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3D PRINTING TECHNOLOGY IN PHARMACEUTICAL SECTOR: A REVIEW

[1]Satyajit Sahoo, [2]Sohan Patel, [3]Tejas Patel, [4]Archana Kaushik, [5]Jaydeep Parmar

[1]Professor,[2]Professor,[3]Associate Professor,[4]Assistant Professor,[5]Student

[1]Department of Pharmaceutics

[1]Pioneer Pharmacy College, Vadodara, India

Abstract: The aim of this review article is to share some information about the 3D printing technology, which can be widely used in pharmaceutical sector to prepare medical devices, personalised medicines, multi-drug formulations and many more uses. It is more advantageous than the conventional or traditional manufactured preparations. We can prepare medicines of different size, shape, flavour and mainly personalised dosages from different kind of drugs with the help of 3D printing technology. There are some methods which are widely used in pharmaceutical sector for 3D printing. There is a comparison between 3D printing technology and traditional manufacturing which will give idea about both comparatively. The review gives idea about 3D printing that how this technology can be useful for different kind of patients such as paediatrics, geriatrics, women, blind or visually impaired and patients who are suffering from various chronic diseases. The 3D printing technology have various applications such as personalised medicines and dosage forms, microneedles, nanosuspension, implants, polypills, complex oral solid dosage forms and even pharmacies can be digitalised.

Key words: 3D Printing, medicines, pharmaceutical sector, digitalised.

1. INTRODUCTION

Three-dimensional(3D) printing, also known as additive manufacturing, is gaining interest, due toits versatility, ease of use and its huge variety of applications among different fields. [1] Nowadays, three-dimensional(3D) printing is one of the fastest developing branches of technology, art and science, and still broadens the applications. International Standard Organization (ISO) defined 3D technology as: “Fabrication of objects through the deposition of a material using a print head, nozzle, or another printer technology”. In this technique 3D model are used for preparing the parts in the process of joining materials layer by layer. [2] 3D printing refers to a various processes used to synthesize a three dimensional object. In 3D printing successive layers of material are formed under computer control to create an object. [3] 3D printing is a layer-by-layer process having capability to produce 3D drug products from digital file. The 3D printing technology is unparalleled, flexible, rapid and with exceptional manufacturing capability of pharmaceutical drug products of desired quality. [4] This is a process in which 3D models are constructed from a computer aided design (CAD) or digital 3D model. During the process, the material is deposited layer-by-layer to form the desired object. 3D printing, as a technology, has advanced a lot since its invention by Charles Hull in 1983. It was initially designed as a rapid prototyping method but has now grown into a true manufacturing process. 3D printing offers many advantages to the manufacturing industry, including design freedom, the ability to create complex

designs, mass customization, and cost-effective, low-volume production method material jetting, powder bed fusion, and sheet lamination. [5] 3D printing technology play a significant role in multiple active ingredient dosage forms, where the formulation can be as a single blend or multilayer printed tablets with sustained release properties. This results in reduction of frequency and number of dosage form units consumed by the patient on a daily routine. 3D printing technology has high potential in personalized dosage form concept called the polypill concept. This brings about the possibility of all the drugs required for the therapy into a single dosage form unit. Three layered printing innovation is a clever fast prototyping procedure in which solid objects are developed by sequencing multiple layers. The rapid prototyping involves the construction of physical models using computer-aided design in three dimension. [6] Different types of drug delivery systems such as oral controlled release systems, micro pills, microchip, drug implants, fast dissolving tablets and multiphase release dosage forms have been developed using 3D printing technology. [7] In novel drug delivery system 3D printing are used for viable tablet production. These tablets are manufactured in such a way that that are capable of satisfying regulatory tests and matching the standards of commercial tablets. [8] In the case of cancer, 3D printing comes in handy because it is difficult to reach the specific tumour site. Because chemotherapeutic agents have low aqueous solubility during intravenous or oral drug administration, acting at the tumour site is not possible. In such a complex process, 3D printing technology can succeed. Recently, a 5-fluorouracil patch made of poly lactic-co-glycolic acid (PLGA)and polycaprolactone was successfully printed. It is implanted directly into pancreatic cancer sites. After four weeks of effective treatment, the drug release becomes steady and constant. With the help of the patch, a total of four weeks of drug release kinetics are maintained throughout. Afterwards, it gets easily biodegraded inside the body. [9] These initiatives are outlining how to move away from the ‘one-size-fits-all’ approach towards personalisation, requiring medication to be tailored to individuals, considering factors such as physiology, concurrent therapy, drug response, genetic makeup, disease state and other factors (e.g. sex, weight and age). [10] Personalising treatments by tailoring medicines (e.g. combining more than one drug into the same tablet or selecting appropriate dosages) offers a plethora of opportunities including improved medication adherence, reduced adverse drug reactions and better therapeutic outcomes. [10,11] Utilising a layer-by-layer production process, 3D printing can produce printlets (3D printed tablets) that are individualised to a patient’s therapeutic requirements (e.g. dosage, drug combination and drug release profiles) and personal preferences (e.g. shape, size, texture and flavour). [12,13]

Advantages: [14,15]

1) High drug loading can be achieved with precision and accuracy especially in case of potent drug in small dose, when compared to conventional dosage forms.
2) Reduces cost of production due to lesser material wastage.
3) High production rates due to its fast operating systems.
4) Narrow therapeutic window.
5) Medication can be prescribed to a patient in particular based on genetic variations, ethnic differences, age, gender and environment.
6) In case of multi-drug therapy with multiple dosing regimen, treatment can be customized to improve patient adherence.
7) As prompt and controlled discharge layers can be incorporated because of the adaptable plan and production of this measurement structure, it helps in picking the best remedial system for a person.
8) Avoids batch to batch varieties found in mass assembling of ordinary measurements structures.
9) 3D printers occupy minimal space and are affordable.
10) The ability to create tablets(printlets) of any shape, size and dose.
11) The products with an excellent surface finish are produced.

12) The ability to set the dosage individually for each patient (personalised medication).
13) The ability to regulate the number of active substances in the composition of the tablet, remove or replace individual components.
14) The ability to control the process of release of active substances allows to slow down or accelerate the effect of the drug, which will increase the effectiveness of tablets.

Disadvantages: [16,17]

1) Minimum job opportunity. This disadvantage can have a large impact to the economies of third world countries especially China, that depend on a large number of low skilled jobs.
2) Precise ink viscosity must be achieved for proper flow with inkjet printing.
3) Large structure is challenging for production.
4) Product liability.
5) Limited number of ingredients are compatible with this technology.
6) The misuse of this technology is easily done.
7) The copyright is another problem rising in printing replica from original product.
8) Binding to other elements may interfere with the timing of the drug release, parameters such as speed and rate of printing must be taken into account and may not be suitable for all drug candidates.
9) A need exists for proper post printing process that will not interact or counter interact with the finished printed process.
10) The cost of buying a 3D printer still does not make its purchase by the average householder possible.
11) In inkjet printing, proper flow of ink can only be achieved with ink that has precise viscosity.
12) Rate of drug release may get affected due to binding of ink with other printer materials.

Challenges: [18,19,20,21]

1. **Drug loading capacity:** To increase the drug loading capacity in 3D printed processed tablet, uniaxial compression and suspension dispersed methodologies are adopted, but this technique suffers from increased complexity and clogging of spray nozzle.
2. **Printing software and instrument:** While achieving diversified formulas, the positioning of the double nozzles may be inaccurate, which severely affects the products' properties, such as content uniformity, hardness, and friability. Therefore, the mechanical equipment, operating procedures, driving control system, and key components of 3D printers urgently need to be further optimized and upgraded.
3. **Raw material selection:** Printability, thermal conductivity, physicochemical characteristics, Print fluid characteristics and viscoelastic property has to be carefully scrutinized along with safety of the raw materials for human use.
4. **Nozzle mechanism:** During 3D printing, nozzle mechanism is used to form the layers of the dosage form. As the printer head stops and restarts during the sequenced layer formation, consistent flow of the printing material is necessary. The common problems faced at this level are clogging of the nozzles in printer head, scraping, binder migration and bleeding and improper powder feeding.
5. **Powder based 3D printing:** Confined or Special area is required to perform the printing as powder spillage is critical and can pose as an occupational hazard.
6. **Surface imperfections in finished product:** Due to the stacking of plastic beads or large-sized powder on top of each other. Since the drying time required for the dosage form made with powder based and extrusion based techniques, there is more possibility of surface imperfections. Rate and method of drying can also affect surface imperfections.
7. **Mechanical resistance:** Friability is higher in 3D dosage forms especially in powder based technique. Production technology is important for good dosage form strength.
8. **Temperature:** Certain manufacturing process may not be appropriate for thermo-labile drugs, when printing at high temperature.

