An Impact of 3D Printing Technology in pharmaceutical formulation

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Abstract: One cutting-edge method for customising the design and production of medications is 3D printing. It is quickly evolving and employed in a variety of industries, including the aviation and defence sectors. Surgery, the pharmaceutical business, disease modelling, the creation of custom implants, the printing of organs, veterinary medicine, tissue engineering, and biomedical technology all employ 3D printing. The significance of current medication developed is the reliance on the "one-size fits all" approach. it is compounding process to improve flexibility, efficiency, safety, quality, trust, utility, and usefulness are all being improved through a compounding process.

The "layer by layer fabrication" of three-dimensional objects using 3D printing technology uses computer designs. Depending on the material stacking technique, 3D printers often use laser, extrusion, or inkjet technologies. In addition to highlighting prospects, the assessment highlighted the technical and regulatory obstacles impeding the use of such technologies in the pharmaceutical and healthcare industries and offered solutions. The use of 3D printed, customised medications may be the solution to the issue, drastically decreasing the need for dosage mistakes, treatment monitoring, and routine follow-ups with medical professionals.

INTRODUCTION

Charles Hull developed 3D printing technology in the early 1980s, which was used in engineering and several non-clinical assembly fields, such as the automobile, aircraft, and consumer goods sectors. Nevertheless, it has been widely employed since the year 2012. The widespread use of 3DP technology in the pharmaceutical industry is made possible by the technology's quick development as well as the appearance of flexible and biocompatible materials. A quick prototyping technique known as "three-dimensional printing methods" was created and licenced by Sachs et al. at MIT (Massachusetts Institute of Technology, Cambridge, MA, USA) [1,2] in the early 1990s, which marked the beginning of 3D printing innovation in the pharmaceutical business.

Fig (1). different forms of 3D printing medicines [1].

Printing a range of pharmaceutical formulations made up of poorly water-soluble medicines and proteins revealed 3D printing to be a potential method. According to several scientific databases including Scopus, MEDLINE, EMBASE, Pub Med, and Science, the 3DP technique has attracted more interest recently in innovative drug delivery systems [3,4]

Spritam ®, the first 3D-printed drug approved by the FDA, along with its commercial manufacture, proved that 3D printing techniques could be used to produce medications in large quantities[5].Using computer-aided designs (CAD) and printing parameters, three-dimensional (3D) printing technology is a technique for creating drug formulations that are adjustable

before being printed[6]In both a virtual and physical, 3D-printed version, 3D bio models are employed. Using 3D viewing software, users may browse virtual 3D bio models that have transparency, 360-degree exploration, and colouring, all of which help users better understand the details of the human anatomy [7].

3D printing technology in pharmaceutical formulations:

There are different systems of 3D printing technology. Some of them are:

1 . Laser based writing systems (SLA)
2 .selective laser sintering (SLS)
3. Ink based printing technology (inkjet printing)
4 .Material extrusion (or) nozzle based deposition system
5 .Fused deposition modelling (FDM)
6 .Electrodynamics 3D print (EHD)

1 .LASER BASED WRITING SYSTEM (SLA):

Rapid prototyping now makes extensive use of stereo lithography (SLA), which was the first laser-based liquid resin polymerization technique developed. It is a technique that uses a computer-controlled laser beam to turn liquid polymer or resin into a solid, so producing a three-dimensional structure. A strong laser is used to treat a powder bed, melting a specific area of the powder bed. Once more, the molten slices will all splice to create the ideal architecture of layers. The resolution of the light source and the layer height are crucial factors in determining the surface quality. The method's ability to guarantee that intricate, tiny, and complex pieces are manufactured in the proper proportions is one of its main benefits. Charles et al.'s 1986 invention of solid-free manufacturing is its source [8]. SLA provides significant benefits in modelling exact structures since it is the best 3D printing method in terms of resolution (20 mm as opposed to 50e200 mm for other fabrication technologies).

