

provide “Tailor-made” medicines for each patient. The review article begins with an overview of 3D printing technology. We describe the most common 3D printing methods applied to drug product manufacturing and discuss recent advances in 3D printing technology that

METHODS

1. Fused deposition modelling
2. Powder bed fusion
3. Inkjet Printing.
4. Stereo lithography
5. Direct Energy Deposition
6. Laminated Object Manufacturing

1. Fused deposition modelling (FDM)

In FDM method, a continuous filament of a thermoplastic polymer is Used to 3D print layers of materials. The filament is heated at the nozzle to reach a semi-liquid state and then extruded on the platform or on top of previously printed layers. The thermo plasticity of the polymer filament is an essential property for this method, which allows the filaments to fuse together during

affects drug product development. In 3D printing pharmaceutical drug delivery medication could be customized as per the need of treatment & not “One fits all” approach.

printing and then to solidify at room temperature after printing. The layer thickness, width and orientation of filaments and air gap (in the same layer or between layers) are the main processing parameters that affect the mechanical properties of printed parts. Inter-layer distortion was found to be the main cause of mechanical weakness. Low cost, high speed and simplicity of the process are the main benefits of FDM. On the other hand, weak mechanical properties, layer-by-layer appearance, poor surface quality and a limited number of thermoplastic materials are the main drawbacks of FDM. The development of fiber-reinforced composites using FDM has strengthened the mechanical properties of 3D printed parts. However, fiber orientation, bonding between the fiber and matrix and void formation are the main challenge that arise in 3D printed composite parts.

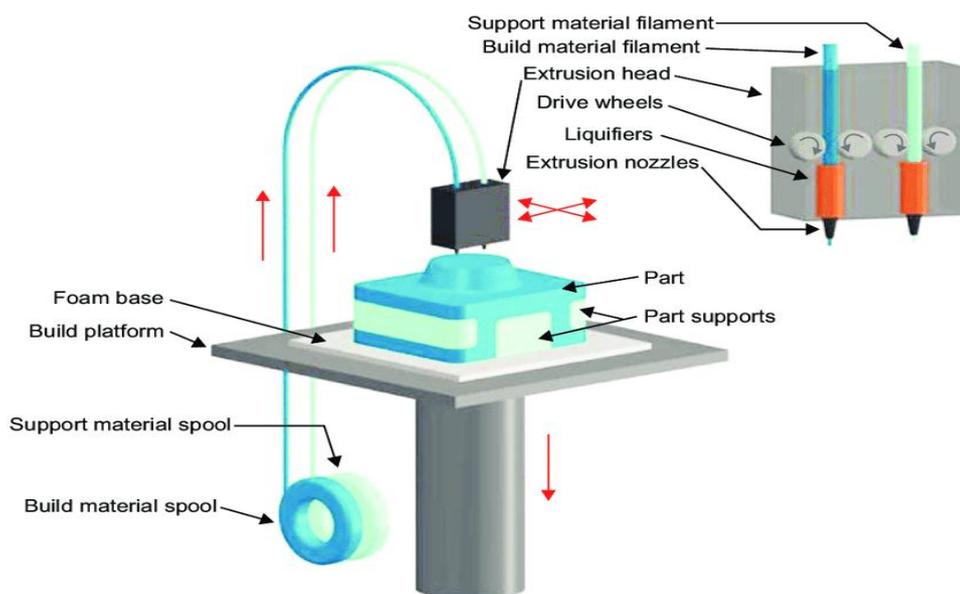


Fig. No:2 Fused Deposition Modeling

2. Powder bed fusion

Powder bed fusion processes consist of thin layers of very fine powders, which are spread and closely packed on a platform. The powders in each layer are fused together with a laser beam or a binder.