HISTORY

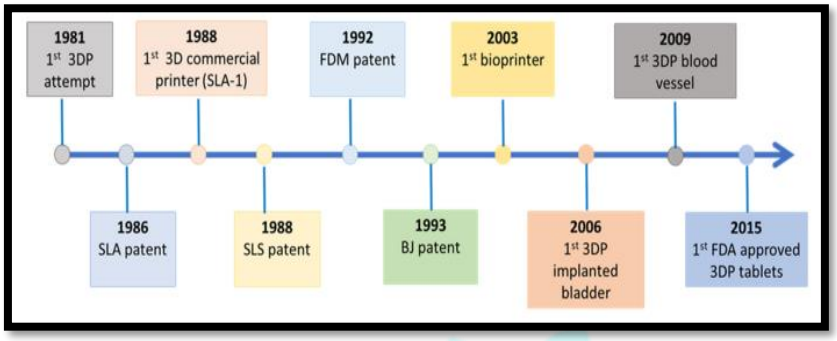


Fig.1: Invention and development of different 3D printing techniques and products[22]

At the first, Charles Hull invented 3D printing, which he called as Stereolithography, in the early **1980s**. Later he founded the company 3D systems, which developed the first 3D printer, called as Stereolithography apparatus (SLA). [23] Then in **1989**, Scott Crump, filed a patent on another 3D printing technology i.e.,Fused depositionmodeling (FDM), where extruded polymer filaments heated into a semi-liquid state and were extruded through a heated nozzle and deposited onto a build platform layer by layer to harden. Since there are many other methods have been developed for 3D printing techniques. [24,25] In **2015**, The US Food and Drug Administration (FDA) approved the first 3D printed drug product Spritam®, developed by Aprecia Pharmaceuticals as the first 3D printed orodispersible tablet Levetiracetam for seizure treatment. Seizures (tonic-clonic and partial-onset) in adults and in children can be treated from this drug.[26] FDA approved Spritam as the first 3D printed drug and in summers of **2016** Aprecia Pharmaceuticals released it in the market. [25] The Academy of Pharmaceutical Sciences (APS) organised in **2019** Additive Manufacturing symposium to bring together academics, industry, biotech companies and regulators to discuss the concept of 3D printing pharmaceuticals, and in March **2021** set up the APS emerging Technologies Focus Group that aims to advance technologies, such as 3D printing into practice. [16] In February **2021**, FDA approval was granted for a clinical study using a 3D printed drug for patients with rheumatoid arthritis.[27,28] Several studies have highlighted the potential for 3D printing technologies to be combined with AI for a multitude of benefits, including AI determining printability, as well as ensuring the quality and safety of the final printed drug product.[29-32]

Pharmaceutical Industries usingor working on 3D printing technology:[33]

Table.1: Pharmaceutical Industries using or working on 3D printing technology

Pharmaceutical industries	**Headquarters**
Aprecia Pharmaceuticals	Pennsylvania, U.S.
FabRx	London, U.K.
Merck	Darmstadt, Germany
Triastek, Inc.	Nanjing, China
GlaxoSmithKline	Brentford, U. K.

COMPARISON: TRADITIONAL MANUFACTURING and 3D PRINTING TECHNOLOGY [34]

Table 2: Comparison between Traditional Manufacturing and 3D Printing Technology

FACTORS / ATTRIBUTES	TRADITIONAL MANUFACTURING	3D PRINTING TECHNOLOGY
COST	Higher cost of manufacturing and shipping.	More than 700 savings due to prototyping costs.
DESIGN	Less innovative design due to cost constraints.	Allows for easy yet inexpensive innovation in design.
TIME / SPEED	More time to build final product.	Lesser time taken due to compressed design cycles.
QUALITY	Creates more waste; subtractive process will compromise on precision.	Lighter and smaller amount of waste; higher precision with layer by layer manufacturing.
PRODUCT VOLUME	Not well suited for low-volume, customized products.	Also suitable for low-volume, customized products.
LABOUR	Intensive labour needed.	Less or no labour needed.
LEADTIME	Slow	Fast
SURFACEFINISH	Excellent	Moderate
PROFITABILITY	Large-scale production	Independent from scale
DESIGNCOMPLEXITY	No	Yes
CUSTOMIZABILITY	No	Yes
PERSONALISATION	No	Yes
WAREHOUSING	More warehousing needed.	Very less warehousing needed.

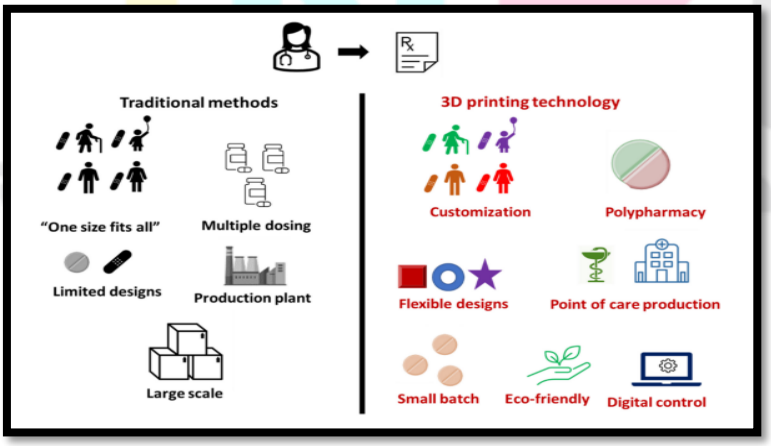


Fig. 2: Comparative advantages of 3D Printing technology over traditional methods.[22,35]

WORKING / STEPS: [36]

1. Firstly, the product is designed using computer-aided design (CAD) software before converted into a 3D printer readable file, which is usually in the (.stl) file format.
2. Then, the materials are processed to aid the printing process. Following this, the raw materials are used in printing and they are made into the desired shapes layer-by-layer until the product is formed.
3. Lastly, the product is removed, whereby some may require post-processing such as polishing and drying to be done (any unused material can be recycled for reuse in subsequent printing cycles).

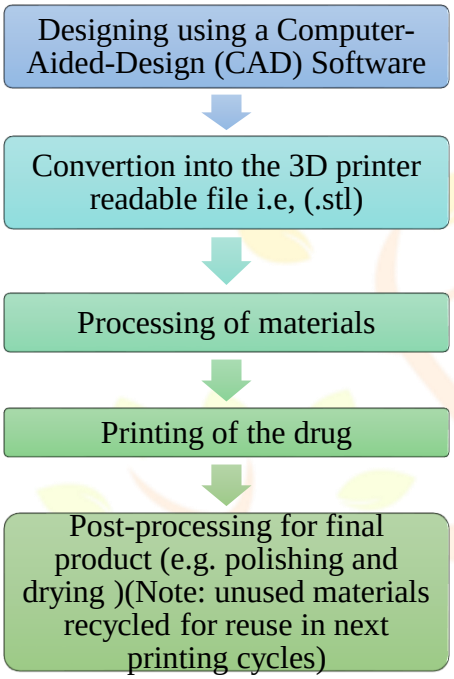


Fig. 3: Basic steps involved in the fabrication of 3D-printed drugs [37,38]

METHODS / TYPES OF 3D PRINTING:

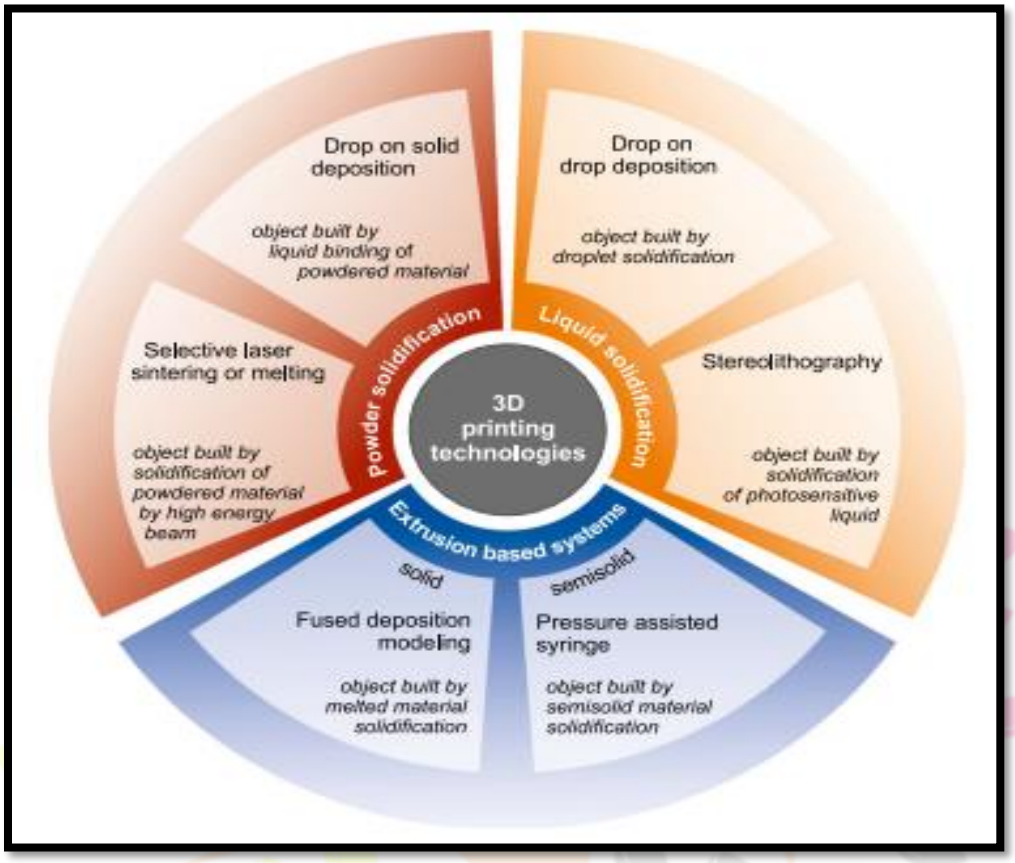


Fig. 4: 3D printing methods applied for drug formulation. [26,39]