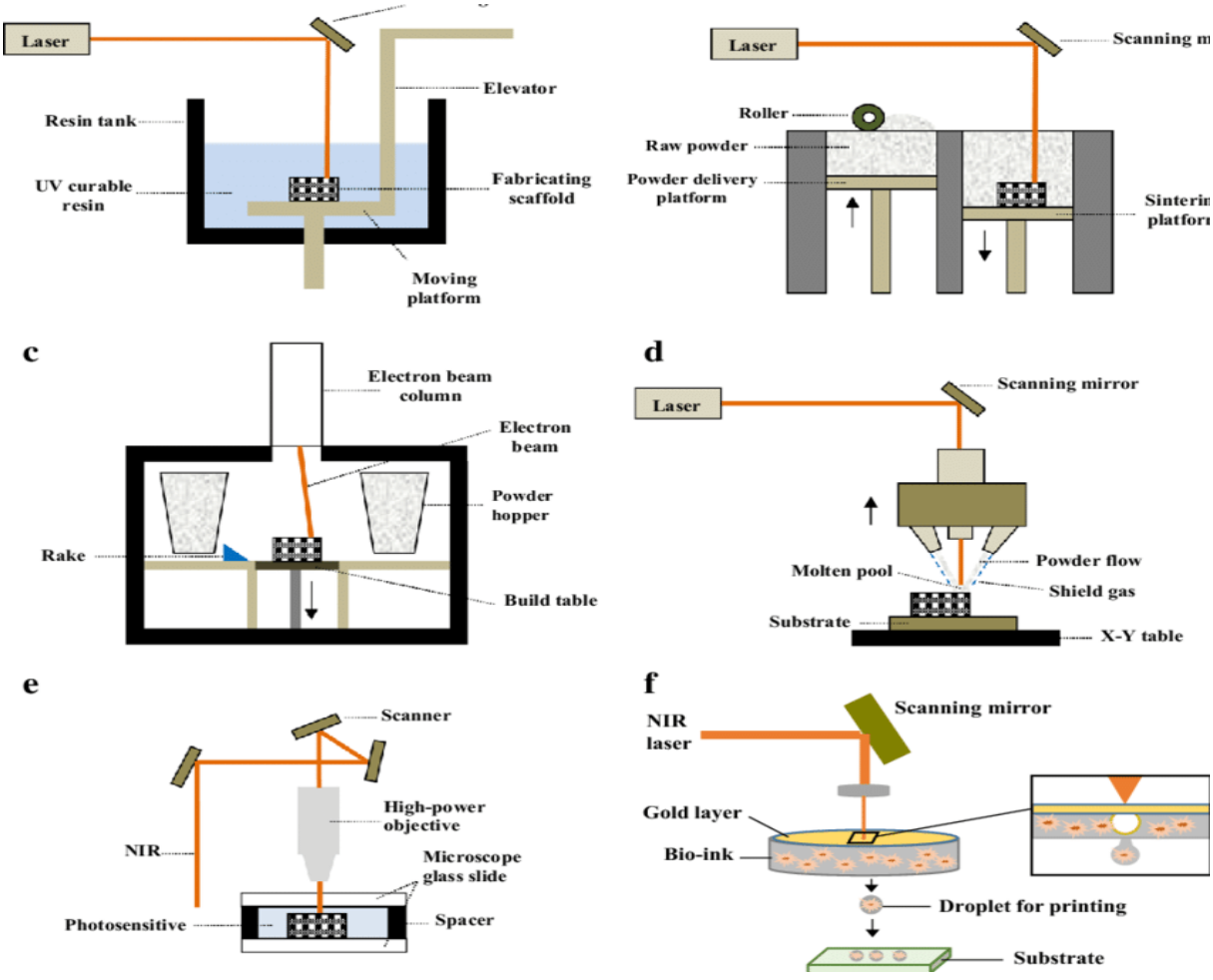
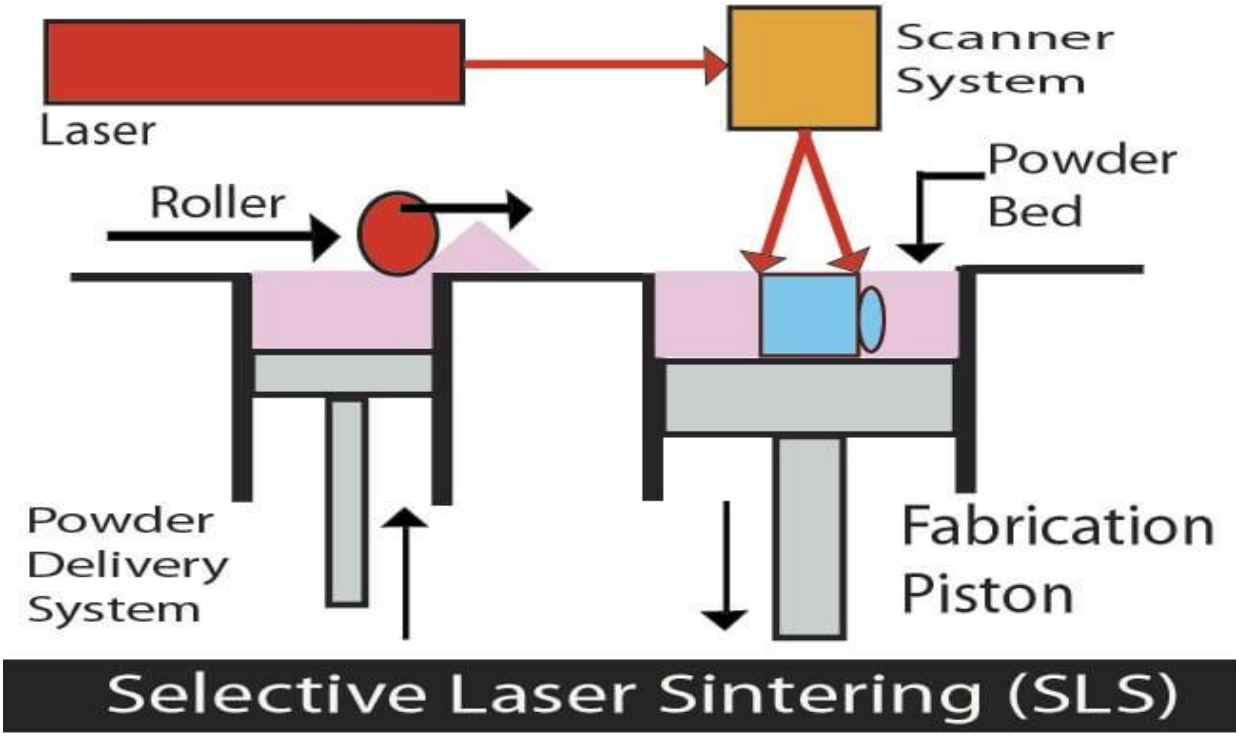


fig (2). Laser based writing systems [8].

