A Overview on 3D printing – current pharmaceutical applications and future directions

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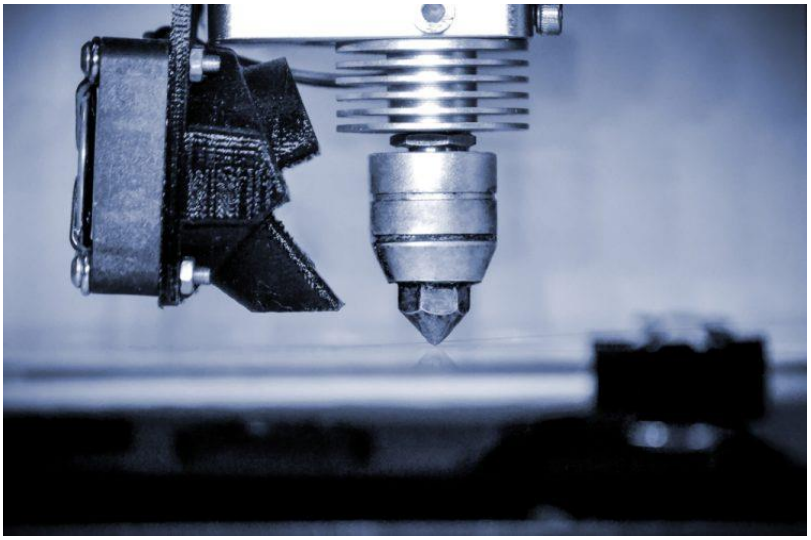
Abstract:

3D printing which has turned into a remarkable point in today's innovative exchange. In this paper, we will look at additive manufacturing or 3D printing. We will firstly characterize what we mean by this term and what is so noteworthy about it. We will dive a bit into the history. At that point, we should see about the procedure of 3D printing and the materials utilized as a part of the production of 3D printed objects. We might likewise see the focal points and burdens of 3D printing. We should watch the various applications it is being out to utilize today. At last, the future capability of this innovation is illustrated.

Keywords: *3D printing, 3D printers, polymers, Stereolithography, Additive manufacturing.*

Introduction

3D printing has the potential to revolutionise the pharmaceutical manufacturing industry; however, few 3D-printed products have been approved since the first in 2015. In this article, *EPR's* Hannah Balfour explores the technologies currently being evaluated for use in the 3D printing of pharmaceuticals, and the work of key market players to develop and advance their applications from research to commercial.[1-2]



The healthcare needs of the population, and the therapeutics we use to treat them, are changing. Though generics are undeniably important, there is a noticeable shift towards personalisation and customisation of treatment – stimulated by the adoption and enhancement of omics technologies in healthcare. This, in turn, is affecting the way we manufacture drugs: drawing the industry away from large-scale batch manufacturing to more continuous, non-batch and/or small-scale production efforts.

One technology that could fulfil the requirement of personalised therapies is three-dimensional (3D) printing, also known as additive manufacturing, which uses a computerised model to guide the layer-by-layer construction of a 3D shape. Its potential to disrupt the pharmaceutical industry is vast, as 3D printing technologies could enable on-demand production of products with personalised dosages, drug combinations, geometries and release characteristics, not afforded by existing conventional manufacturing technologies like tableting and encapsulation.

The first 3D-printed pharmaceutical – Spritam® (a levetiracetam tablet) – was approved by the US Food and Drug Administration (FDA) in July 2015, and since then articles describing the 3D printing of pharmaceuticals have increased year on year. Valued at $175.19 million in 2020 and anticipated to grow to $285.17 million by 2025, the 3D-printed pharmaceuticals market represents a significant opportunity to those able to capitalise on its benefits and overcome its challenges.[3,4]

The term 3D printing encompasses several manufacturing technologies that build parts layer-by-layer. Each vary in the way they form plastic and metal parts and can differ in material selection, surface finish, durability, and manufacturing speed and cost.

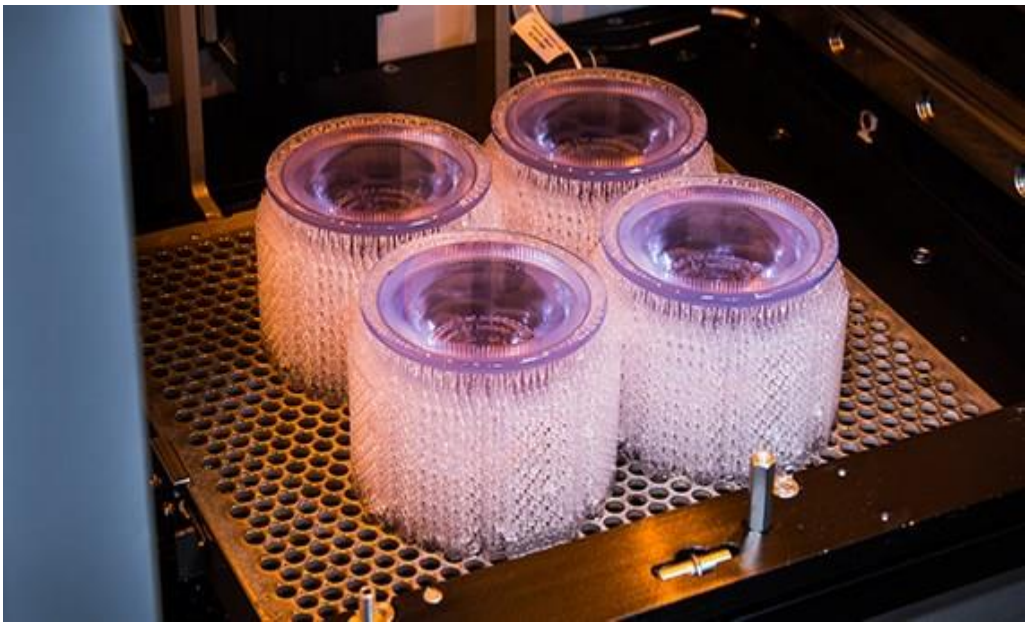
There are several types of 3D printing, which include:

