dosage forms and transdermal delivery systems that seem to be undergoing relatively greater progress and are more suitable for wide applications of 3DP.
- Potential use in improving processes, and modifying performance for industrial design, aerospace, medical engineering, tissue engineering, architecture, and pharmaceuticals.
- It mostly targets the two potential sites to rise pharmaceutical product development to unexplored areas, manufacturing sophisticated structures for the delivery and personalized medicine.
- In the 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 **[20].**

1. Tablets

Oral dosage formulations are the most preferred form of pharmaceutical products. Tablets and capsules are typical examples of widely used solid oral dosage forms. Particularly, tablets have been extensively examined for the feasibility of 3DP technologies in pharmaceutical manufacturing. Generally, tablets produced by 3DP methods can be categorized into two groups: single API tablets and multiple API tablets. Selective examples of each category are described in the next two sections, respectively.

2. Single API tablets

Initially, 3DP technology was applied to fabricate simple immediate-release (IR) tablets comprising a single API. In many studies, the FDM method was adopted for producing IR tablets, probably due to its simple fabricating procedures. Selective examples of single API IR tablets obtained by using the FDM method are reported in previous studies **(Goyanes et al. 2016a; Okwuosa et al. 2016; Sadia et al. 2016).** Not only low-drug-loaded dosage forms but also high-drug-loaded dosage forms can be prepared using 3DP technology. For example, a thermoplastic polyurethane-based dosage form loaded with 60% drug was successfully developed via the FDM method **(Verstraete et al. 2018**). Similarly, an IR tablet loaded with a very high dose of 80% paracetamol was prepared using an extrusion-based 3D printer **(Khaled et al. 2018).** In addition to IR tablets, 3DP is applicable to produce extended-release (ER) tablets. **(Skowyra et al. 2015)** examined the feasibility of the FDM method to fabricate ER tablets using prednisolone-loaded polyvinyl alcohol filaments, achieving the drug release up to 24h prepared by the FDM method was reported by **(Alhijjaj et al. 2016),** using polymer blends of polyethylene glycol, Tween 80, and polyethylene oxide with Eudragit EPO. When fabricating tablets by using 3DP techniques, the selection of 3DP materials and methods dramatically affects the physical properties of the obtained tablets, leading to different drug release profiles. The ratios of the formulation components also influence the physical properties of tablets, resulting in altered drug release profiles. For example, **(Wang et al. 2006)** have developed three near zero-order controlled-release pseudoephedrine hydrochloride dosage forms by using 3DP technology. The drug release rates were adjusted by varying the proportion of SR and hydroxy propyl methyl cellulose (HPMC) while the fabrication parameters remained constant. These formulations also showed a good correlation between their in vitro dissolution profiles and clinical pharmacokinetic parameters. The doughnut-shaped multi-layered acetaminophen delivery devices were also developed by varying the amount of drug and release-retardant materials using 3DP technology, providing linear release profiles of a poorly water-soluble drug **(Yu et al. 2009)**. In addition to immediate or extended drug release, 3DP technology applies to other types of modified-release tablets. Using three different grades of Hypromellose acetate succinate (grades LG, MG, and HG), enteric tablets were manufactured by the FDM method to enable manufacturing the delayed-release tablets without the need for an outer enteric coating **(Goyanes et al. 2017).** Furthermore, 3D extrusion-based printing has the potential to fabricate gastro-floating tablets **(Li et al. 2018)** available for manufacturing tablets. For example, SLA was successful in fabricating ER tablets of 4-aminosalicylic acid or paracetamol, using polyethylene glycol diacrylate, diphenyl (2,4,6-trimethyl benzoyl) phosphine oxide, and polyethylene glycol at various composition ratios, where the drug release profiles. Recently, **(Clark et al. 2017)** developed a ropinirole hydrochloride tablet using the IJ method with UV-customized IJ-based additive manufacturing for the pharmaceutical sector also showed that drug-loaded solid dosage forms with complex geometries, such as honeycomb architecture, can be manufactured using hot melt 3D IJ printing and also indicated that variation in drug release profiles could be obtained in a controllable manner, predictive computational approaches. Taken together, IJ and FDM processes are currently the most promising approaches to the manufacturing of oral solid dosage forms. Particularly, FDM has shown a potential to prepare modified-release dosage forms with complex geometries, but the number of polymer excipients is limited. Although polymeric excipients modifying drug release properties are limited, the use of polymer blends may provide another option to overcome this issue. The interplay of the miscibility between excipients in the blends, the solubility of the materials in the dissolution media, and the degree of fusion between the printed strips during the FDM process may affect the drug release rate from the matrix.

3. Multiple API tablets

Sophisticated drug release profiles. These polypills can help patients to rely on comparatively fewer pills, and improve to combine complex medication regimes into one, multiple APIs can be loaded in a single tablet, called a polypill. In recent studies, 3DP

