Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [7] June 2023: 274-281

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

3d Printing Technology: A Novel Breakthrough in the Field of Pharmaceutical Drug Delivery Systems – An Extensive review

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ABSTRACT
3D printing, known formally as an additive manufacturing process, began in the late 1980s. It is a digital manufacturing process that creates 3-dimensional objects, layer upon layer, using a variety of polymers, metals, and ceramics. 3D printing technology relies on computer-aided design to achieve the utmost flexibility, time savings, and exceptional manufacturing capabilities of pharmaceutical medicines. This technology also tackles one of medicine's most prominent issues: targeted therapies. Numerous benefits, such as individualized doses, quick disintegration using the SLS technology, incorporation of high doses, and taste masking ability, have made 3D printing necessary. Fused deposition modeling (FDM), stereo lithography (SLA), selective laser sintering (SLS), Hot melt extrusion (HME), and inject printing are the methods employed. But the most recent reports from the association for pharmaceutical 3D printing technology show that this technology is still in its infancy and has a lot of potential. The current overview covers sections on the introduction, applications, and breadth of 3D printing, as well as sections on the many 3D printing techniques, challenges, and approaches to tailored medications.s
KEYWORDS: *3D printing, Personalized medicine, on demand manufacturing, Filaments, Process optimization.*

Received 09.05.2023 Revised 19.05.2023 Accepted 30.06.2023

INTRODUCTION

The development and use of 3D printing has sparked immense innovation across a wide range of industries, including the aerospace industry, architecture, tissue engineering, biomedical research, and pharmaceuticals. Based on its adaptability and diversity, 3D printing technology appears to be the driving force behind the next industrial revolution. As science and technology advance, 3D printing technology becomes more developed and affordable for anyone with open-source software to use (Fig 1). The recent release of the first 3D-printed medication that the FDA has approved has stoked excitement about this emerging technology, which is poised to transform healthcare (1). However, this technology is still in its infancy, and its potential has not yet been completely exploited in the pharmaceutical business. As a practical solution to some problems with traditional pharmaceutical unit operations, 3DP is gaining more and more attention in the production of pharmaceutical formulations. For example, the traditional production unit operations of milling, mixing, granulating, and compression might provide different end product attributes with regard to drug loading, drug release, drug stability, and pharmaceutical dosage form stability (2). A new level of flexibility in the design and production of complex products has been made possible by 3D printing technology, which can be used in personalized and programmed medicine. When the phrase "3D printing" was first coined, it referred to a method of layer-by-layer inkjet printing of a binder material onto a powder bed (3). A larger range of additive manufacturing methods are now included in the phrase "3D printing." Due to its larger meaning and longer presence, the term "additive manufacturing" continues to be more common among professionals (4). With effective material management, additive manufacturing techniques can produce a variety of complicated shapes and structures with less waste and a number of other advantages over traditional production, which is why they are growing in popularity. Rapid prototyping (RP), also known as additive manufacturing (AM), solid freeform technology, or 3D printing (3DP), is a relatively recent idea in the pharmaceutical industry (5).

The American Society for Testing and Materials defines 3DP as the "fabrication of objects through the deposition of materials using a print head, nozzle, or other printing technology" (6). Despite the fact that a number of standard dosage forms and formulations have been created over time by traditional medicine, they are unable to meet the specific requirements of a patient or a cohort. These problems are addressed by 3DP technology, which also helps modernise and advance traditional pharmaceutical formulation methods. The AM techniques are a subset of a collection of methods that also includes bioprinting, digital light processing (DLP), extrusion-based fused deposition modelling (FDM), and hot-melt extrusion (7)