Subsequent layers of powders are rolled on top of previous layers and fused together until the final 3D part is built. The excess powder is then removed by a vacuum and if necessary, further processing and detailing such as coating, sintering or infiltration are carried out. Powder size distribution and packing, which determine the density of the printed part, are the most crucial factors to the efficacy of this method. The laser can only be used for powders with a low melting/

sintering temperature, whereas a liquid binder should otherwise be used. Selective laser sintering (SLS) can be used for a variety of polymers, metals and alloy powders while selective laser melting (SLM) can only be used for certain metals such as steel and aluminum.

In the case of using a liquid binder, the method is referred to as three-dimensional printing or 3DP. Binder deposition is generally higher compared to laser sintering or melting, which can print dense parts. Laser power and speed of scanning are the main parameters affecting the sintering process.

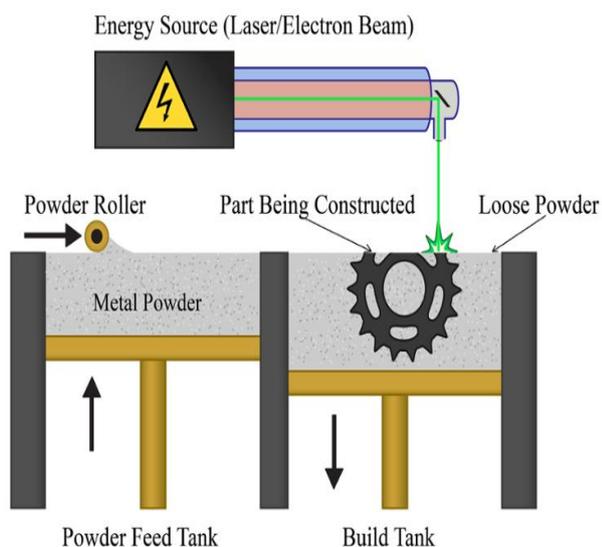


Fig. 3: Powder Bed Diffusion

Fine resolution and high quality of printing are the main advantages of powder bed fusion, which make it suitable for printing complex structures. This method is widely used in various industries for advanced applications such as scaffolds for tissue engineering, lattices, aerospace and electronics. The main advantage of this method is that the powder bed is used as the support, which overcomes difficulties in removing supporting material.

However, the main drawbacks of powder bed fusion, which is a slow process, include high costs and high porosity when the powder is fused with a binder.

3. Inkjet printing

Inkjet printing is one of the main methods for the additive manufacturing of ceramics. It is used for printing complex and advanced ceramic structures for applications such as scaffolds for tissue engineering.

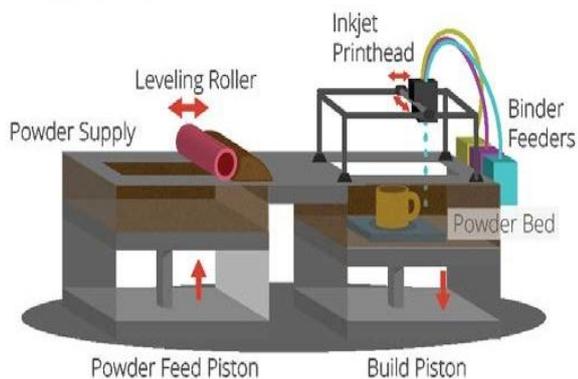


Fig. 04: Inkjet Printing.

In this method, a stable ceramic suspension e.g. zirconium oxide powder in water is pumped and deposited in the form of droplets via the injection nozzle onto the substrate. The droplets then form a continuous pattern which solidifies to sufficient strength in order

to hold subsequent layers of printed materials. This method is fast and efficient, which adds flexibility for designing and printing complex structures. Two main types of ceramic inks are wax-based inks and liquid suspensions. Wax-based inks are melted and deposited on a cold substrate in order to solidify. On the other hand, liquid suspensions are solidified by liquid evaporation. The particle size distribution of ceramics, viscosity of the ink and solid content, as well as the extrusion rate, nozzle size and speed of printing, are factors that determine the quality of inkjet-printed parts.