Typically, SLA is used to create oral solid dose micro needle patches [9]. It is employed mostly in the automotive and medical industries as a result of these characteristics. It is obvious that its use will grow during the next several days. SLA has been utilised to create specific dental implants that may be used in oral surgery and has been effectively used to the area of orthodontics. In addition to these uses, there are further applications in neurosurgery, spine surgery, traumatology, behavioural and tissue interaction studies, and treatments for cardiovascular illnesses. [10,11].

2. SELECTIVE LASER SINTERING (SLS)

SLS creates solid pieces by layer-by-layer hardening powder-like materials. On the surface of the powder bed, parts are made using a laser or similar high intensity beam. The process fuses powdered materials into solid parts using laser radiation as the energy source. The method's benefit is that it makes it possible to produce pieces with a density that is almost full density. Long post processing processes are averted in this manner. The mechanical qualities of a product created by SLS are influenced by the quality and properties of the materials used, as well as some technique factors as laser energy density, laser scanning speed, scanning strategy, distance between layers, and bed temperature [12-15]



Additionally, metals like Ti, Al, Co, and Cr as well as ceramics and composites can be employed with the SLS process in addition to polymers. Polycarbonates (PC), polyamides (PA), poly lactides (PLLA) , poly lactic acid (PLA), poly (ether-ether- ketone) (PEEK), poly capro lactone (PCL), polyethylene (HDPE), polymethylmethacrylate (PMMA), polyurethane (PU), and polyvinyl alcohol (PVA) are the thermoplastic polymers most often utilised in SLS.[16]

3 INK BASEDPRINTING TECHNOLOGY (INKJET PRINTING):

A wide term used to describe many techniques for digitally managing the creation and placement of tiny liquid drops is inkjet printing. The two promising inkjet technologies, Continuous Inkjet Printing (CIJ) and Drop on Demand Printing (D o D), are separated by the method used to create the drips. A consistent stream of fluid is discharged during CIJ printing through a nozzle with a diameter of 50 to 80 microns"[17].

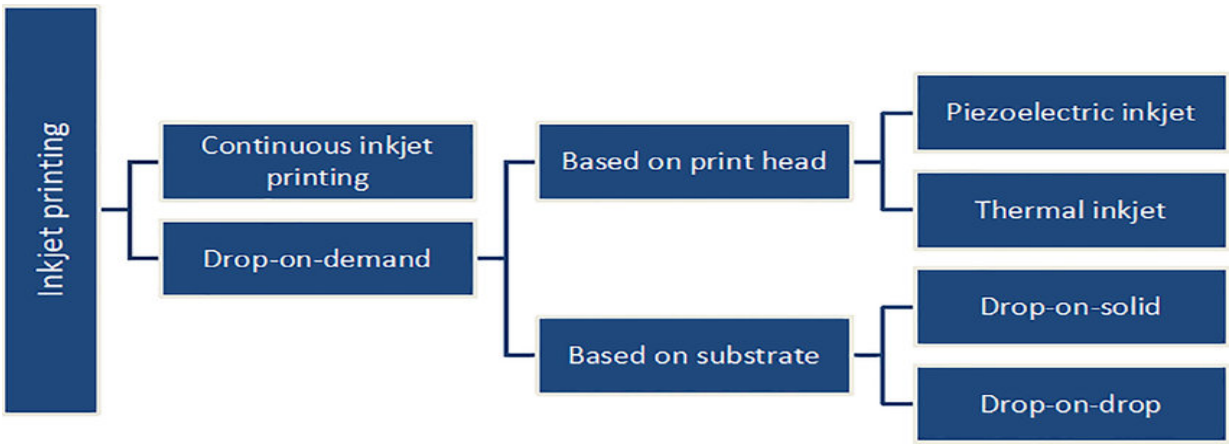


Fig (3).different types of inkjet printing [17]

Inkjet printing exhibits product transition through the innovation pipeline and exhibits a wide range of applications, where it can effectively enable continuous and semi-continuous manufacturing as well as a faster feed of the innovation pipeline according to research published in the journal Innovation The use of API/polymers in various formulations for pharmaceutical applications of inkjet printing is demonstrated. The first solid FFF to be employed in pharmaceutics was inkjet printing. A desktop version of the 3D printing technology, which was created at the Massachusetts Institute of Technology in 1996, was used to create a controlled medication delivery system. In that work, poly- capro lactone (PCL) was used as the top and bottom layers and polyethylene oxide (PEO) as the middle layer to create a controlled-release drug delivery system. [18,19]

4 .MATERIAL EXTRUSION (OR) NOZZLE BASED DEPOSITION SYSTEM:

A filament of the desired material is created, and the melted material is forced through the right nozzle to create the desired product. This process is known as material extrusion. In this technique, rollers with filament spools inside them travel through a nozzle that has been heated to a temperature where the filament may melt. The melted filament is placed on the build platform in accordance with the software-generated design. As the construction platform descends and the completed product is created, the melted material is placed layer by layer and fused together since the layers are in the molten condition. Extrusion-based printing is also employed for many diverse applications, ranging from cell loaded connections that are very promising for the biomedical sector in recent years.[20]

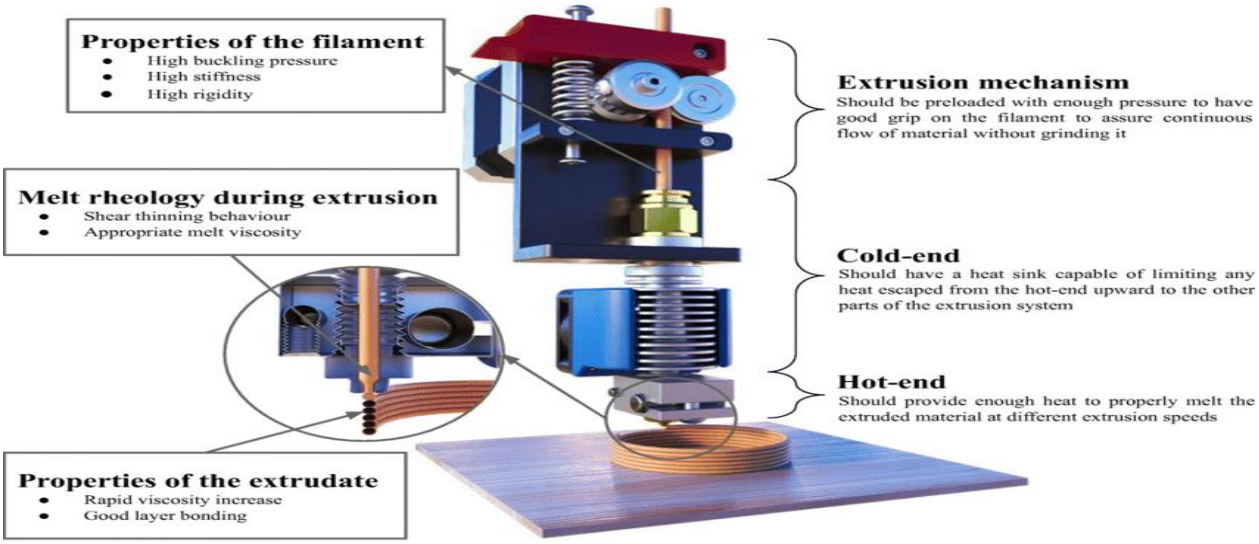


fig (4). Material extrusion system[21,22].

In FDM technology, as the process progresses, the build platform descends vertically and the nozzle travels horizontally. The build platform descends after each layer, and a new layer is deposited on top of the preceding layer. FDM has strong XY resolution, but poor Z resolution, which causes the thickness to not be consistent. As a result, if a smooth surface is desired, further finishing steps may be needed. The standard size of a nozzle or tiny tip utilised in FDM technology is 50–100 m. Polyvinyl alcohol (PVA), Acrylonitrile butadiene styrene (ABS), and poly lactic acid (PLA) are the three main polymers utilised in FDM. PLA and PVA are also employed in the creation of medicinal dosage forms. Used polymers used should be thermally stable, non volatile and non-aerosolizing [21].

5. FUSED DEPOSITION MODELING:

S. Scott Crump, the creator of Stratasys, created and developed fused deposition modelling (FDM) technology in the 1980s [22]. Due to its adaptability and affordability, FDM has become a technology that is often used in the pharmaceutical industry to fabricate dosage forms. Thermoplastic polymers are melted, extruded in filament form via a heated nozzle in consecutive layers, and then deposited on a collector to produce an item with a 3D shape during the FDM printing process. FDM enables 3D printed items to be customised items density, size, and shape. Auto genous bone grafts are often the gold standard for these sorts of fractures, but they have significant drawbacks since they require considerable surgery and have a limited supply. In light of this, Bao et al. [23]. created a bio-inspired hydroxyl apatite (HA)/PCL scaffold utilising FDM 3D printing in conjunction with CT reconstruction. Following that, these porous scaffolds were filled with a thermo sensitive poly (lactic-co-glycolic acid) (PLGA)-PEG-PLGA hydro gel containing BMP/VEGF for local distribution of the growth factors for accelerated healing abilities. Auto genous bone grafts are often the gold standard for treating these kinds of fractures, but they have significant drawbacks due to the considerable operation required and the scarcity of available donors.[24].