technology has been used to manufacture polypills showing controlled release profiles. First, **(Khaled et al.2015a)** by using 3D extrusion-based printing, to treat patients with diabetes, suffering hypertension. This polypill was composed of a captopril osmotic pump compartment, joining layer, and sustained release compartments of nifedipine and glipizide. After taking the pill, the joining layer disintegrated quickly, thereby the polypill split into a captopril compartment and sustained release compartment. The captopril compartment showed a zero-order drug release porosity shell while the sustained release compartments released the drugs (nifedipine and glipizide) via diffusion through the gel layer. They also applied DP technology to fabricate a polypill containing five APIs **(Khaled et al.2015b).** This polypill comprised two compartments showing independent controlled release profiles; one for sustained release and the other for immediate release. The sustained release compartment contained ramipril, atenolol, and pravastatin while the immediate release compartment contained aspirin, and hydrochlorothiazide. In a 3DP extrusion system, the cellulose acetate shell is first extruded, and then the APIs (ramipril, atenolol, pravastatin) were mixed with HPMC. Rapid hydration of HPMC a next step, aspirin and hydrochlorothiazide were extruded to cover the top of the sustained release compartment, displaying immediate drug release due to the inclusion of a disintegrant (sodium starch glycolate). Through this drug combination in a tablet, patients who have various risk factors such as hypertension and dyslipidemia can be treated simultaneously with just one tablet. To use 3DP to control more complex release profiles, various shapes of drug carrier templates (or molds) are fabricated. Through complex templates, it is possible to create tablets that contain multiple components, to generate a multi-action releasing profile. In this way, APIs are not just released in zero- or first-order but more complicated release profiles can be acquired. Recently, **(Sun and Soh 2015)** reported a 3DP method to fabricate customizable tablets composed of three components, such as a surface-eroding polymer with the drug, a surface-eroding polymer without the drug, and an impermeable polymer that forms a protective coating. Particularly, the surface-eroding polymer containing the drug is fabricated with a specific shape, allowing the desired drug release profile. Varying the shape of the surface-eroding polymer carrying the drug leads to the release, decreasing release, and pulse release are acquired through designing the surface-eroding polymer with the drug compartment. Complicated drug release, like pulse release, can be used for a drug that needs to be synchronized with the biological cycles of the patient. The Decreasing release can be used in cases that require a relatively large dose of drug initially to act against a target rapidly, followed by gradually lower levels to prevent toxicity. As this method can modulate the drug release profiles through the shape of the inner compartment, it seems promising to make customized drug tablets for complicated medications**. (Goyanes et al. 2015b)** also reported the potential of 3DP to fabricate multiple-drug-containing devices, with specialized design configurations and unique drug release characteristics. They used a multi-nozzle 3D printer to fabricate capsule-shaped solid devices loaded with acetaminophen and caffeine. The design structures included a multi-layer device, in which each layer contained a different drug, and a two-compartment device comprising a caplet embedded within a larger caplet (Duo Caplet), with each compartment containing a different drug. They demonstrated the unique drug release profiles, depending on the macrostructure of the devices. In multi-layer devices, the release of both drugs was simultaneous and independent of the drug solubility. In the Duo Caplet design, it was possible to achieve either immediate release or delayed release, by selecting the site of incorporation of the drug in the device and also the characteristics of the external layer. This research group also developed modified release oral dosage forms (caplets) of budesonide using the FDM method combined with hot melt extrusion and fluid bed coating. **(Wang et al. 2016)** demonstrated the use of the SLA method to fabricate modified-release tablets loaded with both 4-aminosalicylic acid (thermo-labile) and paracetamol (thermostable), suggesting that SLA reduces drug degradation compared to FDM and offers an alternative way to produce tablets with thermo-sensitive drugs. In summary, 3DP technology has a high potential to manufacture various polypills containing multiple APIs in a tablet and also to achieve complex and patient compliance, and allow personalized dosing regimens. Although there are still many limitations to applying 3DP to the pharmaceutical manufacturing process, 3DP would be an inexpensive and efficient way to produce customized tablets.

4. Implants

An implant is a dosage form containing active drugs within a sustained-release delivery matrix, providing benefits to patients who need long-term treatment of drugs. While the traditional approach for implant development was mainly focused on extended and prolonged drug release, recent 3DP-based implants are designed to have complex micro- and macro-structures in a single device, for multi-API loading and achieving more sophisticated drug release characteristics. For example**, (Huang et al. 2007)** fabricated the implant of levofloxacin with a predefined microstructure, exhibiting complex release profiles from a single implant. This implant displayed a bimodal profile, with pulsatile (day 5–25) and steady-state drug release (day 25–50), and then the pulse release began again on day 50 and continued up to day 80. Fabricating scaffolds for bone defect healing is one of the developing fields using 3DP. Particularly, in recent studies, multiple APIs were loaded inside the 3DP-based implants to acquire additional therapeutic effects. For bone defect healing, complex scaffolds were fabricated using 3DP, by combining calcium phosphate cement with vascular endothelial growth factor (VEGF)-loaded hydrogel strands **(Ahlfeld et al. 2017). (Wu et al. 2009)** designed a multi-drug implant for bone tuberculosis treatment, using 3D printers. Isoniazid and rifampicin were incorporated into each layer alternatively in a specific sequence, forming a multi-layer concentric cylinder. Drugs were released sequentially from the outside layer to the center, creating a multi-drug therapeutic system. Due to their ideal pharmacological action and cytocompatibility, 3DP-based multi-drug implants could be a promising approach for the treatment of bone tuberculosis**.** Recently, **(Wu et al. 2016)** designed a 3DP-based multi-drug implant for chronic osteomyelitis. Levofloxacin (LVFX) and tobramycin (TOB) were loaded into an implant as APIs, and the scaffolds were designed as multilayers where each layer's volume was 0.4 cm3. The odd-number layers were loaded with LVFX, and the even-number layers were loaded with TOB. In this implant, each layer released API stepwise and exhibited a sustained drug release for 60 days to retain the ideal drug concentration, leading to the successful control of chronic osteomyelitis in rabbits. A patch-like implant is a new type of implant developed by 3DP and focused on extended drug release for chronic diseases. For the treatment of pancreatic can apply 3DP fabricate an implant designed appropriately for a specific tissue or organ (in this case, the pancreas) so that the implants could allow site-selective drug release. Polylactic-co-glycolic acid, polycaprolactone, and 5-fluorouracil were blended to produce the biodegradable implant patch with high drug loading efficiency (90%). This patch was attached directly to the pancreas of an athymic mice model and showed significant efficacy, suggesting the utility of 3DP-based

biodegradable implants for effective local delivery of anticancer drugs **(Yi et al. 2016).** Owing to the high performance, controlled drug release for an extended duration, and effective local delivery, 3DPbased implants appear to be a promising dosage form for chronic diseases and expand the pharmaceutical applications of 3DP technology.