1) Selective Laser Sintering (SLS):

Introduction: Selective Laser Sintering (SLS) or Selective Laser Melting (SLM) is an additive and quick manufacturing process based on the use of powder coated metal additives and that uses a laser as the power source to sinter (melt) powdered material (typically nylon or polyamide), aiming the laser automatically at points in the space defined by a 3D model, binding the material together to create a solid structure, a process generally used for rapid prototyping. For e.g., Paracetamol as an orodispersible tablet. [40]

Working: A continuous laser beam is used as heating source, for scanning and aligning particles in predetermined sizes and shapes of the layers. The geometry of the scanned layers corresponds to various sections of the models established by Computer-aided design or from files produced by stereo-lithography. After scanning the first layer, the scanning of second layer continues which is placed over the first, repeating the process from the bottom to the top until the product is complete. To fuse small particles of plastic, metal, ceramic or glass powders into a mass that has the desired three dimensional shapes, this technology uses high power laser. Scanning the cross section or layers generated by 3D modeling program on the surface of powder bed, laser selectively fused the powdered material so that the powder bed is lowered by one layer thickness. Then a new layer of material is applied on top and the process is repeated until the object is completed. [41]

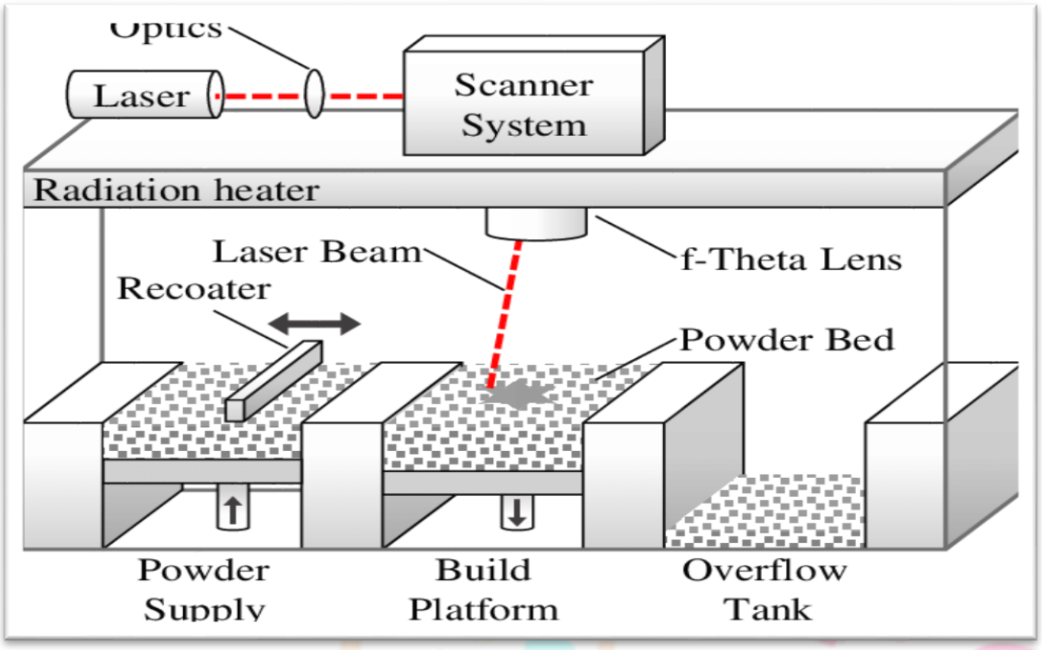


Fig. 5: Schematic diagram of Selective Laser Sintering (SLS) method [42]

- **Advantages [10]: 1)** Capable of forming highly porous dosage forms(rapidly dissolving). **2)** Capable of producing dosage form such as immediate, controlled-release and medical devices**. 3)** High resolution. **4)** Suitable for production of polypills.
- **Disadvantages [10]: 1)** May be unsuitable for photosensitive &thermos-sensitive drugs. **2)** Requires precise control over powder flow characteristics. **3)** Post-processing required.

2) Stereolithography or Stereolithography Apparatus (SLA):

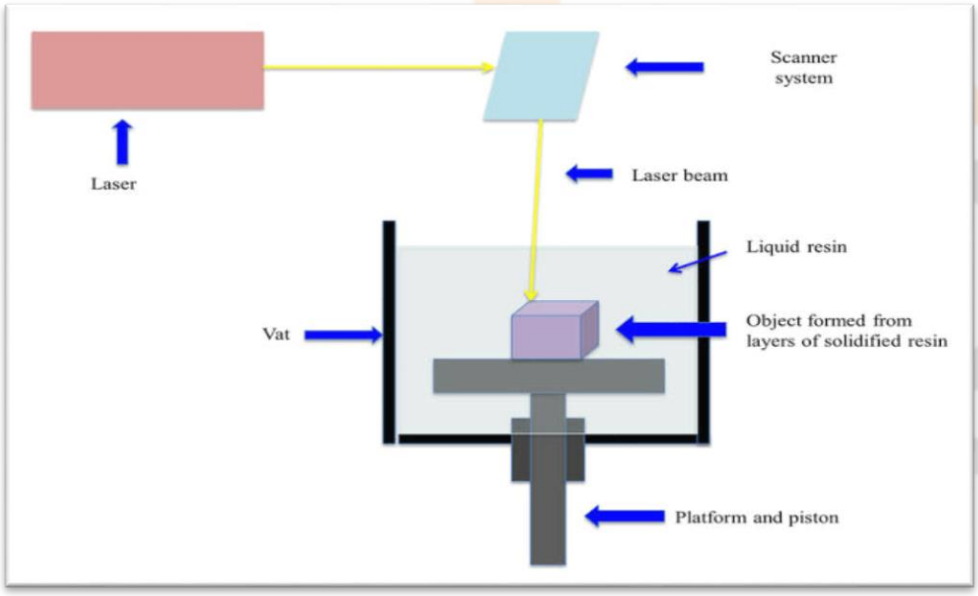


Fig. 6: Schematic diagram of Stereolithography method [43]

Introduction: In 1988, Charles Hull discovered this technique as a first method for 3D printing technology. It is rapid and popular prototyping technology which can produce highly accurate and detailed product. This method is also called Stereolithography apparatus (SLA) and photo-polymerization. The drug would be dissolved into a liquid pool of hydrogel or resin material. The material of choice must be photosensitive. [44]

Working: Stereolithography (SLA) builds objects one layer at a time by tracing a laser beam on the surface of a vat of liquid photopolymer, inside of which is a movable stage to support the part being built. Stereolithography utilises a laser or projector to solidify material while in bulk setting. During the printing process, photopolymer material like resin or acrylate were used which can cure by UV laser. When the laser beam strikes onto the surface of the pool/bed of liquid photosensitive, drug-loaded material, the material cures and quickly solidifies. This method has extremely high resolution and considerably fast, but the nature of the pool of drug-loaded material has an inherent risk of cross-contamination between the fabrications of different drug products. A resultant layer is formed on top of the previously completed layers. Thus 3D object out of many layers formed completely due to the self-adhesive property of material causes each succeeding layer to bind to the earlier one. Once complete, the part is elevated above the vat and drained. Excess polymer is swabbed or rinsed away from the surfaces. In several cases, a final cure is given by placing the part in an UV oven. After the final cure, supports are cut off the part and surfaces are polished, sanded or otherwise finished. [45]

Advantages [16]:1) Widely explored for production of sustained-release drug products and medical devices. **2)** High resolution and accuracy. **3)**Suitable for production of multi-layered polypills.

Disadvantages [16]: 1) May be unsuitable for photosensitive drugs. **2)** Potential issues around material toxicity.

3) Fused Deposition Modeling (FDM) [For Solid]:

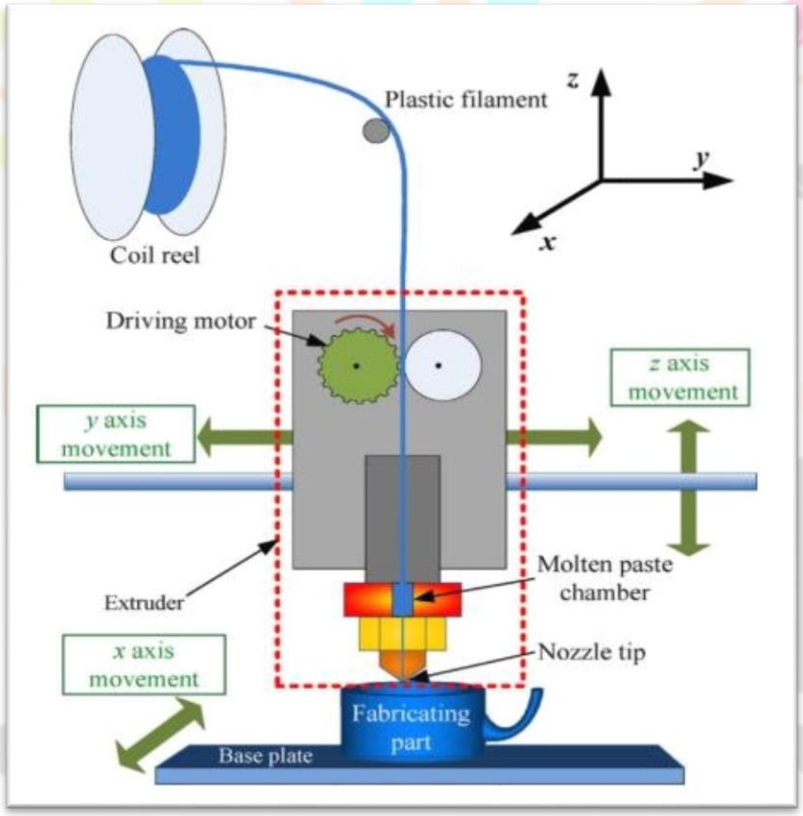


Fig. 7: Schematic diagram of Fused Deposition Modeling (FDM) method [46]