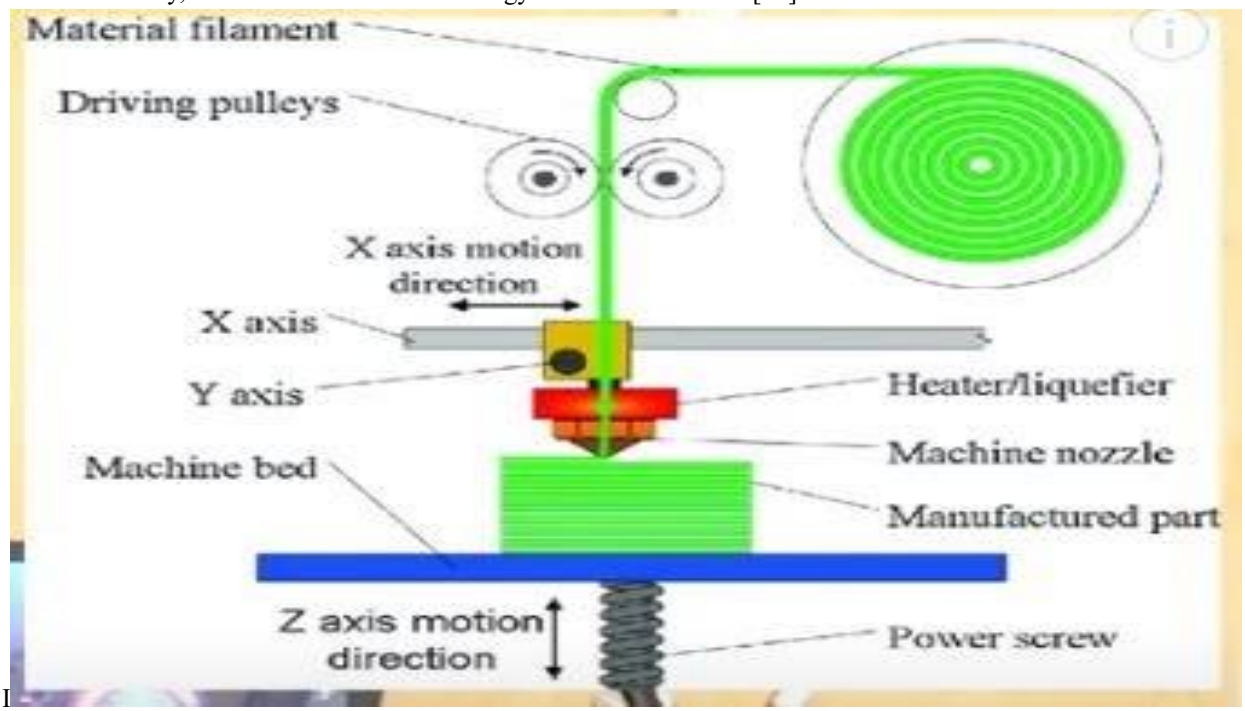


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fig (5). fused deposition modelling [25]

In light of this, Bao et al. created a bio-inspired hydroxyl apatite (HA)/PCL scaffold utilising FDM 3D printing in conjunction with CT reconstruction. A thermo sensitive bone morphogenic factor/vascular endothelial growth factor (BMP/VEGF)-containing poly (lactic-co-glycolic acid) (PLGA)-PEG-PLGA hydrogel was created. The creation of drug-loaded filaments is a crucial stage in the development of FDM. Poly lactic acid (PLA), polylactide -co glycoside (PLGA), polyvinyl alcohol (PVA),

polycaprolactone (PCL), and other cellulose derivatives are often used as filament materials. The findings demonstrated that filaments with lower melting points can drop the temperature of the printing process to as low as 90 C. Other studies have reduced the printing temperature even further by adding water as a temporary plasticizer during the filament preparation stage or by switching filaments out for softer extruded polymer strands as low as 54 C.48To lessen the thermal stress of the printing process; FDM has undergone a number of improvements. For instance, Kollamaram et al.46 produced drug-loaded filament using low-melting point povidone.[25-26]

6. ELECTRODYNAMIC 3D PRINTING:

With the aid of digitally controlled layer-by-layer material deposition, the electro hydrodynamic 3D printing (EHD) technique can shape fibrous materials to produce well-organized free-form geometries.[27] A high voltage power supply, a high precision XeYeZ moving stage, the controller, one or more syringe pumps, and a fine nozzle print head are the major components of this functioning system. The majority of medications and polymers, especially those that are thermally stable, can be used in this technology's ambient environment.[28] Based on this method, pharmaceutical drug carriers have been created using a variety of polymers, including polyvinyl alcohol (PVA), cellulose acetate (CA), polycaprolactone (PCL), and poly (ethylene oxide) (PEO)

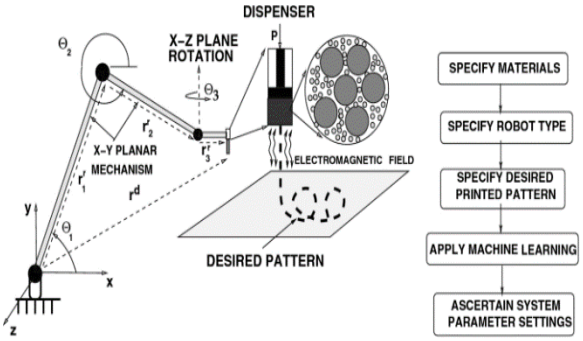


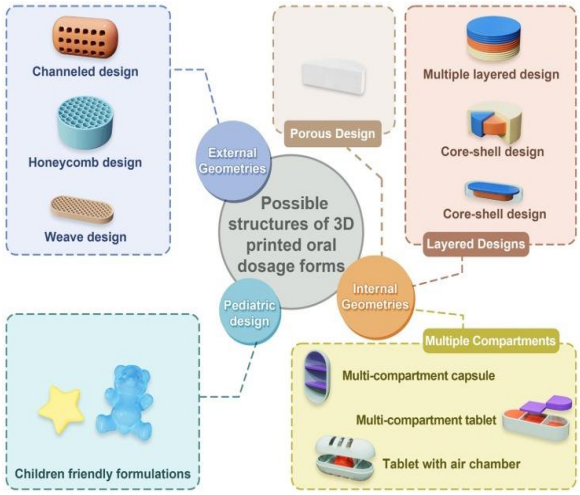
Fig (6). Electrodynamics 3D printing technology [28,32]