- Stereolithography (SLA)
- Selective Laser Sintering (SLS)
- Fused Deposition Modeling (FDM)
- Digital Light Process (DLP)
- Multi Jet Fusion (MJF)
- PolyJet
- Direct Metal Laser Sintering (DMLS)
- Electron Beam Melting (EBM)

Selecting the right 3D printing process for your application requires an understanding of each process' strengths and weaknesses and mapping those attributes to your product development needs. Let's first discuss how 3D printing fits within the product development cycle and then take a look at common types of 3D printing technologies and the advantages of each.

3D Printing for Rapid Prototyping and Beyond

It's safe to say 3D printing is most often used for prototyping. Its ability to quickly manufacture a single part enables product developers to validate and share ideas in a cost-effective manner. Determining the purpose of your prototype will inform which 3D printing technology will be the most beneficial. Additive manufacturing can be suitable for a range of prototypes that span from simple physical models to parts used for functional testing.



SLA technology forms plastic parts by curing a liquid thermoset resin with a UV laser. As parts are built, they require support structures which are removed once the build completes.

Despite 3D printing being nearly synonymous with rapid prototyping, there are scenarios when it's a viable production process. Typically, these applications involve low-volumes and complex geometries. Often, components for aerospace and medical applications are ideal candidates for production 3D printing as they frequently match the criteria previously described.

Five 3D Printing Considerations

Like most things in life, there's rarely a simple answer when selecting a 3D printing process. When we assist customers evaluating their 3D printing options, we typically point to five key criteria to determine what technology will meet their needs:

1. Budget
2. Mechanical requirements
3. Cosmetic appearance
4. Material selection
5. Geometry

Polymer 3D Printing Processes

Let's outline some common plastic 3D printing processes and discuss when each provides the most value to product developers, engineers, and designers.

Stereolithography (SLA)

Stereolithography (SLA) is the original industrial 3D printing process. SLA printers excels at producing parts with high levels of detail, smooth surface finishes, and tight tolerances. The quality surface finishes on SLA parts, not only look nice, but can aid in the part's function—testing the fit of an assembly, for example. It's widely used in the medical industry and common applications include anatomical models and microfluidics. We use Vipers, ProJets, and iPros 3D printers manufactured by 3D Systems for SLA parts.

Selective Laser Sintering (SLS)

Selective laser sintering (SLS) melts together nylon-based powders into solid plastic. Since SLS parts are made from real thermoplastic material, they are durable, suitable for functional testing, and can support living hinges and snap-fits. In comparison to SL, parts are stronger, but have rougher surface finishes. SLS doesn't require support structures so the whole build platform can be utilized to nest multiple parts into a single build—making it suitable for part quantities higher than other 3D printing processes. Many SLS parts are used to prototype designs that will one day be injection-molded. For our SLS printers, we use sPro140 machines developed by 3D systems.

PolyJet

PolyJet is another plastic 3D printing process, but there's a twist. It can fabricate parts with multiple properties such as colors and materials. Designers can leverage the technology for prototyping elastomeric or overmolded parts. If your design is a single, rigid plastic, we recommend sticking with SL or SLS—it's more economical. But if

you're prototyping an overmolding or silicone rubber design, PolyJet can save you from the need to invest in tooling early in the development cycle. This can help you iterate and validate your design faster and save you money.

Digital Light Processing (DLP)

Digital light processing is similar to SLA in that it cures liquid resin using light. The primary difference between the two technologies is that DLP uses a digital light projector screen whereas SLA uses a UV laser. This means DLP 3D printers can image an entire layer of the build all at once, resulting in faster build speeds. While frequently used for rapid prototyping, the higher throughput of DLP printing makes it suitable for low-volume production runs of plastic parts.

Protolabs uses Concept Laser's Mlab and M2 machines for metal, 3D-printed parts.