4. Stereo lithography

SLA is one of the earliest method of manufacturing. Which was developed in 1996. It uses UV light to initiate chain reaction on a layer of resin or monomer solution. The monomers are UV active and instantly convert to polymer chain after activation. After polymerization, a pattern inside the resin layer is solidified in order to hold the subsequent layer. The unreacted resin is removed after the completion of printing.

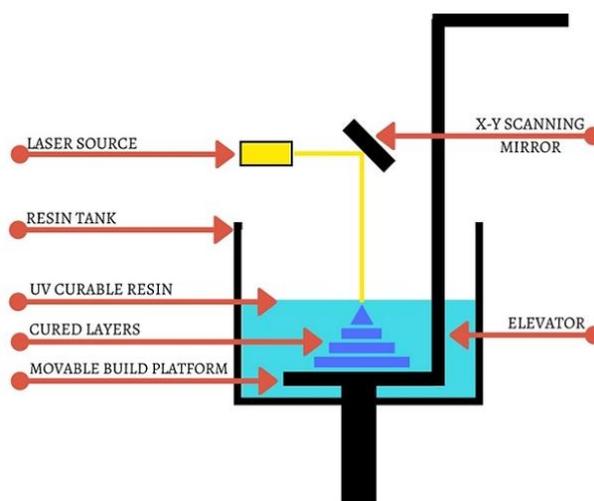


Fig. 05: Stereo lithography.

A post process treatment such as heating or photo curing may be used for some printed parts in order to achieve the desired mechanical performance. A dispersion of ceramic particles in monomers can be used to print ceramic polymers composite or polymer derived ceramifiable monomers e.g. silicon oxycarbide. SLA prints high quality part at high resolution as low as 10micrometers. On the other hand it is relatively slow, expensive and the range for printing material is very limited. Also the kinetic of the reaction and curing process are complex. The energy of the light source and exposure are the main factors controlling the thickness of the layer. SLA can be effectively used for the additive manufacturing of complex nano composites.

5. Direct energy deposition

Direct energy deposition has been used for manufacturing high-performance super alloys. This method is also known as laser engineered net shaping (LENS), laser solid

forming, di-reacted light fabrication(DLF), direct metal deposition(DMD), electron beam. DED uses a source of energy which is directly focused on a small region of substrate and is also used to melt a feedstock material simultaneously. The melted material is then deposited and fused into the melted substrate and solidified after movement of laser beam. The difference between DED and SLM is that on powder bed is used in DED and feedstock is melted before deposition in layer by layer fashion similar to FDM but with an extremely higher amount of energy for melting metals. There for it can be helpful for filling cracks and retrofitting manufactured parts for which the application of the powder bed method is limited. This method allows for both multiple axis deposition and multiple materials at the same time.

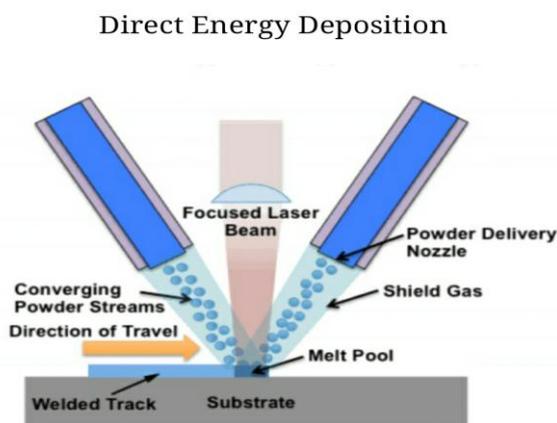


Fig. 6: Direct Energy deposition.