These materials have viscosities ranging from 1 to 10,000 mPasEHD 3D printing also offers the benefit of a greater controlled resolution[29] With the aid of concentrated organic/polymer solutions, EHD 3D printing enables micro to nanoscale fibre engineering and alignment as well as digital control of the deposition of materials to fabricate complex structures with well-ordered geometries, including Janus fibers, dual-core graphene composite matrices, film patches, and customised cylindrical capsules[30]. EHD, as a new technology, provides a strong method for the developing area of small-scale pharmaceutical technologies for customising medications to individual patient requirements by printing a wide range of predetermined therapeutic quantities organised in a particular pattern on a porous film. The EHD 3D printing method is expected to be adaptable and suit the dose requirements.[31]

7. 3D PRINTING TECHNOLOGY IN DRUG DELIVERY:

1. ORAL DOSAGE FORM:

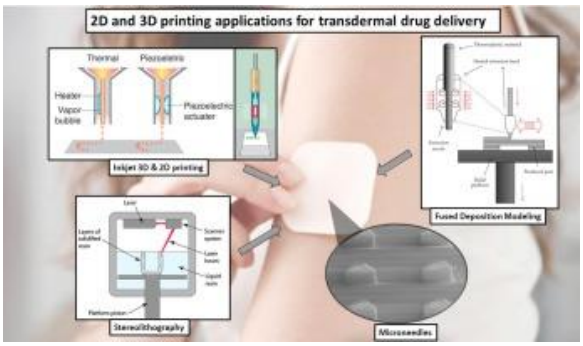
The creation of solid oral dosage forms using 3D printing technology has shown to be promising. With the help of this technology, it is now possible to create innovative formulations that get around many of the drawbacks of traditional medication manufacturing techniques. To meet the demand for customized pharmaceuticals, 3D printing has the capacity to create various sizes and intricate shapes with calibrated release properties. Extrusion-based 3D printing methods are the ones that are most frequently used in the creation of oral dosage forms. [33]The development of immediate-release systems, delayed-release systems, polypills that contain the entire dosage regimen for a patient with diabetes or hypertension in a single pill, and gastro-retentive drugs was made possible by the oral drug delivery methods created by 3D printing techniques.



The tablets were prepared with the same composition and are of the same dimensions. The physical and drug release characteristics of the tablets prepared by three different techniques showed a statistical variation. The drug release profile of the tablet prepared by direct compression (DC) method was immediate whereas the tablet prepared by injection modelling (IM) exhibited a sustained release profile for 48 h and similarly the tablet prepared by fused deposition modelling (FDM) exhibited both immediate and sustained release characteristics based on printing parameters. This concept provides evidence that 3D printing techniques have the capability to alter the drug release characteristics [34]

2. TRANSDERMAL DRUG DELIVERY SYSTEM:

By creating intricate and unique geometries for pharmaceutical medicinal items and medical devices, 3D printing has received attention as a viable method for transdermal drug delivery. According to the patient's needs, the 3D printing process has been effectively used in a number of transdermal formulation approaches, including implants, microneedles, masks, and patches for local and systemic API delivery.[35]