Multi Jet Fusion (MJF)

Similar to SLS, Multi Jet Fusion also builds functional parts from nylon powder. Rather than using a laser to sinter the powder, MJF uses an inkjet array to apply fusing agents to the bed of nylon powder. Then a heating element passes over the bed to fuse each layer. This results in more consistent mechanical properties compared to SLS as well as improved surface finish. Another benefit of the MJF process is the accelerated build time, which leads to lower production costs.

Fused Deposition Modeling (FDM)

Fused deposition modeling (FDM) is a common desktop 3D printing technology for plastic parts. An FDM printer functions by extruding a plastic filament layer-by-layer onto the build platform. It's a cost-effective and quick method for producing physical

models. There are some instances when FDM can be used for functional testing but the technology is limited due to parts having relatively rough surface finishes and lacking strength.

Metal 3D Printing Processes

Direct Metal Laser Sintering (DMLS)

Metal 3D printing opens up new possibilities for metal part design. The process we use at Protolabs to 3D print metal parts is direct metal laser sintering (DMLS). It's often used to reduce metal, multi-part assemblies into a single component or lightweight parts with internal channels or hollowed out features. DMLS is viable for both prototyping and production since parts are as dense as those produced with traditional metal manufacturing methods like machining or casting. Creating metal components with complex geometries also makes it suitable for medical applications where a part design must mimic an organic structure.

Electron Beam Melting (EBM)

Electron beam melting is another metal 3D printing technology that uses an electron beam that's controlled by electromagnetic coils to melt the metal powder. The printing bed is heated up and in vacuum conditions during the build. The temperature that the material is heated to is determined by the material in use.

When to Use 3D Printing

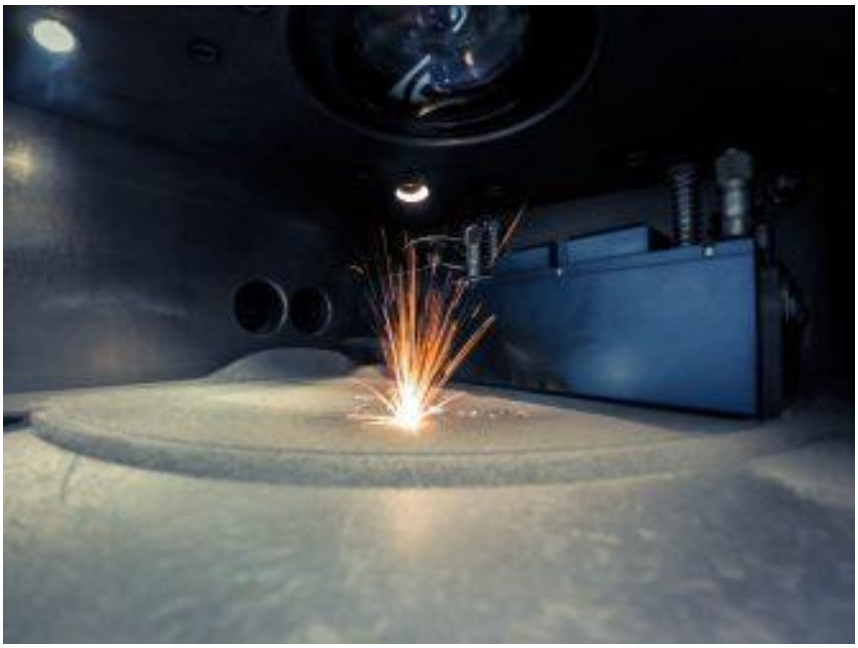
As stated earlier, there are a couple common denominators among 3D printing applications. If your part quantities are relatively low, 3D printing can be optimal—the guidance we give our 3D printing service customers is usually 1 to 50 parts. As volumes start to near the hundreds, it's worth exploring other manufacturing processes. If your design features complex geometry that is critical to your part's function, like an aluminum component with an internal cooling channel, 3D printing might be your only option.

Selecting the right process comes down to aligning the advantages and limitations of each technology to your application's most important requirements. In the early stages when ideas are being thrown around and all you need is a model to share with a colleague, those stair-stepping surface finishes on your part aren't of much concern. But once you hit the point where you need to conduct user testing, factors like cosmetics and durability start to matter. Although there is no one-size-fits-all solution, properly utilizing 3D printing technology throughout product development will reduce design risk and, ultimately, result in better products.

Technologies applied in the 3D printing of pharmaceuticals

There are currently several examples of 3D-printed healthcare products on the market, ranging from ibuprofen hydrogels and drug delivery devices for progesterone and pseudoephedrine, to polypills such as guaifenesin and the multi-active combination of nifedipine, captopril and glipizide[6,7.]