5. Microneedles

Microneedles are a class of transdermal drug delivery systems, which has arrays of micron-sized needles on the surface of a matrix to enhance the skin penetration of biologically active molecules. Notably, microneedles may be more effective to deliver macromolecules through the skin than traditional patches, due to their microstructure. Recent advances in high-resolution 3DP techniques fabricating tiny structures, accelerate the application of 3DP in manufacturing microneedles. While traditional microfabrication techniques are limited to microneedles with simple geometries, new 3DP technology enables fabricating microneedles having more sophisticated and complex geometries. Some selected examples are described in the remaining paragraphs of this section**. (Ochoa et al. 2015)** developed a new fabrication process for polymeric microneedles of complex geometries, by coupling 3DP with hydrogel casting/shrinking techniques. This technique effectively enhanced the resolution limit of 3DP and fabricated sharp microneedles having tips with a 9.6 µm radius of curvature, which may be applicable for vaccine delivery. Continuous liquid interface production (CLIP) has also been developed using photoreactive resin and UV light to form 3D structures, like pyramids, pillars, or even more complicated structures **(Johnson et al. 2016).** In this method, CLIP microneedles were composed of trimethylolpropane triacrylate, polyacrylic acid, and photopolymerizable derivatives of polyethylene glycol and polycaprolactone, and the fabrication of microneedles was a mold-independent one-step process, requiring less than 10 min per patch. The fabricated microneedles were very small with a uniform shape, where the tip radius was less than 3.5 µm and 400–1000 µm in height. **(Lu et al. 2015)** fabricated poly (propylene fumarate)-based microneedles for anticancer drugs, using micro stereolithography to treat skin carcinoma. In their studies, poly (propylene fumarate) was mixed with diethyl fumarate to adjust viscosity and improve mechanical strength. This microneedle system achieved the controlled release of dacarbazine, an anticancer drug for 5 weeks. The drug release rate could be controlled by altering the drug loading and the molecular weight of the polymer monomer. This study suggests that micro stereolithography could be a valuable technique to fabricate drug-release devices requiring high structural stabilities. Although microneedles do not necessarily require biodegradability because they are attached outside the body, needle-shaped microstructures need to penetrate the skin without irritation and, thus, biodegradable scaffolds should be preferable for safety purposes. Recently, developed biodegradable microneedles by a new microfabrication technique, using an FDM 3D printer with improved resolution, demonstrating that the printing parameters could be tuned to create microneedles of various shapes, lengths, and array densities, without a master template. The study also showed the degradability of polylactic acid (a renewable, biodegradable, and thermoplastic polymer) in the skin, leading to the drug release also fabricated biocompatible polymeric microneedle patches for insulin skin delivery. Using the SLA method, a biocompatible resin was photopolymerized to make microneedles of cone and pyramid geometries, followed by IJ print coating of insulin formulations. The developed microneedles, with excellent mechanical strength and piercing capacity, released insulin rapidly within 30 min regardless of the microneedle shapes reported a microneedle splint fabricated by 3DP, as a new approach for personalized medicine to treat trigger fingers. They prepared the dual-function microneedle array on personalized curved surfaces for both effective drug delivery and splinting of the affected trigger finger. This microneedle splint showed biocompatibility with human dermal cell lines and significantly enhanced the skin permeation of the loaded drug (diclofenac) compared to intact skin **(Lim et al. 2017).**

ADVANTAGES OF 3D PRINTING TECHNOLOGY:

- High drug loading capability compared to conventional dosage forms.
- Accurate and Precise dosing of potent drugs which are administered at small doses for activity.
- Reduced production cost due to less wastage of materials
- Suitable drug delivery for difficult-to-formulate active ingredients like poor water solubility and narrow therapeutic windows drugs.
- Medication can be tailored to a patient in particular based on age, gender, genetic variations, ethnic differences, and environment.
- Treatment can be customized to improve patient adherence in the case of multi-drug therapy with multiple dosing regimens.
- As immediate and controlled release layers can be incorporated owing to flexible designs, and manufacturing methods of dosage form and it helps in picking out the best therapeutic regimen for an individual.
- Evades batch-to-batch variations met in bulk manufacturing of conventional dosage forms.
- Manufacture of the small batches is feasible and the process can be completed in a single run **[47].**
- 3D printers capture minimal space and are affordable.
- **Enhanced productivity:** 3D printing works more quickly in contrast to traditional methods especially when it comes to the fabrication of items like prosthetics and implants with the additional benefit of better resolution, repeatability, accuracy, and reliability.
- **Customization and personalization:** One of the pioneer benefits of this technology is the liberty of fabrication of customized medical equipment and products. Customized implants, prosthetics, surgical tools, and fixtures can be a great boon to patients as well as physicians.
- **Increased cost efficiency:** Objects produced by 3D printing are of low cost. It is an advantage for small-scale production units or for companies that produce highly complex products or parts because almost all ingredients are inexpensive.
- By eradicating the use of unnecessary resources, manufacturing costs can also be reduced. For instance, 20-mg tablets could be potentially formulated as 1-mg tablets as per need.
- 3DP allows the controlled size of droplets, complex drug release profiles, the strength of dosage and multi-dosing

DISADVANTAGES OF 3D PRINTING TECHNOLOGY:

- Problems related to the nozzle are a major challenge as stopping the print head affects the structure of the final products.