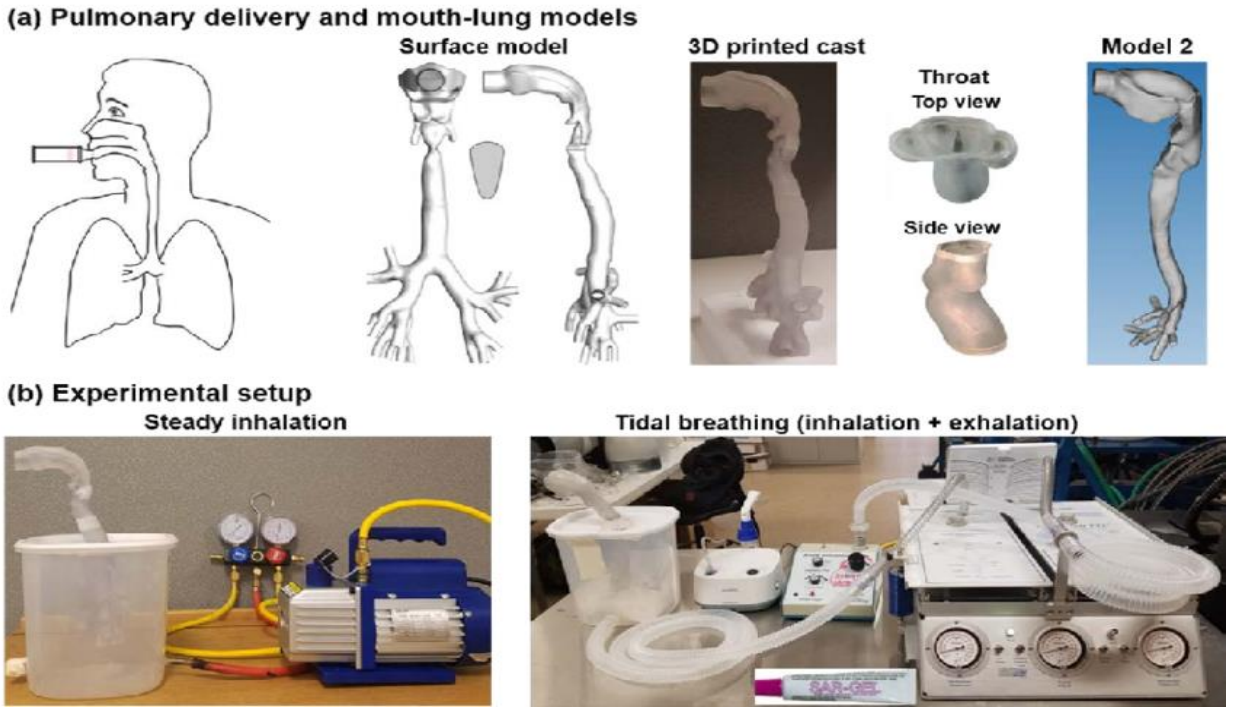


A method by Kempin et al. created an implant that could be applied to a particular application site, and a 3D printing technology was used to customize the implant's geometry for the application site. This study used fluorescent dye quinine as a model medication to show how an implant may be made.

This implant was made using the extrusion-based FDM technology in conjunction [36].

3. PULMONARY DRUG DELIVERY:

By creating 3D printed medical equipment and models, respiratory disorders are treated using 3D printing, a new technology. Prototypes of lungs that were 3D printed help doctors better comprehend the diseased state and may one day be used to identify and cure disorders of the respiratory system. [37]By utilizing 3D printing processes, these strategies will help manufacture tailored inhaled medications



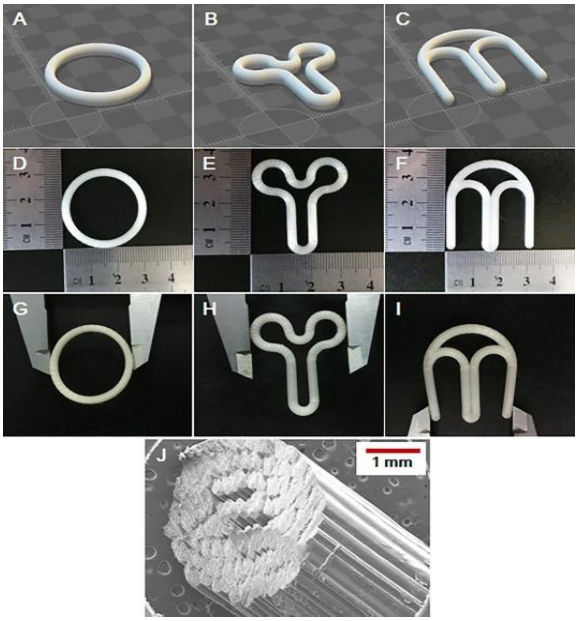
Morrison et al.'s fabrication of 3D printed bioresorbable airway splints for the treatment of pediatric patients' tracheobronchomalacia serves as a demonstration of the application of 3D printing in pulmonary medicine [38]. By creating specialized devices for the treatment of life-threatening disorders, the 3D printed airway splints were discovered to be a useful option to reduce patient airway collapse and offer a root map.[39]

4. INTRAUTERINE DRUG DELIVERY:

3D printing methods have been employed to fabricate drug delivery

Devices and implants for Intrauterine drug delivery. The 3D printing

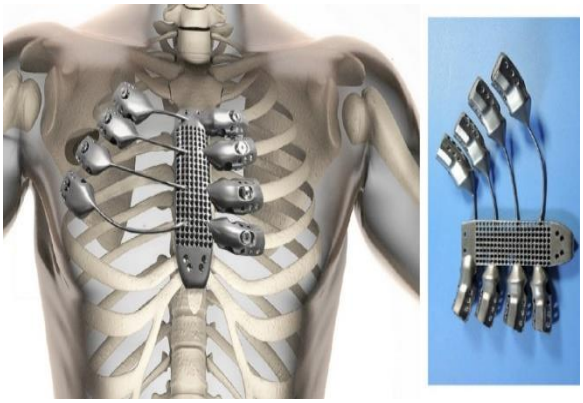
Technology provides a reliable solution for fabricating personalized size and shape devices for local and systemic delivery of API through the intrauterine route. These devices will deliver a precise dose of the API with tuned release characteristics [40].