To create these products, five core techniques are currently applied: extrusion moulding printing (EMP), drop on powder (DOP) printing, selective laser sintering (SLS), stereolithography (SLA) and electrohydrodynamic 3D printing (EHD)



EMP is one of the most frequently used – sub-divided into fused deposition modelling (FDM) and semisolid extrusion moulding technology (SSE). In FDM, drug-loaded polymers are heated to a semifluid state, extruded from a printing nozzle and allowed to solidify on the printing platform, creating the desired product. Despite being a relatively cheap and operationally simple process, it is limited by the potential for active pharmaceutical ingredients (APIs) to thermally degrade during the heating process and exacerbated by low drug loading.SSE, conversely, uses pressure to extrude a paste through a syringe-based print head to deposit material on the printing platform. This is the method used to produce guaifenesin, a bi-layered polypill with controlled release. While SSE avoids the thermal degradation problem, its limitations include the necessity for organic solvents and complex requirements for preparing the paste, as well as the need for heavy machinery.[8,9]

DOP printing, or binder jetting, uses droplets of a binding agent from a print head to bind powder deposited on the build platform in layers into the desired product. It is relatively low cost, easy to scale up and creates tablets with high porosity, but is limited by the need for post-processing – wherein residual solvent must be eliminated and unprocessed powder recovered – low resolution and high fragility.

A type of powder bed fusion called SLS is another powder-based processing 3D printing technique; however, it uses a CO_2 laser to selectively sinter (heat to create solid material) selected regions of layers of powders. While its precision enables manufacturers to greatly control the microstructures of the drug products produced, SLS is low speed and has the potential to degrade drug products through the heat produced by the laser.[10]

3D printing Procedure

First avirtual 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 standandard 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 in to G file by slicing the design in to design in to series of 2D horizontal cross-sections by the help of specialized slice software ,which is installed in the 3D printer

Year	Major development
1980	Dr. Hideo Kodama filed first patent for RP technology
1984	Stereo lithography apparatus (SLA) was invented by Charles Hull
1986	Carl Deckard invented apparatus for producing parts by selective sintering
1989	Patent was granted to Carl Deckard for SLA
1990	Fused deposition modeling (FDM)
1992	First SLA machine was produced using 3D system
1993	3D printing patent was granted to E.M Sachs
1996	Clinical application of biomaterials for tissue regeneration
1999	Luke Massella received first 3D printed bladder which was an amalgamation of 3D printed biomaterials own cells
2000	MCP technologies introduced the SLM technology
2002	Miniature functional kidney was fabricated
2003	Term organ printing was coined
2004	Dr. Bowyer conceived the RepRap concept of an open-source, self-replicating 3D printer
2005	First color 3D printer was introduced by Z Corp
2007	Selective layer customization and on-demand manufacturing of industrial parts
2009	Organovo, Inc., announced the release of data on the first fully bioprinted blood vessels
2011	3D printing was applied in gold and silver World's first 3D printed car, robotic aircarft was introduced
2012	Extrusion-based bioprinting for an artificial liver

Year	Major development
	3D printed prosthetic jaw was implanted
2013	SolidConcepts produced a 3D printed metal gun
2014	Implementation of multi-arm bioprinter to integrate tissue fabrication with printed vasculature
2015	First 3D printed pill was approved by US FDA Organovo announced the release of data on the first fully bioprinted kidney

3D printing has the potential to revolutionise the production of pharmaceutical products, allowing for decentralised and customised manufacturing of therapeutics"

SLA, a type of vat photopolymerisation,[1] uses ultraviolet lasers to polymerise photosensitive resins in layers, repeating until the desired dosage form is created. It has the best resolution of the technologies, facilitating precise structures, and is typically used to produce oral solid dosages, hydrogels and microneedle patches for drug delivery. While it has low requirements for which chemical structures or drug/excipient properties can be used, it requires post-processing to eliminate resin toxicity, the equipment is costly, there are few approved resins for the pharmaceutical field, and efficiency is low.

EHD is an emerging technology which utilises digitally controlled deposition of materials to pattern fibrous materials, creating drug products. It enables fibre engineering on the micro-to-nano scale, allowing customised geometries and well-ordered complex structures to be formed. Researchers believe it could one day engender the small-scale manufacturing of medicines tailored to individual patient needs, such as personalised dosage form requirements or API release. EHD is a one-step process for which there are a wide range of applicable materials; however, its limits include low efficiency, the potential for remaining solvent in the dosage forms and high requirements for solution properties.

Challenges facing printed pharmaceuticals

Despite the potential of 3D-printed technologies to advance the pharmaceutical industry, the complications impacting application are four-fold: the requirements for excipients, the development of printing software and instrumentation, optimising the mechanical properties of products and the regulatory landscape.

Generally, excipients for use in pharmaceutical 3D printing are relatively limited, compared to traditional manufacturing processes, especially for specialised dosage forms and technologies that use heat. To promote its application by pharma, further investigation into non-toxic, biodegradable, biocompatible and stable excipients is required.[6]

As the complexity of the structure of a dosage form increases, the modelling and slicing software used to design and inform its production must be continuously updated. The mechanical equipment, operating procedures and control system must also be updated and optimised to meet the needs of the various processes, whether to prevent clogging or promote product uniformity. At present, 3D printers used in pharmaceutical formulation preparation do not meet good manufacturing practice (GMP) standard and thus need to be validated to ensure they meet the required safety standards.