- Powder printing clogging is another hurdle.
- Possibility of modifying the final structure on to mechanical stress, storage condition adaptions, and ink formulation effects.
- In inkjet printing, proper flow of ink can only be achieved with ink that has precise viscosity.
- Ink formulation material should have the property of self-binding but should not bind to other printer elements. In some formulations when the ink does not possess adequate self-binding properties or binds with other elements of the printer then the resultant formulation does not have the required hardness.
- The rate of drug release may get affected due to the binding of ink with other printer materials.
- Printer-related parameters and these effects on printing quality and printer cost **[48].**

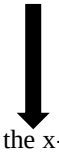
STEPS INVOLVED IN 3D PRINTING TECHNOLOGY:

First, a virtual 3D design of an object using digital design software like on shape, Solid works, Creo parametric, AutoCAD, Autodesk, etc. is created.

This digital model is then converted to (.STL) digital file format which stands for standard tessellation language or stereolithography.

Triangulated facets give information regarding the surface of the 3D model that is present in the (.STL) file.

The (.STL) file is converted into G file by slicing the design into a series of 2D horizontal cross-sections with the help of specialized slicer software, which is installed in the 3D printer.



Now the print head is moved in the x-y axis to create the base of the 3D object.

The print head is now allowed to move in the z-axis, thereby depositing the layers sequentially of the desired material, hence creating a complete 3D object.

Maximum numbers of 3D printing technologies are compatible with (.STL) file format. Some errors might occur during the conversion of the 3D model. STL digital file; therefore, software like Magics (Materialise) can be employed to correct the errors during conversion. File formats other than. STL like additive manufacturing file format (AMF) and 3D manufacturing format (3MF) is used. STL does not have information regarding the type of material, its colour, texture, properties, and features.

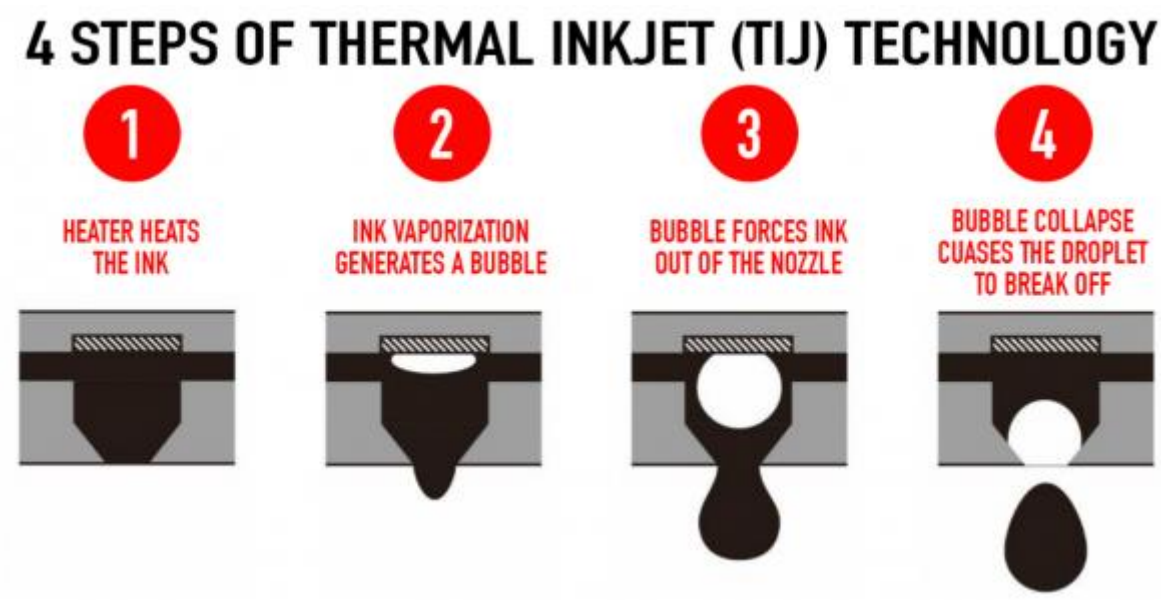
TECHNIQUES OF 3D PRINTING TECHNOLOGY:

1. THERMAL INKJET PRINTER

Thermal inkjet printers, sometimes referred to as bubble jet printers, use thermal energy or electricity to heat ink and apply it to a medium. They can provide a low-cost option for high-speed printing, and can print on a variety of surfaces. HP and Canon are two of the leading manufacturers of this kind of printer. As opposed to the replenishable tanks used by CIJ machines, TIJ printers use a system of replaceable cartridges for ink delivery. Through a process called “drop ejection,” TIJ models propel the ink from these cartridges and onto the desired substrate via these 4 steps.

WORKING PROCEDURE:

- **Heat the ink:** To start the process, the ink is delivered by the cartridge to a firing chamber where electronic resistors heat it at a rate of 1,800,032°F / 1,000,000°C per second.
- **Generate a bubble:** Once the heat from the resistors causes the ink to reach a temperature of 644°F / 340°C, the ink is vaporized and generates a bubble.
- **Propel the ink:** As the bubble expands, the ink droplet is propelled from the chamber and out of the nozzle.
- **Collapse the bubble:** Once the droplet breaks away from the nozzle and onto the substrate, the bubble it was propelled by collapses. This creates a vacuum effect that pulls more ink into the chamber, causing the entire process to repeat.