In an approach, Hollander et al. developed a T-shaped prototype intrauterine device by using FDM based 3D printing technique. The Drug release profile of the model drug indomethacin from the 3D Printed devices fabricated by using poly-caprolactone was found to Be faster compared to extruded filament itself. As shown in fig.[41]The drug release was through polymer diffusion and the efficient drug release profile was achieved through the 3D printed devices because the drug was found to be in an amorphous state in the devices compare to the crystalline existence of the drug in the filament In another approach, the same group of researchers demonstrated the effect of ethylene vinyl acetate (EVA) as a polymer to fabricate intrauterine systems (IUS) and subcutaneous rods (SR) by using FDM based 3D printing technique. The custom-made T- shaped 3D printed prototype devices exhibited a faster drug release profile for 30 days. This concept provides a test bed to develop drug-loaded implantable Devices by using ethylene vinyl acetate (EVA) as a polymer suitable for 3D extrudable printing [42]

5. IMPLANTS:

An implant can be a drug delivery system that contains effective drugs within a sustained release delivery matrix, benefiting patients who demand long-term medication treatment. An embed is a dosing structure containing dynamic medications inside a supported delivery conveyance grid, giving advantages to patients who need long haul treatment Of medications.[43]



For instance, micro structured embeds of levofloxacin display complex

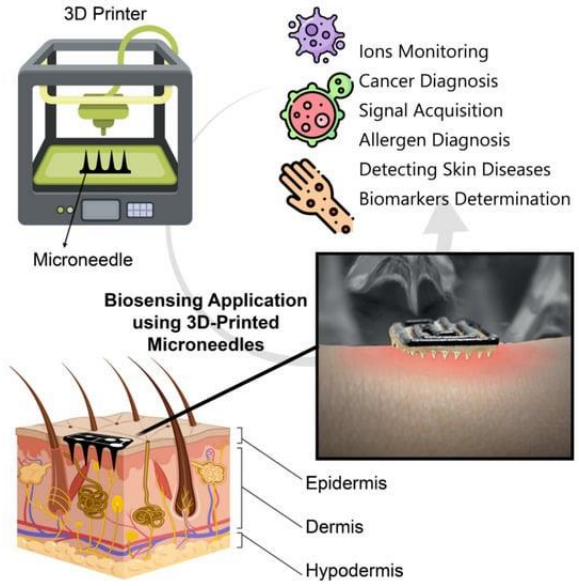
Delivery profiles obtained from a solitary embed. These embed showed a bimodal profile, with pulsatile. (Day 5–25) and consistent state drug discharge (day 25–50) afterward, the beat discharge started again on day 50 and proceeded up to day 80 [44]. By utilizing 3D printers, Wu et al. planned a multi-drug embed for the treatment of bone tuberculosis. Isoniazid and rifampicin, antitubercular agents have fused into each layer to get a particular grouping, shaping a multi-facet concentric chamber. Recently developed a 3DP-based multi-drug implant in which tobramycin (TOB) and levofloxacin (LVFX) as API were loaded and multi-layeredscaffoldswere introduced (layers 0.4 cm3) for

the treatment of chronic osteomyelitis [45]. This work explores the utilization of polycaprolactone.

6. MICRONEEDLES:

A novel inkjet printing technique, a process for coating micro needle

Arrays made up of metal with three anticancer components such as curcumin, cisplatin and 5-fluorouracil, for transdermal drug delivery [46]. Farias et al. used stereo lithography to design a cell-hydrogel having 3Dprinted methacrylate-based custom hollow micro needle assembly (circular array of 13 conical frusta) to evaluate the potentiality of cells named human hepatocellular carcinoma (HepG2) cells [47]. Economidou et al. designed 3D printed micro needle arrays by stereo lithography (SLA) using a biocompatible resin for transdermal insulin delivery [48]



Notable novel drug delivery approaches have been accorded by 3D

Printing technology. Gastro retentive floating pulsatile drug delivery,

Transdermal drug delivery, micro porous bio ceramics, multiple pills,

Micro fluidic pump etc [49]

APPLICATIONS:

-Tissues and organs can be bio-printed instead of having to wait for 4years

-Time and stress is reduced by implementation of 3D printing

-Bio printed medicines can be customised to have unique dosage instead of standard dosages

-Diseases like cancer can be treated with higher efficiency using 3D printed drugs

-Prosthesis and implants can also be customised as per client need

-Printing of anatomical structures for surgical analysis, instead of using cadavers

-Medicines can be printed in a boost complex drug release profile

-Chemical structures can be treated as per requirements

-It Increases solubility and dosage specific parameters

9.CONCLUSION:

The advancement of 3D printing is a significant and likely instrument for the area of drug design, enabling the production of customised drugs targeted at the requirements of the patients. It improves output and assembly efficiency, among other benefits. Due to 3D printing, the method that assembly is finished has altered. It enhances plan manufacturing, reduces lead times, and lowers the cost of tooling for new goods. This practise clearly works well for some patients since it puts the group near to them and offers customised treatment. It is now feasible to model, diagnose, and follow the evolution of cancer, one of the most urgent diseases, thanks to the application of this technology, especially in the modelling and diagnosis of diseases.

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[42] Images (A-C) of the vaginal rings designed by CAD (computer-aided design) and pictures of 3D printed vaginal rings (D-F) with the shapes of "O", "Y", and "M", respectively. Graphs G, H, and I show the rings compressed with a caliper. Graph J is the SEM image of a cross-section of rings. Reprinted from [63] with permission from Elsevier.

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