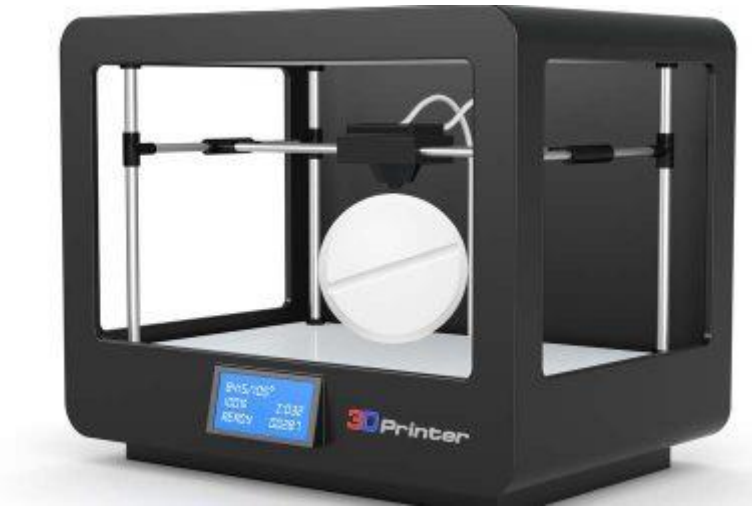
The mechanical properties of the dosage forms are a quality control parameter – that ensures the products are reproducible and suitable for post-processing. There are various factors that can influence product properties with 3D manufacturing, from nozzle fineness and adhesive viscosity to drying methods and temperature. To ensure the mechanical properties are suitable, the equipment and control programmes must be enhanced, adhesive nozzles refined and printing process parameters optimised

In terms of regulation, there are many questions surrounding how 3D-printed pharmaceuticals can be monitored and evaluated for quality. The FDA issued its final guidance on technical considerations for the regulation of 3D-printed medical devices in 2017 however, they may not apply to all 3D-printed medical devices as a separate assessment of safety and effectiveness may be required, especially for personalised products. In instances where products are customised to the patient, the question of whether 3D printing is classed as a manufacturing process or compounding, would also impact regulatory guidance. Additionally, though the FDA authorised the first 3D-printed tablets, no regulations or guidelines regarding 3D-printed medicines are currently available. There remain several regulatory challenges, such as how the performance of 3D-printed pharmaceuticals should be measured or their quality controlled, though the FDA's Office of Testing and Research is currently working to answer them.[8]

A developing sector

Merck is one of the major players in the pharmaceutical 3D printing sphere, with work undergoing at its Innovation Center to test various technologies, including powder jetting, material extrusion and SLS. In a presentation at PHARMAP 2021, I listened as Dr Christoph Huels, Founder Additive Manufacturing of Tablets at Merck, explained that they are primarily focused on SLS, having found that it creates oral solid dosage forms with desirable mass, hardness, roughness and shape, as well as tablets with uniform API content and comparable dissolution to traditional manufacturing.

Merck's current goal, according to Huels, is to establish 3D printing for clinical trial supply. It plans to offer the technology to customers for exploratory studies in the course of the next year while working to develop a GMP solution for market introduction in two or three years' time. He explained that he anticipates it will be 10-15 years before additive manufacturing is fully developed for broad application in the production of pharmaceuticals, though added that experts do not believe the scale up from the thousands of tablets required for clinical trial phases to commercial scale should be too challenging.



In a recent interview with 3D Printing Industry,[10] Huels stated: "Commercial manufacturing requires so-called 'blockbuster drugs' and billions of tablets per year for global supply. 3D printing technologies are not able to secure the supply with the current throughput today. Significant improvements need to be done to reach that in the longer-term future. Nevertheless, the current throughput is already, or will be soon, well suited to supply orphan or smaller oncology indications, where only millions of tablets are required per year." He added that smaller indications are where 3D printing will likely have the most commercial viability, especially in the short term.