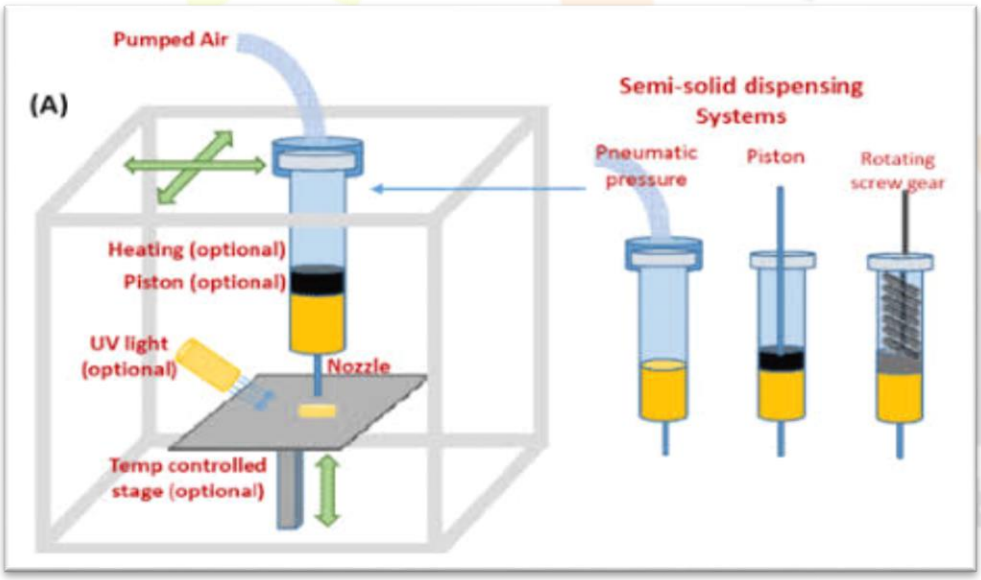
Introduction: Fused Deposition Modeling(FDM) is the second most important commercial layered manufacturing technique and an additive manufacturing technology which is used for modeling, prototyping, and batch production applications. This process is used to fabricate final products directly without the use of any tooling, die, or molds, which are some of the major constraints of the traditional manufacturing process. Fused Deposition Modeling (FDM) printers are much more common and inexpensive than the selective laser Sintering (SLS) type.FDM printer uses a print head similar to an inkjet printer.FDM method helps in

manufacturing delayed release printlets without an outer enteric coatingand also provides a personalized dose medicines.[47]

Working: In this process, the materials are soften or melted by heat to create objects during printing, hence there are several dosage forms. However instead of ink, beads of heated/melted plastic are released from the print head. FDM printers has a specific category of extrusion-based printers which uses a solid polymer filament. The filament is fed through an electronically controlled nozzle which melts the filament and deposits it onto the print bed where the melted filament solidifies into the final 3D printed form. Such printers are simple and versatile, and are compatible with filaments such as poly(lactic acid) (PLA), poly(vinyl alcohol) (PVA), and ethylene vinyl acetate (EVA). Due to the polymer nature of the filaments, they exhibit considerable structural stability after printing and solidifying. These filaments are also largely water-soluble and are capable of being loaded with a drug in solution. Filament can be loaded with varying concentrations of drugs for specified doses by dissolving the drug in an ethanolic solution and submerging the unprinted, solid filament in the solution. Filament can also be loaded with drugs by melting the filament and re-solidifying it after the addition of the drugs. Once the 3D printed drug product is placed in vivo, the drug itself will diffuse out of the print, while the biodegradable filament will dissolve over time.[48,49]

Advantages [10,16]: 1) Cheaper. **2)**Capable of producing immediate and sustained-release formulation. **3)** Can improve solubility of poorly soluble drugs. **4)** Portable, compact and user friendly.**5)** Short cycle time. **6)** Easy integration with different CAD software.

Disadvantages [10,16]: 1) Supports leave marks that require removing and sanding. **2)** Limited testing allowed due to thermo-plastic material.**3)**Low drug loading. **4)** Challenging to scale-up. **5)** Drug may trapped in polymer and may have incomplete release.



4) Semi-SolidExtrusion(SSE) / Pressure Assisted Syringe (PAS)[For Semi-solid]:

Fig. 8: Schematic diagram of Semi-Solid Extrusion(SSE) method [50]

Introduction: Several studies have demonstrated the suitability of SSE for the production of thermo-sensitive drugs. The tablet was produced using a hybrid approach that uses an extrusion-based system delivered by a simple metal syringe. Likewise, semi-solid extrusion (SSE) was used to produce solid lipid tablets incorporating a poorly water-soluble drug, fenofibrate. The pharmaceutical ink was prepared using different

grades of polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP), together with plasticiser and lubricants.[51]

Working: A drug-loaded semi-solid material (e.g. Gel or Paste) is extruded using a syringe-based tool head. The printer head is moved along the x-y-z axis to releasethe extrudate, which solidifies at room temperature onto a build plate.[52]

Advantages [16]: 1) Suitable for production of chewable and palatable formulations.**2)** Capable of producing a range of formulation types, including immediate-release and controlled-release dosage forms, polypills and oral films.

Disadvantages [16]: 1) Low resolution compared to other methods. **2)**Only suitable for drugs that can be formulated as a semi-solid.**3)** Low throughput.

5) Hot Melt Extrusion (HME):

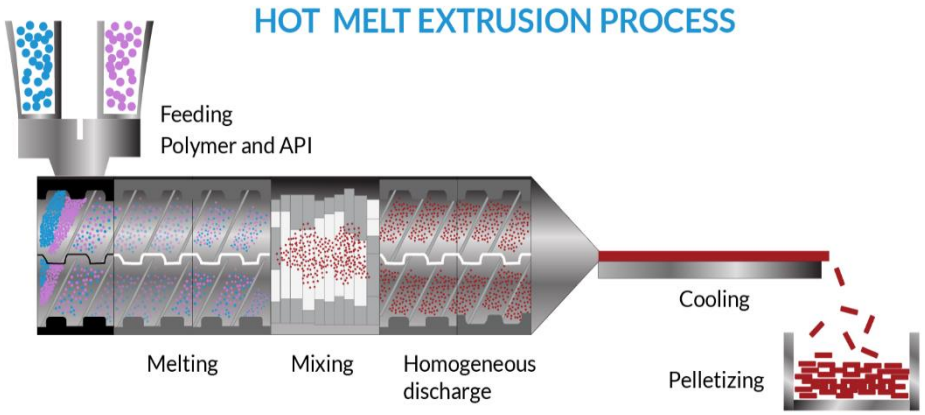


Fig. 9: Schematic diagram of Hot Melt Extrusion (HME) method [53]

Hot MeltExtrusion (HME) is the process of melting polymer and drug (API) at high temperature and pressure applied in the instrument continuously for blending. It is a continuous manufacturing process that includes several operations such as feeding, heating, mixing and shaping. HME is used to prepare solid solutions/dispersions for drug delivery systems such as pellets and granules. [54,55]

Advantages [53,54]: 1) Reduces the number of processing steps in dosage form manufacturing. **2)** It can be automated as a continuous process to give better drug homogeneity and to improve capabilities of sustained, modified and targeted release dosage forms. **3)** It has the ability to improve the solubility and bioavailability of poorly soluble drugs.

Disadvantages [53,54]: 1) Temperature sensitive drugs or excipients can be used very rarely. **2)** The drugs which have low melting point can't be used.

6) Inkjet Printing:

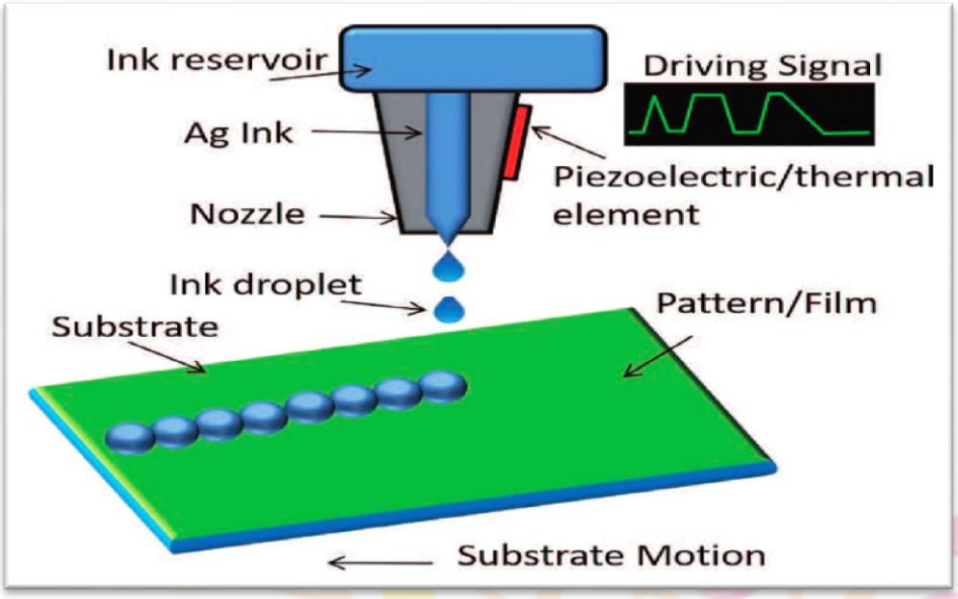


Fig.10: Schematic diagram of Inkjet Printing method [56]