6. Laminated Object Manufacturing

Laminated object manufacturing is one of the first commercially available additive manufacturing method, which is based on layer by layer cutting and lamination of sheets or rolls of materials. Successive layer are cut precisely using a mechanical cutter or laser and are then bonded together. The form then bond method is particularly useful for thermal bonding of ceramics and metallic materials, which also facilitates the construction of internal features by removing excess materials after cutting are left for the support and after completion of the process, can be removed and recycle. LOM can be used for variety of material such as polymer composite, ceramics, paper and metal filled tapes. Post processing such as high temperature treatment may be required depending type of material and desired properties Ultrasonic Additive Manufacturing (UAM) is new subclass of LOM has been used in various industries such as paper manufacturing foundry industries, electronics and smart structure. Smart structure are classified as with the number of sensors and processors .Unlike conventional methods ,UAM can specify cavities and the structure based on the computer aided design for embedded electronic device, sensors, pipes and other features .Electronic device can be printed in the same lamination process of UAM using direct write technologies. LOM can result in reduction of tooling cost

and manufacturing time, is one of the best additive manufacturing method for larger structure. However LOM H has inferior surface quality and its dimensional accuracy is lower compared to powder bed method. Also removing the excess parts of laminates after formation of object is time consuming compare to powder bed method. Therefore, it is not recommended for complex shapes.

Materials Used For Manufacturing

Comparison with Traditional Manufacturing

1. Design- The intended product design rendered. Designs can be rendered in 3D with computer aided design CAD software or in 2D as a series of images corresponding to the 2D printed layers.
2. Conversion of the design to a machine-readable format: 3D designs are typically converted to the STL file format, which describes the external surface of a 3D model .3D printing programs "slice" these surfaces into distinct printable layers and transfer slayer-by-layer instructions digitally to the printer. For 3D printing methods that produce free-standing objects, software can automatically suggest where to print support material to provide scaffolding for the in-process print.
3. Raw material processing-Raw materials may be processed into granules, filaments, or binder solutions to facilitate the printing process.
4. Printing: Raw materials are added and solidified in an automatic, layer-by-layer manner to produce the desired product.
5. Removal and post - processing: After printing, products may require Drying, sintering, polishing or other post-processing steps. At This stage, unprinted material may be harvested and recycled for continued use in the printing process.

Motivation for development of 3D printed drug product

1. Increased product complexity

Pharmaceutical dosage forms have evolved in complexity over millennia from harvested botanicals to ointment, powders, and lotions prepared by Greeks and Romans. Dosage form evolution in 20th century was largely fueled by polymer science, which underpins extended and delayed release tablets, transdermal system, and long acting implants. 3D printing around 1996 introduced a new element into dosage form evolution-digital control over the arrangement of matter. For manufacture with 20th century technology, the distribution of drugs and excipients within a product is controlled almost entirely by blending or film coating. Digital control over the arrangement of matter is step change in dosage form evolution that may produce striking change in immediate release, modified release, and combination drug products. Because a drugs products structure can affects drug release, complex 3D structure create new opportunities for drug delivery. For instance ,the 3D printed drug products recently approved by FDA,SPRITIM , has a unitary porous structure produced by 3D printing without

compression. This structure allows tablets with up to 1000mg of levetiracetam to disintegrate within a seconds take with sip of water.

2. Personalization

Personalized medicine commonly refers to stratification of patient populations based on biomarkers to aid therapeutic decisions of Herceptin to treat HER2 overexpressing breast cancer, but the term can also apply to personalized dosage for design. Compare to traditional processes, 3D printing facilitates personalization.

Modifying designs is easier than modifying physical equipment. Also, automated, small-scale 3D printing may have negligible operating costs in short, 3D printing could make multiple small, individualized batches economically feasible. This mode of production may enable personalized doses, personalized implants, and personalized products designed to improve adherence.

Personalized dosing allows for tailoring amount of drug delivered based on a patient's mass and metabolism. For oral dosage forms, this is often achieved with simple devices such as powder scoops or mini-tablets counters. However, there are certain indications that could potentially benefit more precise, personalized dosing. A 3D printing dosage form could ensure accurate dosing in growing children's and permit personalized dosing of highly potent drug like theophylline. Another personalized

dosing concept is printing multidrug polypills to combine all patient medications into single daily dose.