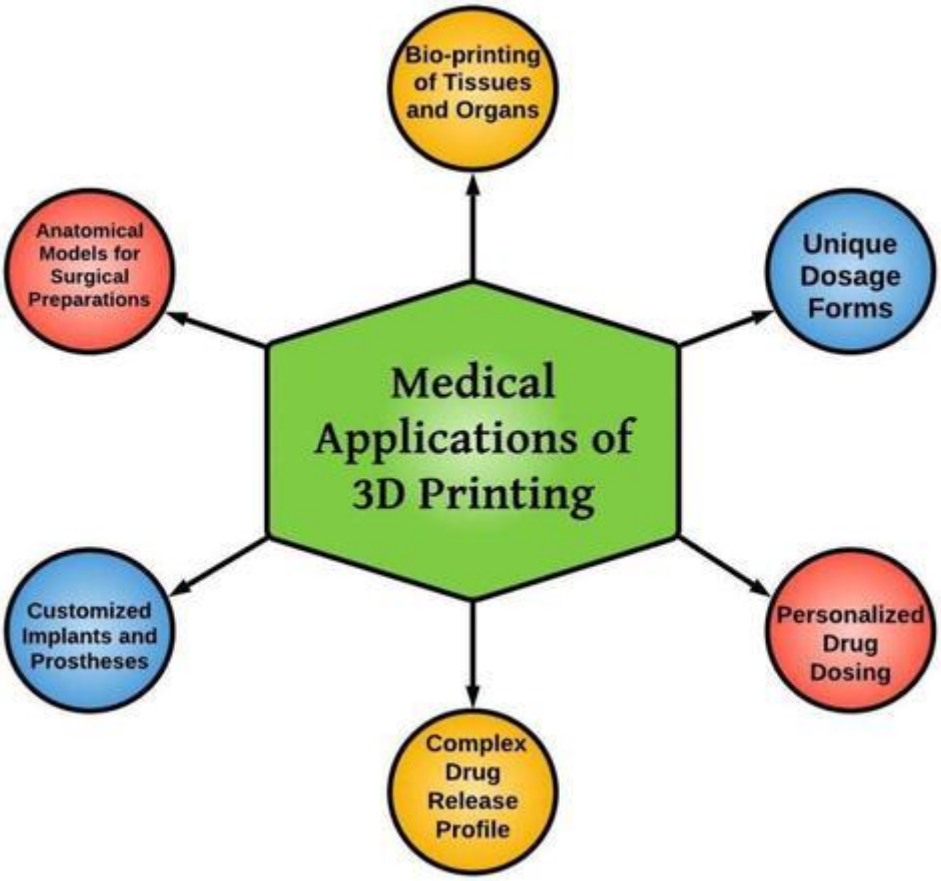
Other companies working on the 3D printing of pharmaceuticals include Aprecia, the developer of Spritam – the first 3D-printed drug ever to be approved, and FabRx. Aprecia's Kirk Donaldson, Vice President Business Development & Alliance Management, recently stated that the company is working to develop new 3D printing formulation platforms, aside from its existing ZipDose and ZipCup binder jetting technologies; the first he said is already

clinic and commercial ready. Donaldson added that they have several 3D-printed pipeline candidates that will advance to clinic in the next few years.

FabRx launched what it claims is the first GMP-ready 3D printer for pharmaceuticals in 2020, the M3DIMAKER, which is currently available for research purposes. "The M3DIMAKER is already taking part in national and international collaborations, which will involve future clinical trials, and we are in communication with the MHRA to aid regulation development for this state-of-the-art technology," stated the company's Co-Founder and Director, Alvaro Goyanes. "It combines multiple 3D printing technologies into one machine, allowing for flexible use and increased personalisation potential.

Overall, 3D printing has the potential to revolutionise the production of pharmaceutical products, allowing for decentralised and customised manufacturing of therapeutics. However, we will have to wait and see whether the challenges facing the market can be overcome to allow the technology to reach its full therapeutic potential.

Different medical applications of 3D printing technology



3D printing has been applied in medicine since the early 2000s, when the technology was first used to make dental implants and custom prosthetics.[6] Since then, the medical applications for 3D printing have evolved considerably. Recently published reviews describe the use of 3D printing to produce bones, ears, exoskeletons, windpipes, a jaw bone, eyeglasses, cell cultures, stem cells, blood vessels, vascular networks, tissues, and organs, as well as novel dosage forms and drug delivery devices. The current medical uses of 3D printing can be organized into several broad categories: tissue and organ fabrication; creating

prosthetics, implants, and anatomical models; and pharmaceutical research concerning drug discovery, delivery, and dosage forms.[2] A discussion of these medical applications follows.

Bioprinting Tissues and Organs

Tissue or organ failure due to aging, diseases, accidents, and birth defects is a critical medical problem. Current treatment for organ failure relies mostly on organ transplants from living or deceased donors. However, there is a chronic shortage of human organs available for transplant.[1] In 2009, 154,324 patients in the U.S. were waiting for an organ. Only 27,996 of them (18%) received an organ transplant, and 8,863 (25 per day) died while on the waiting list. As of early 2014, approximately 120,000 people in the U.S. were awaiting an organ transplant.[1] Organ transplant surgery and follow-up is also expensive, costing more than $300 billion in 2012. An additional problem is that organ transplantation involves the often difficult task of finding a donor who is a tissue match. This problem could likely be eliminated by using cells taken from the organ transplant patient's own body to build a replacement organ. This would minimize the risk of tissue rejection, as well as the need to take lifelong immunosuppressants.

Therapies based on tissue engineering and regenerative medicine are being pursued as a potential solution for the organ donor shortage. The traditional tissue engineering strategy is to isolate stem cells from small tissue samples, mix them with growth factors, multiply them in the laboratory, and seed the cells onto scaffolds that direct cell proliferation and differentiation into functioning tissues. Although still in its infancy, 3D bioprinting offers additional important advantages beyond this traditional regenerative method (which essentially provides scaffold support alone), such as: highly precise cell placement and high digital control of speed, resolution, cell concentration, drop volume, and diameter of printed cells. Organ printing takes advantage of 3D printing technology to produce cells, biomaterials, and cell-laden biomaterials individually or in tandem, layer by layer, directly creating 3D tissue-like structures. Various materials are available to build the scaffolds, depending on the desired strength, porosity, and type of tissue, with hydrogels usually considered to be most suitable for producing soft tissues.