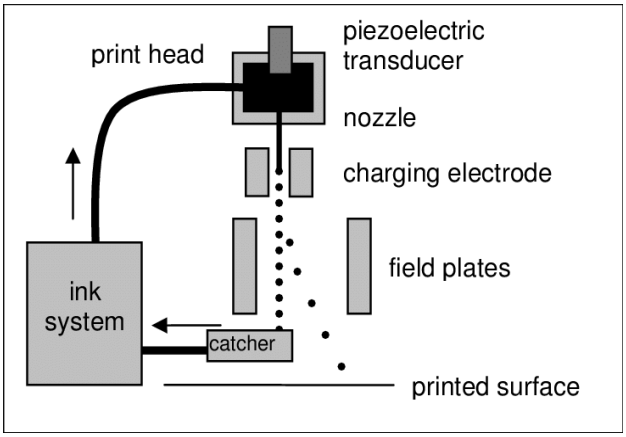


2. INKJET PRINTING

An inkjet printer is a computer peripheral that produces hard copies of a text document or photo by spraying droplets of ink onto paper. A typical inkjet printer can produce color printing copies with a resolution of 1200 x 1440 dpi. This is high enough for printing photos larger than 5 x 7 inches, however, for a project requiring high print quality on a larger scale, there are inkjet printers that provide up to 5760 x 1440 dpi. Many models include other devices such as a scanner, photocopier, and dedicated fax machine along with the printer in a single machine. Recognizable inkjet printer brands and models include the Epson XP, Canon PIXMA, and HP Desk Jet for home office printing, and the Canon Image CLASS and HP Office Jet all-in-one printers for business use.

WORKING PROCEDURE:

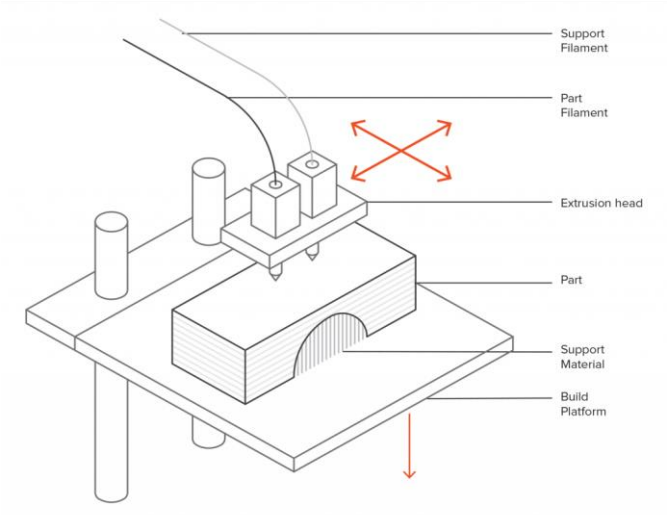
In the inkjet printing mechanism, the print head has several tiny nozzles, also called jets. As the paper moves past the print head, the nozzles spray the ink onto it, forming the characters and images. An inkjet printer can produce from 100 to several hundred pages, depending on the nature of the hard copy, before the ink cartridges must be replaced. There is usually one black ink cartridge and one so-called colour inkjet cartridge containing ink in primary pigments (cyan, magenta, and yellow). Some inkjet printers use a single cartridge with cyan, magenta, yellow and black ink. A few models require separate cartridges for each primary pigment, along with a black ink cartridge.



3. FUSED DEPOSITION MODELLING

Fused deposition modeling is an additive manufacturing technology that creates 3D components using a continuous thermoplastic or composite material thread in filament form. An extruder feeds the plastic filament through an extruding nozzle, where it is melted and then selectively deposited layer by layer onto the build platform in a predetermined automated path. FDM, also known as Fused Filament Fabrication (FFF), is material extrusion technology, one of the seven main types of additive manufacturing technologies. FDM is the most widely used 3D printing technique, with the most 3D printer users globally, and is typically the first 3D printing technology to which people are exposed. Scott Crump pioneered the process in the 1980s under the registered term fused deposition modeling (FDM). Stratasys Inc., a business co-founded by Scott Crump, owns the trademark fused deposition modeling (FDM) and its abbreviation.

The schematic below shows a basic overview of an FDM printer. It consists of two extruding nozzles on linear slides, a build platform on another linear slide, and supports for plastic filament spools.



The extruders are called modern and support extruders. As the name implies, the model extruder prints the material for the 3D shape while the support extruder prints the supports. They can either have the same material or different materials. Hobbyist printers have a single extruder and use the same material for both model and support. Depending on the type and brand of FDM printer, the XYZ movement could come from the extruders and the build platform. As the schematic shows, in this version, the extruder head gantry moves in X & Y while the build platform moves in Z-axis comes. In some versions, the print head moves in X and Z while the build platform moves in Y.

WORKING PROCEDURE:

PART PREPARATION STEP

The first few steps are similar to any other additive manufacturing technology and start with building preparation software. The initial stage is to import the design file, then choose options for the build such as layer height, orientation, and infill percentage. The software then computes sections and slices the part into several layers. The program then creates extruder paths and building instructions based on the sectioning data to drive the extrusion heads. Depending on the printer and the manufacturer, the above process will be different, but the core step of 3D file conversion into layer-based information is the same.

FDM MACHINE SET-UP STEP

The printer is loaded with a thermoplastic filament spool for both model and support extruders. Generally, the build platform is heated and maintained at a higher temperature to control the cooling of the extruded material. Extruders are heated and when the nozzle reaches the required temperature, the head will start pushing and melting the filament into a small ribbon roughly the size of a human hair.

FDM PRINTING STEP

The extrusion head gantry and the build platform are on a three-axis system, which allows the nozzle tip to move in three directions in space. The extruder will start depositing the material layer by layer in predefined areas to cool and solidify. Sometimes the material cooling is assisted using cooling fans mounted to the extrusion head. Multiple passes are necessary to fill a region within a layer. When the gantry completes a layer, the build platform or the heads will move the Z-axis by the layer height. Then the above process starts again to deposit a new later. This procedure continues until all the layers are built.

FDM PART REMOVAL

Like any other 3D printing process, the next stage involves removing the part from the build platform and cleaning them by removing all supports.

POST-PROCESSING

Part can be then further processed remove any remaining supports and finish to suit the end application.