3. On Demand Manufacturing

Like a home inkjet printer, a 3D printer can make a variety of quality products within minutes. We found three instances where this on demand capability could be beneficial for public health. Printing directly on to patient printing in time or other resource constraint setting, and printing low stability drugs for immediate consumption. Although printing on patients sounds fanciful, extrusion and jetting techniques have been applied to create tissue engineering scaffolds and wound healing gels on demand.

On demand printing could prove useful in time or resource constrained settings such as disaster areas, emergency rooms, operating rooms, ambulance, intensive care units and military operations. Another time constrained setting is product development. Drug product formulators could potentially adopt a technique from automotive manufacturing where 3D printing is used to generate and test several product interactions within minimal effort. A team from the University of Milan recently used this concept to print and test variations of an injection molded, delayed release capsule. This use of 3D printing may enable faster formulation optimization during drug product development. Implantable products fall outside the scope of this discussion and readers can refer to a medical device literature to see how 3D printing affects sterility and biocompatibility.

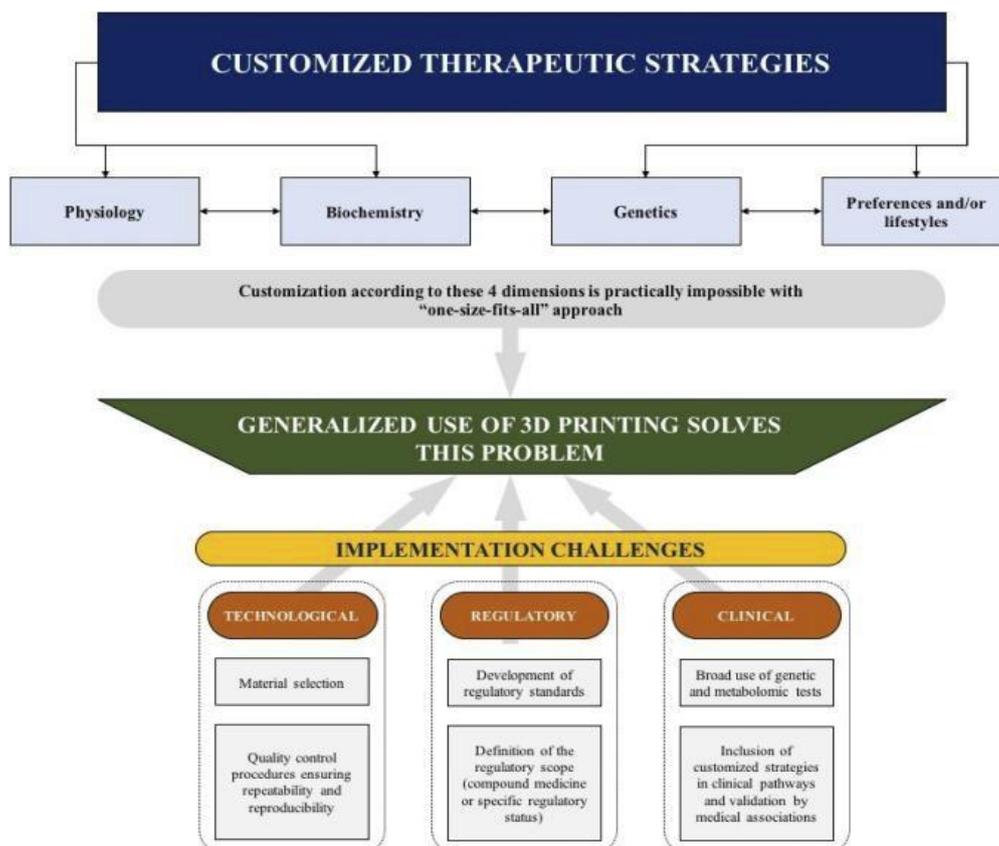


Fig. 7: Customized therapeutic strategies.

Applications

1. Architecture
2. Aerospace
3. Cosmetics
4. Healthcare
5. Automotive
6. Defense

Recent Advancement

FDA recently approved the first 3D printed drug an anti-epilepsy drug called "Spritam" made with "Aprecia pharmaceuticals" proprietary 3D printing technology known as "ZIPDOSE".