Introduction: This approach was adapted for pharmaceutical application by the replacement of the ink with pharmaceutical solutions containing drugs and normal paper with edible sheets known as substrates. The dose alterations are done by altering the number of layers printed in a given area or changing the area to be printed. The drug and excipients are design in a ratio such that it has a potential to print as microdots onto an edible substrate. The two main printing types employed under inkjet printing are:**1)** thermal inkjet printers and**2)** piezoelectric inkjet printers. Ink is deposited onto a substrate by either a thermal-driven or piezoelectric-driven nozzle, offering high resolution printing capabilities. With the introduction of z-axis motion, 3D patterns may be fabricated by this method. [57]

Working: For the **thermal** inkjet printing approach, a thermal element within the print head generates droplets of ink. This heating element is electrically-controlled to cyclically produce brief spikes in thermal energy which is transferred to the ink. The increase in thermal energy causes the formation of a small bubble, which provides a pulse of pressure to force ink out of the nozzle, thereby producing a droplet.[58]

An alternative to thermal inkjet printing is the **piezoelectric** approach, which implements a piezoelectric actuator to form droplets. A piezoelectric crystal within the print head is stimulated when voltage is applied, which induces a rapid, reversible deformation. This deformation propagates acoustic waves which supply the pulse of pressure needed to disrupt the flow of ink through the print head, thereby producing droplets.[59]

The inkjet printing method can further be applied to **microvalve-based** 3D printing. Microvalve printing utilizes a motorized stage comprised of an array of microvalves which are capable of depositing droplets of material. Each microvalve is connected to its own pressure regulator, allowing for individual control of each one. By controlling the stage and the pressure regulators in unison, various materials can be simultaneously deposited. This scheme has been previously applied to cell-laden bioprinting, whereby support material, growth media, and cell-laden material were printed together. Microvalve-based 3D printing can be applied to drug fabrication by depositing various drug-loaded materials along with binders, scaffolds, and other biodegradable materials. [60,61]

Advantages [58,59]**:1)** Low processing cost. **2)**Rapid processing rates. **3)** Generation of minimal waste. **4)** It gives CAD information in a 'direct write' manner and **5)** It process material over large areas with minimal contamination.

Pharmaceutical Preparations Developed Using Various 3D Printing Technology with Examples:

Table 3: Pharmaceutical Preparations Developed Using Various 3D Printing Technology (Examples)

Sr. No.	API	Formulations (Dosage Forms)	Targeted Disease	Effect OR Significance	Reference
(A)	**Fused Deposition Modeling (FDM)**				
1.	Aripiprazole	Orodispersible Films	Schizophrenia	Fast disintegration and dissolution.	**4)**
2.	Caffeine	Caplets (Tablet + Capsule)	-	-	**15)**
3.	Pravastatin	Tablet (Printlet)	For high cholesterol.	Intermediate Release, Sustained Release.	**6)**
(B)	**Selective Laser Sintering (SLS)**				
1.	Paracetamol	Ordispersible ablets	-	Fast drug release.	**4,6)**
2.	Ondansetron	Orally Disintegrating Printlets (ODPs)	Nausea and Vomiting	Rapidly disintegrate.	**88)**
(C)	**Stereolithography(SLA)**				
1.	Chloramphenicol	Printed drug	Chronic Obstructive Pulmonary Disorder (COPD)	Excellent and different release ates.	**62)**
2.	nsulin	Polymeric nicroneedle atches	Diabetes	nsulin was eleased rapidly within30 min rrespective of the nicroneedle lesign.	**62)**
3.	Salicylic acid	Anti-acne patch	Skin isorders	-	**6)**
(D)	**Semi-solid Extrusion (SSE)**				
1.	Dapagliflozin	Self- anoemulsifying ablet	Diabetes	Rapid release rofiles.	**62)**
2.	Glipizide	Tablet (Printlet)	Diabetes	Satisfactory hysical properties nd stability.	**62)**

3.	Guaifenesin	Bilayer tablet	Chest congestion	mmediate and extended release.	**22)**
(E)	**Hot Melt Extrusion (HME)**				
1.	Aspirin, Hydrochlorothiazide, Pravastatin, Atenolol, Ramipril	Polypill	Cardiovascular disease	Aspirin and Hydrochlorothiazide - Rapid release propertyand Pravastatin, Atenolol, Ramipril Sustained releaseproperty.	**62)**
2.	Bicalutamide (BL)	Tablet (Printlet)	Cancer	Enhancement in release as compared to pure BL mixtures.	**62)**
3.	Theophylline	Gastroretentive floating tablets(GRFTs)	Chronic Obstructive Pulmonary Disorder (COPD)	GRFTs floated for 10 h and followed zero-order kinetics.	**62)**
4.	Ethylene Vinyl Acetate Copolymers	mplants, Subcutaneous rods	T-shaped prototypes of ntrauterine ystem IUS)	-	**6)**
(F)	**Inkjet Printing**				
1.	Folic Acid	Nano-suspension	-	Enhanced dissolution velocity.	**13)**
2.	Levetiracetam	Tablet (Printlet)	Epilepsy	Rapidly disintegrates.	**1,9,18**
3.	Rifampicin	mplants, Nanoparticles	T. B.	Prolonged drug release time.	**6)**
4.	Troglitazone (Rezulin)	Human tissue chips	Diabetes	To measure the hepatotoxicity of Troglitazone on thehuman liver cancer cell line (HepG2).	**62)**

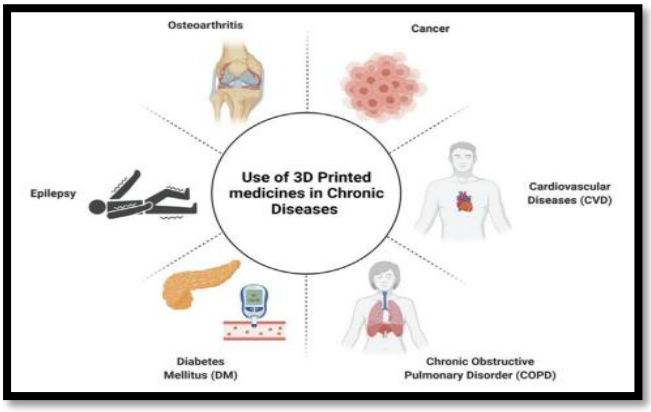


Fig. 11: Graphical abstract on the uses of 3D printed medicine in the management of chronic diseases.[62]

ZIPDOSE TECHNOLOGY: [63,64,65]

- Zip Dose technology is the world's first and only FDA-approved 3D printing technology. Commercially 3D printing has wide and new therapeutic areas for drug manufacturers. It has a unique digitally coded layering and zero-compression processes. It is used for formulating a tablet with high-dose and also have rapid disintegration. Hence it helps in overcoming a difficulty in swallowing.
- Aprecia developed its Zip Dose technology platform using the 3D printing technology that originated at Massachusetts Institute of Technology.
- It is developed with Aprecia's proprietary 3D printing manufacturing process. ZipDose Technology helps patients who need medicines that are easy to take and caregivers—including physicians and nurse practitioners—who want medicines that are easy to administer. By enabling the delivery of high-dose medications in a rapidly disintegrating form. ZipDose overcomes patient adherence and difficulty in swallowing.

Spritam® - FDA Approved First 3D Printed Pill:

Fig. 12: Spritam® - FDA Approved First 3D Printed Pill [65]

Inkjet printing was the strategy used to produce Spritam (levetiracetam) tablets for oral use, the primary 3D printed drug endorsed by the Food and Drug Administration (FDA) in 2015 by Aprecia Pharmaceuticals.[65] Aprecia introduces its first product using the Zip Dose® formulation platform for the treatment of Epilepsy.