4. POWDER-BASED 3D PRINTING

Powder-based 3D printing is an additive manufacturing method that uses raw material in powder form. This is in contrast to the filament materials used in other, more common 3D printing techniques. The powder material, in this case, can be either metal or plastic. The basic principle of powder-based 3D printing is to promote the “binding” of the individual powder particles via the controlled emission of energy. This energy source can be either a printing, hardware parameters, and the size of the powder particles all play a role in determining the characteristics of the finished print laser, a narrow beam of UV light, or an electron beam. The specific method used for 3D.

(a). METAL-BASED POWDER PRINTING

In metal-based powder printing, metal powder is fused through the introduction of a high-energy beam or an agent that promotes binding. Just about all industrially significant metals can be processed via powder-based 3D printing including stainless steel, aluminum, titanium, copper, cobalt, nickel alloy, and chrome. However, energy requirements and appropriate techniques may vary from one metal to another. For this reason, it’s rare to see a metal-based 3D printer that works well with such an expansive suite of powder metal types. There are four major technologies used for metal powder 3D printing, and we shall discuss them in sequence from the simplest to the most complex.

(i)SELECTIVE LASER MELTING

One of the most basic methods of metal 3D printing, SLM uses a concentrated laser beam to melt the raw metal powder. This results in the complete melting of the metal and the fusing together of the neighbouring powder particles to achieve complex geometries. The intensity of the laser beam and the speed at which it traverses the layer of metal powder can be adjusted according to the type of metal being processed and to tweak the properties of the finished print. In any case, SLM is a very energy-intensive process because it requires the complete melting of the metal. The payoff is that SLM produces metal 3D prints with superior mechanical properties. When metal particles melt, they fuse at the molecular level. This process fills in any gaps, creating a denser and stronger product.

(ii)DIRECT METAL LASER SINTERING

DMLS is very similar to SLM to the point that the two terms seem to be used interchangeably. They both use a metal powder raw material and a laser energy source to attain fusion. However, there's a subtle yet essential difference: while the objective of SLM is to completely melt and fuse the metal powder, DMLS strives only to heat the metal particles to the point where their surfaces weld together. This is a process known as sintering and is a more energy-efficient way to fuse metal powder.

(iii)ELECTRON BEAM MELTING

In the EBM process, an electron beam delivers the energy necessary to melt the metal powder. This is also a very energy-intensive procedure. The characteristic of an electron beam that makes it unique is that an electron beam can be dispersed to several points on a single layer of metal powder. This makes EBM a faster 3D printing process compared to SLM and DMLS.EBM 3D printers are much less common than either SLM or DMLS printers, primarily because of how expensive the technology is. Commercial options for EBM 3D printers are also quite limited. EBM printers also struggle with replicating the level of resolution of other 3D printers because of the size of an electron beam.

(iv) MULTI-JET FUSION

In MJF, a liquid binding agent is injected at selected areas on the bed of metal powder. This is done by an array of ultra-fine nozzles, the number of which directly influences the speed of the process. This binding agent seeps into the interstitial spaces between the powder particles. Its primary function is to promote the absorption of infrared energy. After the MJF process, the metal print is still considered to be in a "green" state. This will then have to be treated inside a UV chamber to complete the curing and sintering process, allowing the bonds to develop strength and is certainly the rarest. The Metal Jet printer from HP is one of the few popular examples. With its versatility and level of precision, there is still much to be explored about the potential of MJF technology.

(a). PLASTIC-BASED POWDER PRINTING

Compared to other 3D printing methods for plastics, a powder-based method is easily one of the most versatile. There is a wide variety of plastic materials that can be made into powder including silicates or polystyrene, which are generally not available in filament form. Since plastic does not require a lot of energy to melt, the 3D printing technology for plastic powder does not need as much diversity.

SELECTIVE LASER SINTERING

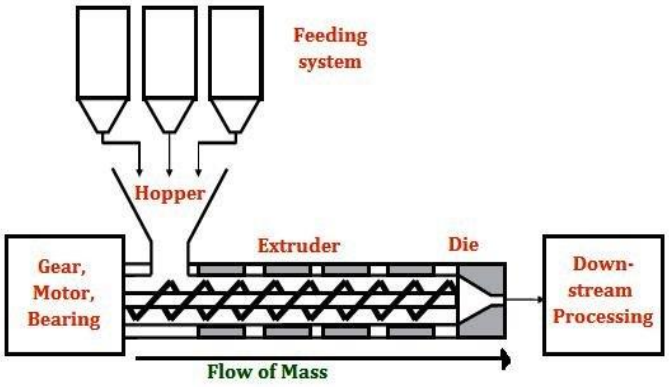
Like the DMLS method for metals, the SLS technique uses a narrow CO2 laser as the energy delivery mechanism to melt the plastic. By varying the intensity and speed of travel of the laser, a single SLS machine can be used across a variety of different plastic materials. In SLS printing, the CO2 laser hits the layer of powder at pre-determined points according to the model generated by the slicer software. Once a layer has been completed, a roller passes through the top of the vat to introduce a fresh batch of raw plastic powder.

5. HOT MELT EXTRUSION PROCESS

Hot melt extrusion (HME) is the processing of polymeric materials above their glass transition temperature to affect the molecular level mixing of thermoplastic binders and/or polymers and active compounds. Used in several industries, HME is a combination of melting and mechanical energy to improve continuous processing for reproducible analysis of materials, dust reduction, and online monitoring. In pharmaceutical manufacturing, HME is used to disperse APIs in a matrix at the molecular level, thus forming solid solutions. This enables drug delivery systems for poorly soluble drugs or specialized drug forms such as films for transdermal patches.

WORKING PROCEDURE:

In the hot melt extrusion process, the API and the excipients are fed into the extruder. All components are sheared, heated, plasticized, mixed and dispersed, and finally shaped by pressing them through a die opening. Developing an HME manufacturing project requires control of several processing parameters that affect residence time distribution, and specific mechanical energy consumption (SMEC) must be considered such as the temperature of the melt at the extruder die pressure at the die, and torque.