Although 3D bioprinting systems can be laser-based, inkjet-based, or extrusion-based, inkjet-based bioprinting is most common. This method deposits "bioink," droplets of living cells or biomaterials, onto a substrate according to digital instructions to reproduce human tissues or organs. Multiple printheads can be used to deposit different cell types (organ-specific, blood vessel, muscle cells), a necessary feature for fabricating whole heterocellular tissues and organs. A process for bioprinting organs has emerged:

1) create a blueprint of an organ with its vascular architecture;
2) generate a bioprinting process plan
3) isolate stem cells
4) differentiate the stem cells into organ-specific cells
5) prepare bioink reservoirs with organ-specific cells, blood vessel cells, and support medium and load them into the printer
6) bioprint; and

7) place the bioprinted organ in a bioreactor prior to transplantation. Laser printers have also been employed in the cell printing process, in which laser energy is used to excite the cells in a particular pattern, providing spatial control of the cellular environment.

Although tissue and organ bioprinting is still in its infancy, many studies have provided proof of concept. Researchers have used 3D printers to create a knee meniscus, heart valve, spinal disk, other types of cartilage and bone, and an artificial ear. Cui and colleagues applied inkjet 3D printing technology to repair human articular cartilage. Wang et al used 3D bioprinting technology to deposit different cells within various biocompatible hydrogels to produce an artificial liver. Doctors at the University of Michigan published a case study in the *New England Journal of Medicine* reporting that use of a 3D printer and CT images of a patient's airway enabled them to fabricate a precisely modeled, bioresorbable tracheal splint that was surgically implanted in a baby with tracheobronchomalacia. The baby recovered, and full resorption of the splint is expected to occur within three years.

A number of biotech companies have focused on creating tissues and organs for medical research.[7] It may be possible to rapidly screen new potential therapeutic drugs on patient tissue, greatly cutting research costs and time. Scientists at Organovo are developing strips of printed liver tissue for this purpose; soon, they expect the material will be advanced enough to use in screening new drug treatments. Other researchers are working on techniques to grow complete human organs that can be used for screening purposes during drug discovery. An organ created from a patient's own stem cells could also be used to screen treatments to determine if a drug will be effective for that individual.

Challenges in Building 3D Vascularized Organs

Proof-of-concept studies regarding bioprinting have been performed successfully, but the organs that have been produced are miniature and relatively simple. They are also often avascular, aneural, alymphatic, thin, or hollow, and are nourished by the diffusion from host vasculature. However, when the thickness of the engineered tissue exceeds 150–200 micro meters, it surpasses the limitation for oxygen diffusion between host and transplanted tissue. As a result, bioprinting complex 3D organs will require building precise multicellular structures with vascular network integration, which has not yet been done.

Most organs needed for transplantation are thick and complex, such as the kidney, liver, and heart.[11] Cells in these large organ structures cannot maintain their metabolic functions without vascularization, which is normally provided by blood vessels. Therefore, functional vasculature must be bioprinted into fabricated organs to supply the cells with oxygen/gas exchange, nutrients, growth factors, and waste-product removal—all of which are needed for maturation during perfusion. Although the conventional tissue engineering approach is not now capable of creating complex vascularized organs, bioprinting shows promise in resolving this critical limitation. The precise placement of multiple cell types is required to fabricate thick and complex organs, and for the simultaneous construction of the integrated vascular or microvascular system that is critical for these organs to function.

TIJ printers are considered to be the most promising for this use. However, various 3D printing techniques and materials have been applied successfully to create vasculature as simple as a single channel, as well as more complex geometries, such as bifurcated or

branched channels. Recently, collaborators from a network of academic institutions, including the University of Sydney, Harvard University, Stanford University, and the Massachusetts Institute of Technology, announced that they had bioprinted a functional and perfusable network of capillaries, an achievement that represents a significant stride toward overcoming this problem.

Customized Implants and Prostheses:

Implants and prostheses can be made in nearly any imaginable geometry through the translatioof x-ray, MRI, or CT scans into digital .stl 3D print files.[2] In this way, 3D printing has been used successfully in the health care sector to make both standard and complex customized prosthetic limbs and surgical implants, sometimes within 24 hours. This approach has been used to fabricate dental, spinal, and hip implants. Previously, before implants could be used clinically, they had to be validated, which is very time-consuming.

The ability to quickly produce custom implants and prostheses solves a clear and persistent problem in orthopedics, where standard implants are often not sufficient for some patients, particularly in complex cases. Previously, surgeons had to perform bone graft surgeries or use scalpels and drills to modify implants by shaving pieces of metal and plastic to a desired shape, size, and fit. This is also true in neurosurgery: Skulls have irregular shapes, so it is hard to standardize a cranial implant. In victims of head injury, where bone is removed to give the brain room to swell, the cranial plate that is later fitted must be perfect. Although some plates are milled, more and more are created using 3D printers, which makes it much easier to customize the fit and design.