BLUE ASH, Ohio, August 3, 2015, Aprecia Pharmaceuticals Company announced that the U.S.Food and Drug Administration (FDA) has approved SPRITAM® levetiracetam for oral use as a prescription adjunctive therapy in the treatment of partial onset seizures, myoclonic seizures and primary generalized tonic-clonic seizures in adults and children with epilepsy. SPRITAM® utilizes Aprecia's proprietary ZipDose® Technology Platform, a ground breaking advance that uses three-dimensional(3D) printing to produce a porous formulation that rapidly disintegrates with a sip of liquid.[63]

SPRITAM utilizes Aprecia's proprietary ZipDose® technology platform, a ground-breaking advance that uses 3D printing to produce a porous formulation that rapidly disintegrates with a sip of liquid. ZipDose technology enables the delivery of a high drug load, up to 1,000 mg in a single dose. SPRITAM enhances the patient experience – administration of even the largest strengths of levetiracetam with just a sip of liquid. [33]

Benefits:

1) Benefits to Patients:

- A 2015 study used FDM 3D printing to produce low-dose antihypertensive polypills containing atenolol, ramipril, pravastatin, aspirin and hydrochlorothiazide. It should be noted that, while the printing of polypills is feasible using 3D printing, this will likely only be suitable for drugs with a low therapeutic dosage (microgram to milligram dose strength) to ensure the size of the formulation is a suitable size for administration.[66]

2) Benefit to Visually Impaired or Blind Patient:

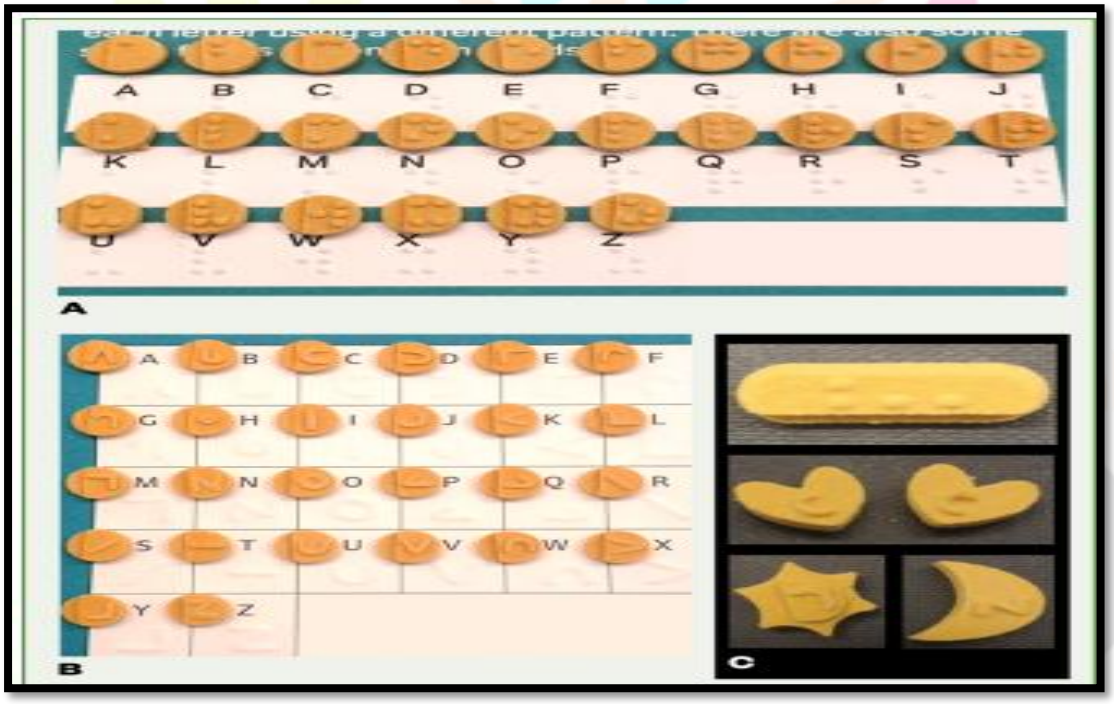


Fig.13: Photographs of orodispersibleprintlets produced using SLS 3D printing, which have the (A) Braille alphabet and (B) Moon alphabets imprinted on their surface. The study also demonstrated the ability to produce printlets of different shapes, including those in the shape of a caplets, heart-shaped tablet, sun and moon(C).[67]

- SLS has been employedto prepare orally disintegrating printlets with Braille and moon patterns on the surface ofthe dosage forms to enable visually impaired patients to identify medications (**see Figure).** The printlets were also produced in different shapes to offer additional information,such as the dosing regimen.[16,33]
- 3D printed Braille-encoded intraoral films were fabricated by Eleftheriadis et al. manufactured 3D printed Braille-encoded intraoral films. These films containedKetoprofen as the model drug and hydroxypropyl methylcellulose (HPMC) as a polymer. Braille-encoded texts were designed on top of the backing layer, along with the Marburg Medium spacing convention for pharmaceutical Braille. The fabricated films were subjected

to a haptic study in which different visually impaired patients received these medications.The outcome of the study reported a great sense of convenience for visually impaired patients for drug administration. [43]

3) Benefit to Paediatric:

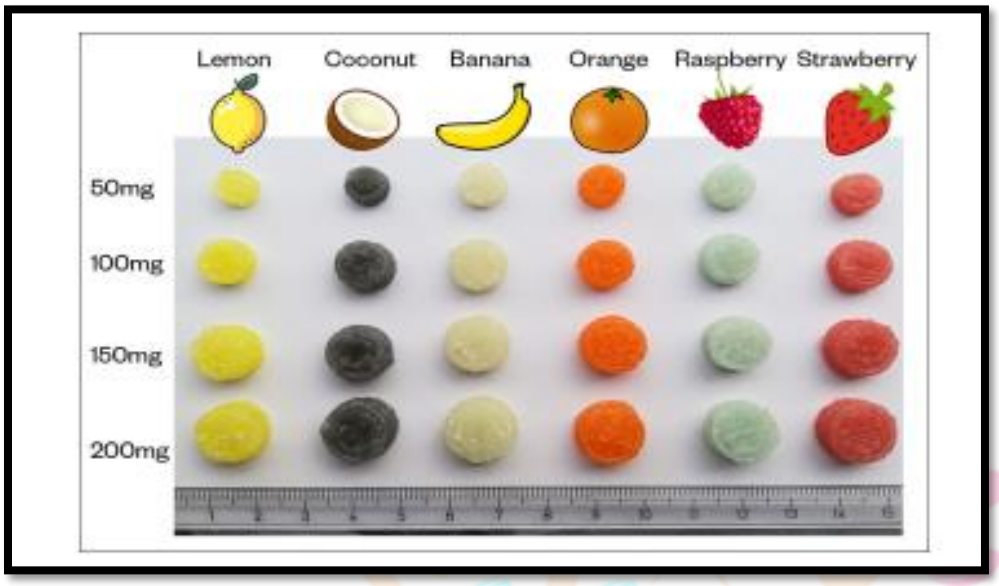


Figure.14: Chewable printlets in different flavours, colours and with different doses of isoleucine for the world-first clinical study using 3D printed chewable tablets to treat children with maple syrup urine disease. [16]

Several studies have focused on producing child-acceptable formulations using3D printing, including the production of chewable and even chocolate-based formulations.[10] For example, a 2018 study by Scoutaris et al. produced 'candy-like' formulations of several drugs, including indomethacin, that imitated Haribo Starmix® sweets using FDM. [10]3D printing technologies have many benefits to the pharmaceutical industry, especially within early phase drug development. The time it takes from drug discovery to a marketed formulation is around 10–15 years, costing an average of $1.6B (USD). There is an urgent need to reduce time and cost to market to expedite drug development timelines, made evident during the recent COVID-19 pandemic requiring rapid drug development and repurposing trials.[10]

4) Benefits for Drug Manufacturing:

- Once an appropriate 3D printing method is determined and the material best suited for the pharmaceutical application is selected, it is a matter of developing and printing the drug itself. It is at this stage in the drug manufacturing process where 3D printing presents itself as the ideal approach, attributed to some noteworthy benefits. [60]

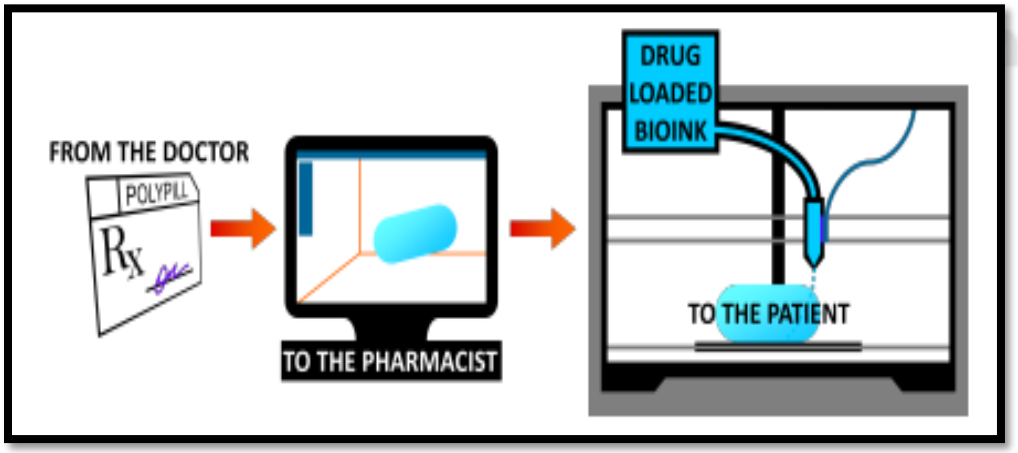
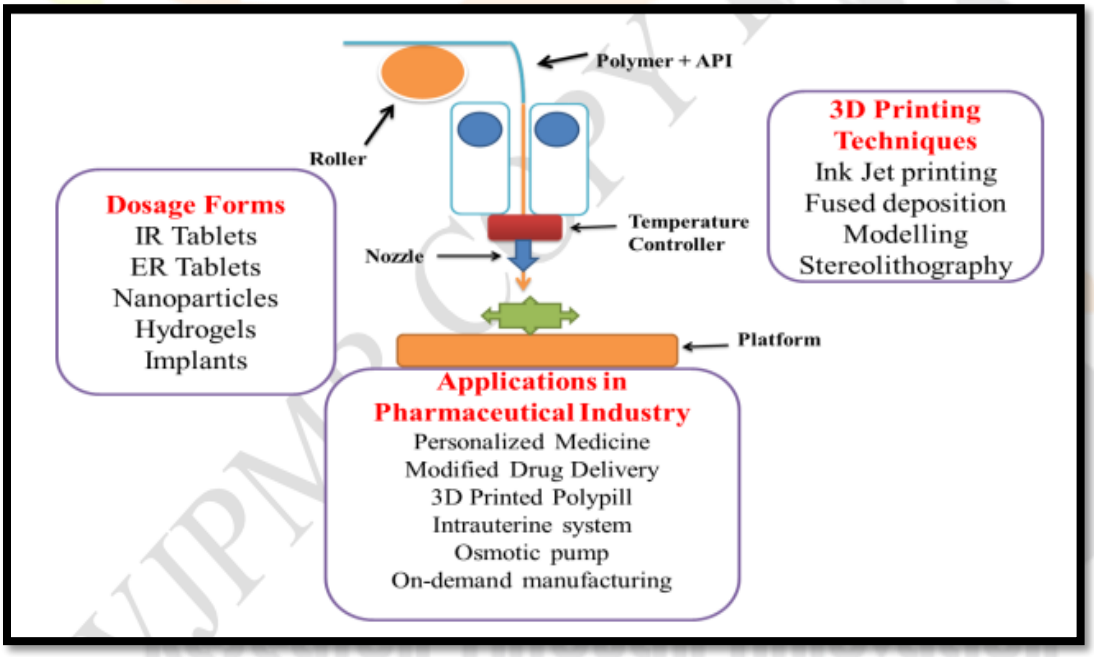