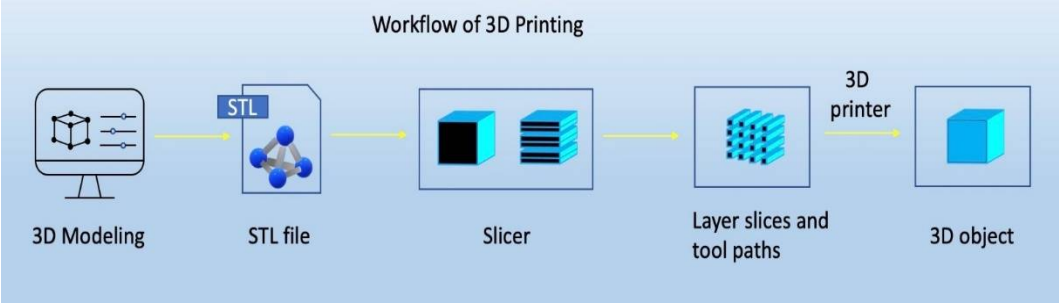

Fig. 1 Process of 3d Printing

CONVENTION VS 3D

In contrast to traditional mass production techniques, 3D printing appears to be a revolution in pharmaceutical manufacturing procedures. Additionally, the capacity of 3D printing to produce a drug product quickly results in a significant cost decrease in the production process, which is very advantageous to the pharmaceutical business (1). In addition to enabling further exploration of previously abandoned raw materials, 3D printing and clean fabrication processes also make medications more widely available and compliant. By allowing for flexibility in the design of oral dosage forms with complicated geometry, 3D printing technology opens up new production options for cutting-edge drug delivery systems (8). This may be able to resolve the problems with the conventional modified-release dosage forms and eventually lead to the development of more effective ways to create customized drugs (9).

BENEFITS OF 3D PRINTING

Increase solubility, Repeatable precision, Dosage-specific parameters, On-demand dosage form, Faster Trails, micro dosing without oxidation, on-contact processing (10).

FUSED DEPOSITION MODELLING

One of the techniques used in 3D printing is fused deposition modelling (FDM). The fused filament fabrication method is another name for the FDM process. In terms of production, injection molding utilizes the FDM technique. The FDM printer is available in various sizes: In the 3D printing industry, filament made from thermoplastic materials is widely used because thermoplastic materials have lower melting points. The thickness of the layers, the width, and the filament orientation are the few processing characteristics that determine the mechanical qualities of the printed object. Since the shapes in FDM are constructed from layers of thin filament, the filament's thermoplasticity is crucial to this process (11). The development of filament materials has been a challenging task due to the FDM's complicated needs. The most widely used filament materials are acrylonitrile butadiene styrene (ABS), polylactic acid, polyether ether ketone, and thermoplastic blends. As a result of its widespread use as a plastic in daily life, other materials like polypropylene (PP) also started to receive attention for development (12).

PRODUCTION PROCEDURE FOR FILAMENTS:

A multi-step process is used by an extrusion machine to produce filament. In the first phase, the diameter of the filament to be produced is decided upon, the extrusion parameters are established, the material is added in the form of a pellet, and extrusion is then carried out from the nozzle die hole until the filament is wrapped around the roller machine (12).

BRIEF EXPLANATION

The main component of the FDM method is the filament. The filament is typically made of pure polymer with a low melting point. The commercially available, pure polymer filaments can be processed right away as FDM material. Extruding pellets or raw materials derived from polymers can be used to create pure polymer filament for FDM materials. Strengthening or creating filament from polymer composites is achieved by mixing the material prior to the extrusion process and preparing each component in preparation .Various techniques can be used to combine the materials, depending on the characteristics of the individual components. It can be finished using either the dry mixing method or by combining the solution and drying it before extracting it. After the addition of additives is done in phases according to the desired percentage, following the compatibilizer procedure, The average time is thirty minutes. Then,

in order to ensure homogeneity, the melted substance is left to stand at room temperature. The finished mixture can then be treated in an extruder to create fabric pellets or pieces as small as 4 mm2 in size (Fig 2). Drug-loaded filaments are needed for the nozzle-based Fused Deposition Modelling (FDM) process. To enable the creation of pharma-grade filaments for the printing of pharmaceuticals, the coupling of hot-melt extrusion with FDM is preferred. Another method for creating filaments is to soak commercial filaments in saturated drug (impregnation), followed by filament drying and 3D printing. Solvent use and low drug loading are two of this method's biggest drawbacks (13). To make sure that both phases are coordinated, real-time monitoring and control are necessary when combining HME with FDM. Despite the fact that HME and FDM 3D printing are independent processes, when one stops working, the other does too, which changes a medicine product's key quality characteristics. Extruders are used in this procedure to push or press the material through die-cut holes to produce the extrudate. The filament is impacted by various factors throughout this extrusion process. The filament cable diameter is influenced by the die temperature, roller puller speed, spindle speed, and inlet temperature. Since the parameters in this procedure will change the material's viscosity, the output of the material will be extruded at the nozzle die instead of according to the required diameter. In contrast, the filament's regularity is impacted by the geometry of the winding screw. The thread's shape, particularly in composite filaments, will influence the filler's direction (14).