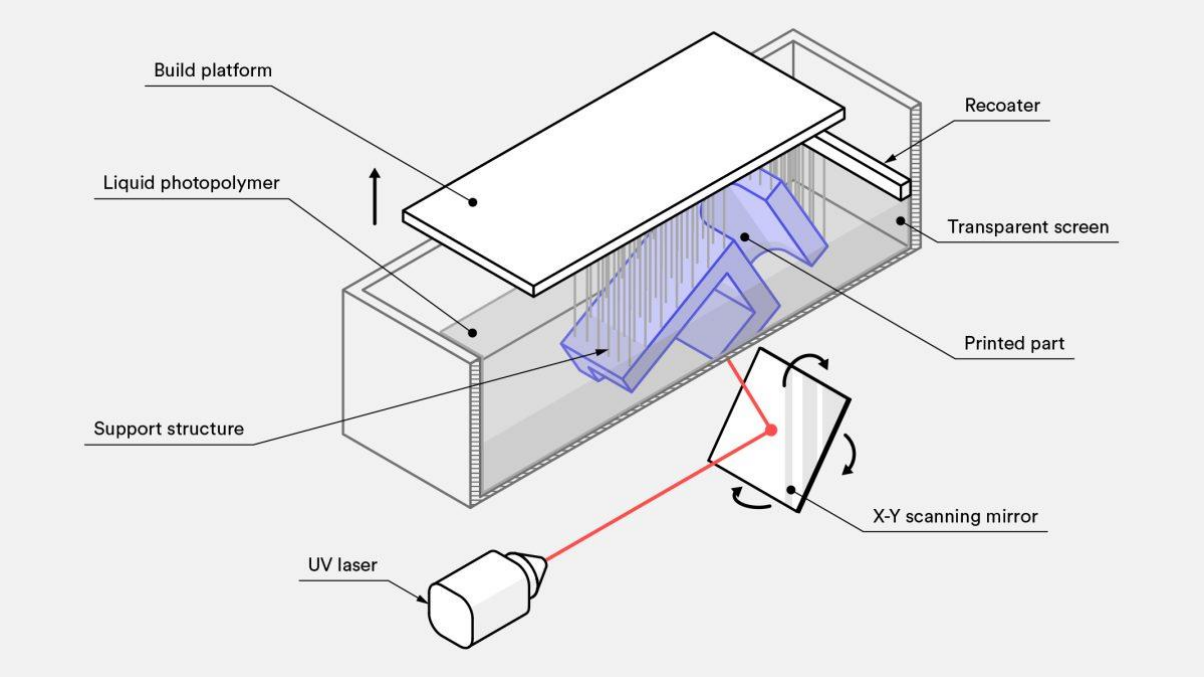


6. STEREO-LITHOGRAPHY PROCESS

The Stereolithography process is one of the rapid prototyping processes in which liquid polymer is used as material for layer-by-layer 3-D part building with the help of a Laser for the solidification of liquid resin.

WORKING PROCEDURE

1. SLA 3D printing works by first positioning the build platform in the tank of liquid photopolymer, at a distance of one layer height for the surface of the liquid.
2. A UV laser creates the next layer by selectively curing and solidifying the photopolymer resin.
3. During the solidification part of the photopolymerization process, the monomer carbon chains that compose the liquid resin are activated by the light of the UV laser and become solid, creating strong unbreakable bonds between each other.
4. The laser beam is focused in a predetermined path using a set of mirrors, called galvos. The whole cross-sectional area of the model is scanned, so the produced part is fully solid.
5. After printing, the part is in a not-fully-cured state. It requires further post-processing under UV light if very high mechanical and thermal properties are required.



LIMITATIONS AND CHALLENGES OF 3D PRINTING DOSAGE FORMS

There are a couple of challenges that 3D printing faces that have to be overcome before it is adopted as a widely used manufacturing technique for personalized dosage forms. Alongside the advantages and opportunities provided,3D printing has to overcome major challenges. These challenges can be classified into three categories:1. Technical challenges;2. Regulatory challenges;3. Good manufacturing practice (GMP)challenges.

1. TECHNICAL CHALLENGES

Depending on the applied printing technology, printed objects might have insufficient mechanical properties and possess a high friability, which makes the further processing of these dosage forms rather difficult. Especially during the packaging of printed tablets defects might occur, which might lead to the rejection of complete batches. For some of the 3DP technologies like BJ or SLA, a lot of unprinted material accumulates after the printing process. On the one hand, technical solutions must be found to avoid excessive amounts of unprinted material and on the other hand, clarification is needed whether unprocessed material might be reused for further printing. Compared to established pharmaceutical manufacturing processes, 3DP is lacking in process control strategies. During the conventional production of tablets, in-process control (IPC) is carried out to monitor the production intensively. For 3DP processes, IPC technologies are currently not commonly implemented, by which printed tablets are assessed analytically after being printed. Further, 3DP is a time-consuming process, whereas conventional tableting equipment can manufacture several hundred thousand tablets per hour (depending on the scale of the tablet press).

2. REGULATORY CHALLENGES

From a regulatory perspective, 3D-printed dosage forms have to meet the same requirements as conventionally manufactured dosage forms. However, at this point, a big gap is existing in the regulatory framework. While for established processes guidelines are well implemented and standardized, the process of 3DP is lacking any guidelines from regulatory authorities. Health authorities around the world recognized the lack of guidance and initiated the process of developing standards and defining practical guidelines. The FDA designated two internal laboratories, the Laboratory for Solid Mechanics as well as the Functional Performance and Device Use Laboratory within the FDA´s Office of Science and Engineering Laboratories (OSEL), to explore the future potential of 3DP in pharmaceutics. The work of these two units should help to gain knowledge in the first step and to help develop standards as well as identify critical aspects affecting product safety. Nevertheless, health authorities must put more effort into defining standard processes and providing guidance for pharmaceutical manufacturers. Furthermore, liability, as well as responsibility, must be discussed in case of occurred incidents. If it is intended to use 3DP as an on-demand manufacturing process in community and hospital pharmacies, different scenarios for the supply chain are possible. Regarding FFF technology, drug-loaded filaments must

be provided by external chemical or pharmaceutical companies, and the printing process executed in the pharmacy itself. The scenario raises the question of how incoming goods should be tested with the equipment at the pharmacy and who would be responsible for the release of the starting material for manufacturing.