Fig.15: Theoretical scheme of 3D printing for drug manufacturing based on a patient's specific prescription from his doctor. A custom medication is designed via CAD. Drug-loaded bioink (biocompatible material) is then 3D printed on-demand.[60]

One of the primary considerations in the delivery of drugs is the release characteristics. 3D printing enables increased geometric and architectural complexity, facile fabrication of multilayer delivery systems, and the application of various controlled release mechanisms. Printing as an approach for drug manufacturing also introduces precise and unique dosing, and the ability to create multi-dose or multidrug pharmaceutical products. Dosing may also be tailored specifically for individual patients. Similarly, the printing of drugs makes point-of-care, pharmacy-based drug production possible, without the risks and extensive fabrication time associated with compounding pharmacies. These benefits of 3D printing for drug manufacturing pave the way for the future of pharmaceuticals. **[60]**

Pharmaceutical Applications of 3D Printing Technology:



Figu.16:3D Printing Techniques and its Pharmaceutical Applications [68]

1) PERSONALISED MEDICINES:

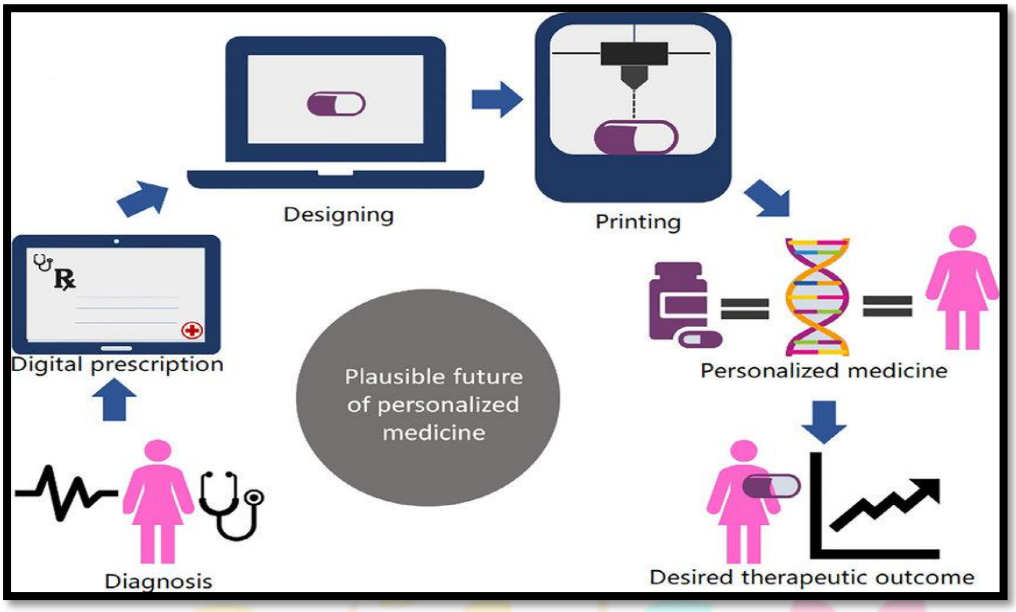


Fig.17: Personalised Medicines using 3D PrintingTechnology [69]

Personalized medication is a patient-specific approach to treating anyone with high precision and accuracy in dose. When compared to other dosage forms, it has a high precision, making it a patient-centric dosage formulation. [69] Complex drug manufacturing methods can also be standardized through use of 3D printing to make them simpler and more viable. 3D printing technology could be very important in the development of personalized medicine, too. [69,70] Increasing the efficacy of drugs and at the same time reducing the chances of adverse reaction should be the aim of drug development, which can be achieved by using 3D printing to fabricate personalized medications. [69] Drugs with narrow therapeutic index can easily be prepared using 3D printing and by knowing the patient's pharmacogenetic profile and other characteristics like age, race etc., optimal dosage can be given to the patient. Preparation of entirely new formulation is another vital potential of 3D printing for instance fabrications of pills that have a blend of more than one active pharmaceutical ingredient or dispensed as multi-reservoir printed tablets. Hence patients suffering from more than one disease can get their formulation ready in one multi-dose form at the healthcare point itself, thereby providing personalized and accurate dose to the patient with better or best compliance. [69,70] Personalized 3D-printed drugs may particularly benefit for patients who are known to have a pharmacogenetic polymorphism or who use medications with narrow therapeutic indices. Pharmacists may analyse a patient's pharmacogenetic profile, as well as other characteristics such as age, race, or gender, to determine an optimal medication dose. A Pharmacist then print and dispense the personalized medication via an automated 3D printing system. If necessary, the dose could be adjusted further based on the clinical response. 3D printing also has the ability to produce personalized medicines in entirely new formulations, such as pills that include multiple active ingredients, either as a single blend or as complex multilayer or multi reservoir printed tablets. Patients who have multiple chronic diseases could have their medications printed in one multidose form that is fabricated at the point of health care. Providing patients with an accurate, personalized dose of multiple medications in a single tablet could potentially improve the patient compliance. [70]

2) POLYPILL CONCEPT:

The concept of "polypill" refers to a single tablet that includes the combination of various drugs. This concept is highly beneficial for geriatric population, as patients of this age category are prone to multiple disorders and hence multiple therapy. The technology has been realized through the research of Khalid et al., where five different active pharmaceutical ingredients with different release profiles have been formulated in a single 3D dosage form. Three drugs (pravastatin, atenolol, and ramipril) were printed in the extended release compartment. The drugs were physically separated by a permeable membrane of hydrophobic cellulose

acetate. An immediate release compartment containing aspirin and hydrochlorothiazide was deposited on top of the extended release compartment. [71]

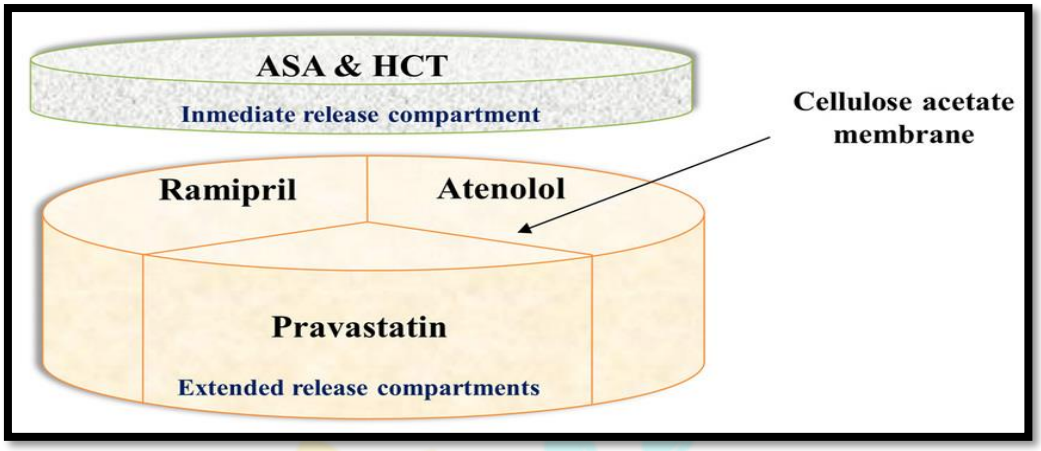


Figure.18: Conceptual Polypill diagram [72]

Three-dimensional(3D) extrusion-based printing was used to manufacture the 'polypill' to demonstrate that complex medication regimes can be combined in a single tablet and that it is viable to formulate and 'dial up' this single tablet for the particular needs of an individual tablet. The tablets used to provide this concept incorporate an osmotic pump with the drug captopril and sustained release compartments with the drugs nifedipine and glipizide. This combination of medicines could potentially be used to treat diabetics suffering from hypertension. The room temperature extrusion process used to print the formulations used excipients commonly employed in the Pharmaceutical industry. [73] By using 3D printing technology to print drug can increase efficiency, accurate control of dropped size and dose, high reproducibility and able to produce dosage form with complex drug-release profiles. [71,73]

3) ORAL SOLID DOSAGE FORMS:

It has been reported that 3D printing technology can be used to prepare both low and high drug loaded-dosage forms. Theophylline-loaded (10% API) lower temperature FDM method was used by Okwuosa et al. to manufacture patient-specific IR Tablets. [74] A high dose of the drug (80% paracetamol) in an IR tablet was prepared using an extrusion-based 3D printer. [21] Chai et al. developed intragastric floating sustained-release (FSR) tablets of domperidone incorporating hydroxypropyl cellulose (HPC) by FDM. [75] H. Wen et al. fabricated stable gastro-retention and controlled-release formulation of ginkgolide using HPMC. [21] Allahham et al. developed oral disintegrating print lets of ondansetron using SLS technology for the improvement of solubility and disintegration. [74,75]

4) IMPLANTS:

By utilizing 3D printers, Wu et al. planned a multi-drug embed for the treatment of bone tuberculosis. Isoniazid and rifampicin, anti-tubercular agents have fused into each layer to get a particular grouping, shaping a multi-facet concentric chamber. [49,76]

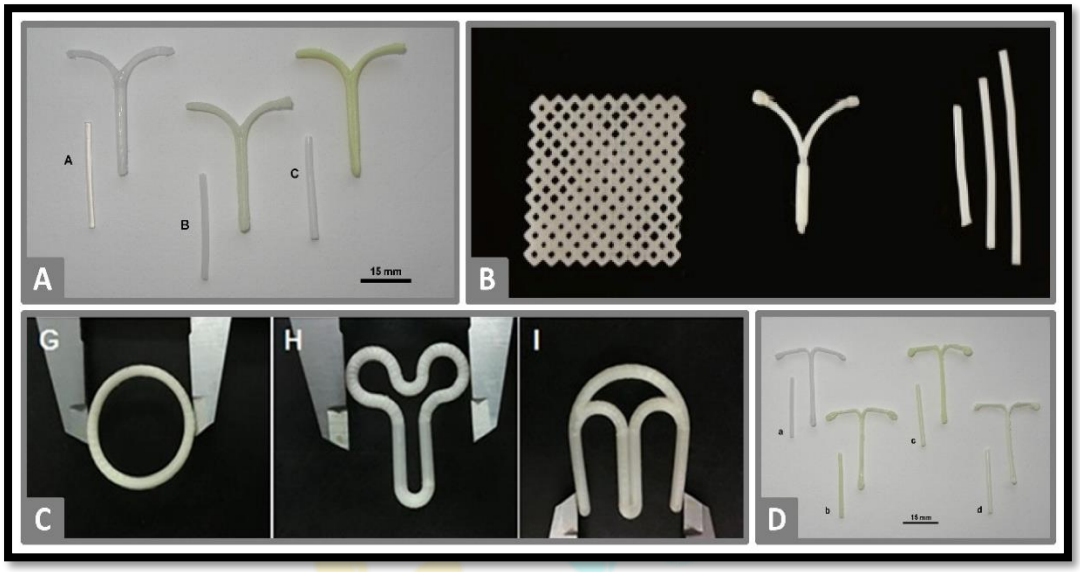


Figure.19: Various 3D PrintedImplants[73]

Wu et al. recently developed a 3D printing-based multi-drug implant in which tobramycin (TOB) and levofloxacin (LVFX) as API were loaded and multi-layered scaffolds were introduced (layers 0.4cm^3) for the treatment of chronic osteomyelitis. [76] Chaudhari et al. have developed skin patches with the incorporation of quercetin-PVP using FDM based on the HME technique to overcome the current drug delivery challenges. [49,76]

5) MICRONEEDLE:

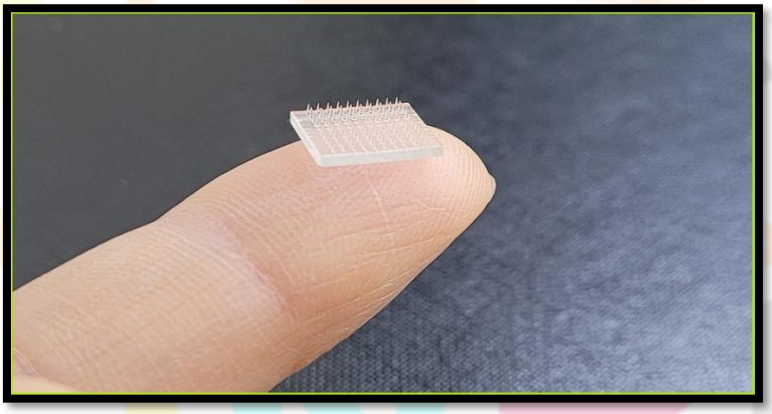


Fig. 20:3D PrintedMicroneedlePatch as customised COVID-19 Vaccine [77]

A novel inkjet printing technique, a process for coating microneedle arrays made up of metal with three anticancer components such as curcumin, cisplatin and 5-fluorouracil, for transdermal drug delivery. [77]

6) DIGITAL PHARMACY ERA:

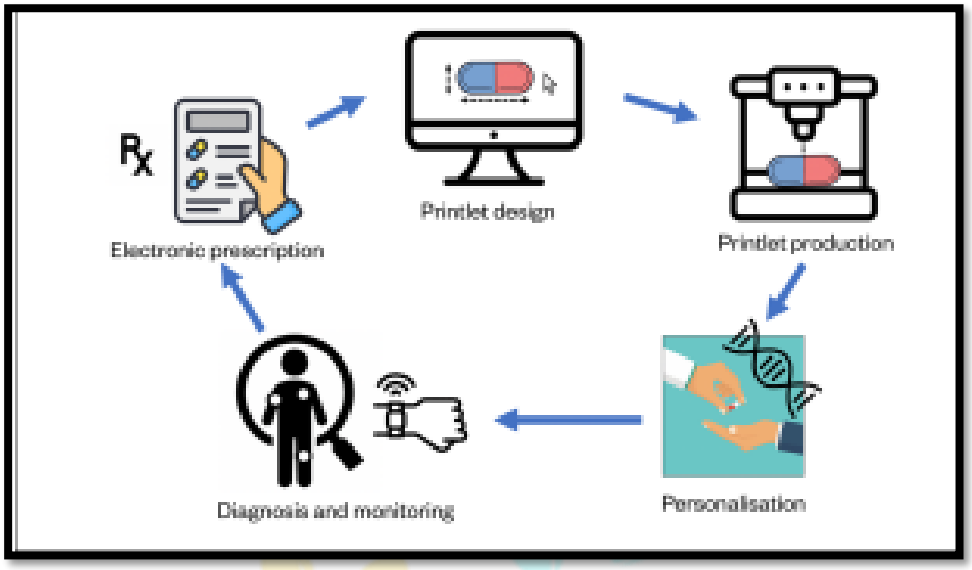


Fig. 21: Components of a Digital Pharmacy Era [78]

This concept could lead to a new era of digital pharmacy, enabling electronic prescriptions to be sent to a decentralised 3D printer location for real-time personalised medicine dispensing. A wide range of stakeholders, including academic researchers, clinical pharmacists, doctors, biotech start-ups, large pharmaceutical companies and research funding bodies, are exploring this vision globally. [78]

7) NASOPHARYNGEAL SWAB FOR COVID-19 DIAGNOSTIC TESTING:

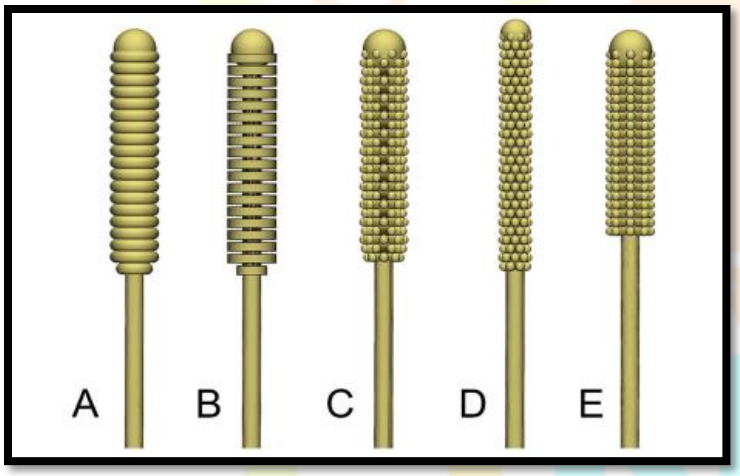


Fig. 22: Early alternate 3D printed nasopharyngeal swab designs. **(C)** is the current version in use [79]

3D printed nasopharyngeal swabs provide a cost-efficient and fast alternative to the standard nasopharyngeal swabs used for COVID-19 testing kits.[79]

CONCLUSION:

The 3D printing of drug delivery systems and medical devices serves as an attractive tool to produce customized product. Since few years the concept of 3D-printed drug formulation quickly evolved and was directed to enhance therapy by patient-centric medicine. This promising technology offers formulation flexibility that is difficult to achieve with the conventional technological processes. Moreover, it provide high precision of API-excipients ratio. The added value of the 3D printing is also opportunity to create multifunctional drug delivery systems, multidrug devices and drug formulations for personalized therapy with accelerated release characteristic. 3D printing has the potential to revolutionise the production of pharmaceutical products. This review summarizes that 3D printing is an innovative and highly promising way

for on-demand manufacturing and dosage form. Thus, future research should prioritize the development of paediatric and geriatric dosage forms in personalized dosing and dimension-specific drug formulations to ensure desired therapeutic effect.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

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