Advantages

1. We can print tens of thousands of tablets a day on a single printer.
2. Many pills in one.
3. 3D printing allows you to change the distribution of drug in single tablet.
4. High & efficient product rates.
5. High drug loading with desired accuracy & precision.
6. Minimum material wastage.
7. Minimizing drug toxicity & side effects.
8. Open structure of tablet that slowly breaks down and release a drug over a seven days period.

Challenges

1. Huge scale of investment required.
2. Actual implementation of application.
3. Safety & security concerns.
4. Lack of regulation of 3D printing.
5. Selection of appropriate excipients & polymers.
6. Post treatment method and optimization.

CONCLUSION

3D printing is an expanding technology which may soon start an industry in which everyone has a possibility of being a manufacturer.

3D printing has a lot of possible benefits to society, although the product created must be regulated.

REFERENCES

1. Hull, C.W., Apparatus for production of three-dimensional objects by stereo lithography, Google Patents, 1986.
2. G.N. Levy, R. Schindel, J.-P. Kruth Rapid manufacturing and rapid tooling with layer manufacturing (LM) technologies, state of the art and future perspectives CIRP Annals-Manuf Technol, 2003; 52(2): 589-609.
3. Tymrak, M. Kreiger, J. Pearce Mechanical properties of components fabricated with open-source 3-D printers under realistic environmental conditions Mater Des, 2014; 58: 242-246.
4. Q. Sun, G. Rizvi, C. Bellehumeur, P. Gu Effect of processing conditions on the bonding quality of FDM polymer filaments Rapid Prototyp J, 2008; 14(2): 72-80.
5. P. Tran, T.D. Ngo, A. Ghazlan, D. Hui Bimaterial 3D printing and numerical analysis of bio-inspired composite structures under in-plane and transverse loadings Compos Part B: Eng, 2017; 108: 210-223.
6. R. Melnikova, A. Ehrmann, K. Finsterbusch 3D printing of textile-based structures by Fused Deposition Modelling (FDM) with different polymer materials Iop conference series: materials science and engineering, IOP Publishing, 2014.
7. B. Caulfield, P. McHugh, S. Lohfeld Dependence of mechanical properties of polyamide components on build parameters in the SLS process J Mater Process Technol, 2007; 182(1): 477-488.
8. C.R. Garcia, J. Correa, D. Espalin, J.H. Barton, R.C. Rumpf, R. Wicker, V. Gonzalez 3D printing of anisotropic metamaterials Prog Electromagn Res Lett, 2012; 34: 75-82.
9. H. Gu, C. Ma, J. Gu, J. Guo, X. Yan, J. Huang, Q. Zhang, Z. Guo An overview of multifunctional epoxy nanocomposites J Mat Chem C, 2016; 4(25): 5890-5906.
10. J. Gu, X. Yang, Z. Lv, N. Li, C. Liang, Q. Zhang Functionalized graphite nanoplatelets /epoxy resin nanocomposites with high thermal conductivity Int J Heat Mass Transf, 2016; 92: 15-22.
11. J. Dou, Q. Zhang, M. Ma, J. Gu Fast fabrication of epoxy-functionalized magnetic polymer core-shell microspheres using glycidyl methacrylate as monomer via photo-initiated miniemulsion polymerization J Magnetism Magnetic Mater, 2012; 324(19): 3078-3082.
12. E. Kroll, D. Artzi Enhancing aerospace engineering students' learning with 3D printing wind-tunnel models Rapid Prototyp J, 2011; 17(5): 393-402.
13. K.V. Wong, A. Hernandez A review of additive manufacturing ISRN Mech eng, 2012; 2012.
14. D.B. Short Use of 3D printing by museums: educational exhibit. 3D Print Addit Manuf, 2015; 2(4): 209-21.
15. S.V. Murphy, A. Atala 3D bioprinting of tissues and organs Nat Biotechnol, 2014; 32(8): 773-785