There have been many other commercial and clinical successes regarding the 3D printing of prostheses and implants. A research team at the BIOMED Research Institute in Belgium successfully implanted the first 3D-printed titanium mandibular prosthesis. The implant was made by using a laser to successively melt thin layers of titanium powders. In 2013, Oxford Performance Materials received FDA approval for a 3D-printed polyetherketoneketone (PEKK) skull implant, which was first successfully implanted that year. Another company, LayerWise, manufactures 3D-printed titanium orthopedic, maxillofacial, spinal, and dental implants.[6] An anatomically correct 3D-printed prosthetic ear capable of detecting electromagnetic frequencies has been fabricated using silicon, chondrocytes, and silver nanoparticles. There is a growing trend toward making 3D-printed implants out of a variety of metals and polymers, and more recently implants have even been printed with live cells.

3D printing has already had a transformative effect on hearing aid manufacturing. Today, 99% of hearing aids that fit into the ear are custom-made using 3D printing. Everyone’s ear canal is shaped differently, and the use of 3D printing allows custom-shaped devices to be produced efficiently and cost-effectively. The introduction of customized 3D-printed hearing aids to the market was facilitated by the fact that class I medical devices for external use are subject to fewer regulatory restrictions. Invisalign braces are another successful commercial use of 3D printing, with 50,000 printed every day. These clear, removable, 3D-printed orthodontic braces are custom-made and unique to each user. This product provides a good example of how 3D printing can be used efficiently and profitably to make single, customized, complex items.

Anatomical Models for Surgical Preparation

The individual variances and complexities of the human body make the use of 3D-printed models ideal for surgical preparation Having a tangible model of a patient's anatomy available for a physician to study or use to simulate surgery is preferable to relying solely on MRI or CT scans, which aren't as instructive since they are viewed in 2D on a flat screen. The use of 3D-printed models for surgical training is also preferable to training on cadavers, which present problems with respect to availability and cost. Cadavers also often lack the appropriate pathology, so they provide more of a lesson in anatomy than a representation of a surgical patient.[3]

Conclusion

This article has summarized different fabrication methods and some notable applications of 3D printing in the healthcare sector,especially in pharmaceutical sciences.3D printing technology is avaluable and potential tool for the pharmaceutical sector, leading to personalized medicine focused on the patients needs .It offers numerous advantagews, such as increasing the cost effiency and the manufacturing speed. 3D printing has revolutionized the way in which manufacturing speed.3D printing has revolutionized the way in which manufacturing is done. It improves the design manufacturing and reduces lead time and tooling cost for new products.

References

1. Seoane-Viaño I, Trenfield S, Basit A, Goyanes A. Translating 3D printed pharmaceuticals: From hype to real-world clinical applications. *Advanced Drug Delivery Reviews*. 2021;174:553-575.
2. Szczerba R. FDA Approves First 3-D Printed Drug [Internet]. Forbes. 2021 [cited 1 September 2021]. Available from: https://www.forbes.com/sites/robertszczerba/2015/…
3. Gioumouxouzis C, Karavasili C, Fatouros D. Recent advances in pharmaceutical dosage forms and devices using additive manufacturing technologies. *Drug Discovery Today*. 2019;24(2):636-643.
4. 3D Printed Drugs Market Research Report by Technology, by Region – Global Forecast to 2025 – Cumulative Impact of COVID-19 [Internet]. Researchandmarkets.com. 2021 [cited 1 September 2021]. Available from: https://www.researchandmarkets.com/reports/4857884/…
5. Overview of Pharmaceutical 3D printing | Pharma Excipients [Internet]. Pharma Excipients. 2021 [cited 1 September 2021]. Available from: https://www.pharmaexcipients.com/pharmaceutical-3dp-overview/
6. Cui M, Pan H, Su Y, *et al*. Opportunities and challenges of three-dimensional printing technology in pharmaceutical formulation development. *Acta Pharmaceutica Sinica B*. 2021;11(8):2488-2504.
7. Technical Considerations for Additive Manufactured Medical Devices [Internet]. U.S. Food and Drug Administration. 2017 [cited 1 September 2021]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/…
8. Zidan A. Promise and Potential of 3D Printed Pharmaceuticals [Internet]. U.S. Food and Drug Administration. 2017 [cited 1 September 2021]. Available

from: https://www.fda.gov/drugs/news-events-human-drugs/cder-researchers-explore-promise-and-potential-3d-printed-pharmaceuticals

9. Huels C. 3D printing or Additive Manufacturing of Tablets. Presentation presented at PHARMAP 2021 2021; Virtual.
10. Everett H. Merck, Aprecia, and FabRx on transitioning 3D printed pharmaceuticals from lab to clinic – 3D Printing Industry [Internet]. 3D Printing Industry. 2021 [cited 1 September 2021]. Available from: https://3dprintingindustry.com/news/merck-aprecia-and-fabrx…
11. FabRx's pharmaceutical 3D printer for personalised medicines, M3DIMAKER™, is now available! – FabRx [Internet]. FabRx. 2020 [cited 1 September 2021]. Available