3.GOOD MANUFACTURING PRACTICE(GMP)CHALLENGES

Moreover, qualification standards for 3D-printer manufacturers must be defined to meet GMP requirements. Especially, the topic of cleaning validation should be addressed to avoid cross-contamination. As long as cleaning concepts are not in place and validated, pharmaceutical manufacturers are obliged to use 3D printers as dedicated equipment. The mentioned regulatory and GMP challenges must be tackled together by health authorities and pharmaceutical manufacturers to establish 3DP as the manufacturing process for pharmaceutical dosage forms.

RISK ASSESSMENT DURING THE 3D PRINTING PROCESS:

Risk determination is an important step in 3D printing technology. Mainly it was performed to prevent failure of quality assurance parameters such as assay, content uniformity, appearance, etc. Risk factors are identified with the process and process variables to confirm the quality of products that were manufactured in industries.

Risk factors are checked in these conditions:

- Software controls should be employed if a particular printer cannot print a particular pattern.
- Layer thickness variability has to be controlled by real-time layer thickness monitoring.
- Controlling the temperature and moisture content of the production place caused improper layering, mainly it was a result of changes in environmental conditions.
- Improper location throughout printing might be avoided by tracking print head height and print head speed can prevent inaccurate position in the printer.
- Monitoring the powder aqueous content and powder molecule size distribution can prevent uneven layers.
- Ensuring the particle size distribution and monitoring inkjet flow can reduce or eliminate print head clogging.
- Binder surface tension or binder viscosity variation leads to inconsistent agglomeration.

FUTURE PERSPECTIVES OF 3DP TECHNOLOGY

1. Scalability from Rapid Prototyping to Production

3D printing use for jigs, fixtures and tooling, bridge production, and production parts has grown remarkably over the last few years. In that time, the heavy equipment and industrial machines industries have seen the highest adoption of use cases for jigs, fixtures, and tooling; healthcare has been the biggest adopter of bridge production, and the orthopaedics and industrial machines industries have seen the highest adoption rates in using 3D printing for production parts.

2. Making the Supply Chain More Resilient Through Digitization

If the global pandemic has taught us anything, it's that global supply chains can be unpredictable. Historically, supply chain management has focused on cost and efficiencies at the expense of resiliency. It's no wonder that many supply chains failed when faced with disruption as big as the pandemic COVID-19 supply chain impact was felt across every industry, but especially in healthcare and medical devices. Now, building supply chain resilience is a key objective across industries. When a shortage of personal protective equipment (PPE) and ventilator parts was crippling the healthcare supply chain, additive manufacturing was a big part of the solution. Faced with pandemic-related obstacles, Super feet, an insole manufacturer, dedicated its available capacity to producing face shields. With 3D printing serving as their main manufacturing method, converting their lines to produce shields was done quickly with little switching cost.

3. Offering Greater Flexibility and More Customized Designs

A prevailing consumer trend transforming numerous industries is the desire for customized products. Rather than purchasing an item that was made through mass production, customers are more frequently wanting a product that is created for them specifically, gratifying their tastes and preferences. Personalization and customization can be easily enabled with the low-volume production capabilities offered by additive manufacturing. 3D printing gives brands more flexibility in responsive design, specifically through design for additive manufacturing. Instead of making advanced market predictions and then spraying large quantities of identical objects into the market, manufacturers can afford to produce smaller batches, allowing designers and engineers to adjust product designs and innovate cost-effectively manner as inspiration strikes, consumer sentiment is known, or customer feedback trickles in. The accessibility of 3D printing is starting to reach the point where you wonder, "what can't we print?" And when we start to dissect everything down to the molecular level, it's just a matter of time before individual consumers can print food or frames for their glasses or… well, anything. In the future, 3D printing and future permutations of digital production will more fully empower consumers.

4. The Future of Digital is all about Materials

While increasing investments in the additive manufacturing ecosystem are fuelling growth, I don't think you can overstate the significance of the materials. Outside of the high cost of the equipment, the next big barrier is materials and closed additive manufacturing ecosystems, which have stymied the 3D printing industry's growth. Numerous types of 3D printing materials are on the market today, but few are advanced enough to meet the quality or regulatory requirements of industries.

5. Creating a More Sustainable Future with 3D Printing

Finally, two of the key tenets of additive manufacturing are sustainability and conservation. One of the intrinsic benefits is that scrap material is reduced, if not eliminated. As Simon Ford and Melanie Despeisse point out in their essay, "Additive Manufacturing and Sustainability: An Exploratory Study of the Advantages and Challenges," additive manufacturing mimics biological processes by creating objects layer by layer, rather than producing a hulking item that must be whittled and chunks carved out to achieve the desired shape. "It is inherently less wasteful than traditional subtractive methods of production and holds the potential to decouple social and economic value creation from the environmental impact of business activities,"

CONCLUSION:

It is generally accepted that 3D printing will be a thoroughgoing force in manufacturing, whether positive (or) negative. The use of 3D printing for medicinal purposes today is beyond astonishing. It is a creation tool among other things and a relatively new technology. If a picture is worth a thousand words, a prototype is worth a thousand pictures.

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