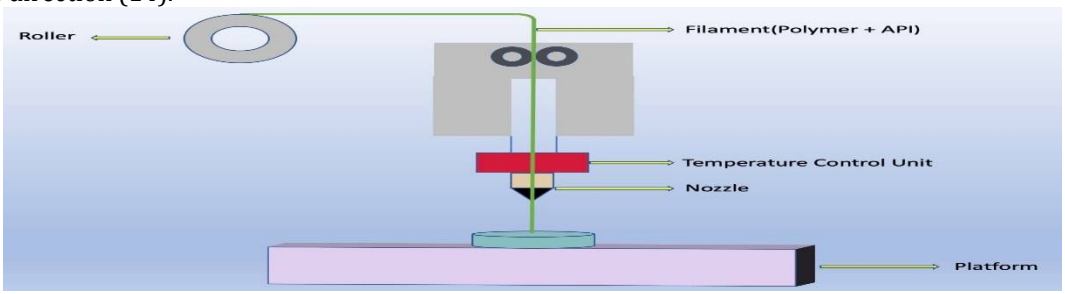

Fig. 2 Fused Deposition Modelling

TYPES OF POLYMERS

Polymer filament is classified into two types based on its composition: pure polymer filament and composite filament. The following is an example of using some pure polymer filaments that are often used in 3D printing and development processes.

- Polylactic acid (PLA)
- Acrylonitrile Butadiene Styrene (ABS)
- Polypropylene (PP)

ACRYLONITRILE BUTADIENE STYRENE

Various acrylonitrile blends and copolymers, butadiene-containing polymers, and styrene are all referred to as ABS together. Since ABS is a petroleum-based polymer that can be recycled but is not biodegradable, it is a synthetic polymer. ABS is considered to be more economical as it is cheaper and exhibits excellent mechanical properties. ABS was introduced in the 1950s. At the time, ABS was a blend of styrene-acrylonitrile (SAN), also known as nitrile rubber. The combination of SAN, which is glassy, and nitrile, which is rubbery, results in a structure that is tough, impact-resistant, and amorphous at room temperature. Styrene offers the product glossy qualities, as seen in, and nitrile serves as an active site for ABS, giving it polar features. Butadiene, meanwhile, gives ABS a material with greater tenacity. Styrene and acrylonitrile copolymerize to create strength and stiffness, while polybutadiene rubber (BR) gives ABS its toughness. Because ABS possesses high-temperature resilience due to acrylonitrile, it may be extruded at a higher temperature (15). ABS is a great thermoplastic because of its abrasion and impact resistance for a variety of applications. This polymer is a fantastic option for the creation of FDM due to its exceptional mechanical properties, thermal robustness, moderate flexibility, and extended serviceability. Shear thinning is another rheological property of ABS. As a result, viscosity decreases during processing because of the heat involved, and flow ability increases during printing (16).

LIMITATIONS OF ABS

Warping, Delamination, not economically beneficial when used at high temperature are some ofthe problems with 3D printing ABS material. (17).

POLY LACTIC ACID

Poly Lactic Acid (PLA) is a well-known polymer in FDM technology because it is a vital biodegradable polymer with superior mechanical properties. Lactic acid is used to produce PLA through the fermentation of carbohydrates found in agricultural crops like maize. PLA is considerably less expensive

to produce, and because its raw materials are widely available and it has many traits in common with the present synthetic polymer, PLA is the one that researchers are most familiar with. Using alpha-hydroxy acids, a category of aliphatic polyesters known as PLA can be created. The high modulus, strength, and improved transparency of PLA are also good mechanical qualities that are comparable to those of conventional polymers. The melting point of PLA is only 60–65 degrees. At temperatures between 155 and 185 degrees Celsius, PLA layers fuse together to form a bond. PLA must be combined with several other polymers and additives in order to change its thermal and physical properties. Its strength has reportedly been enhanced by mixing it with a number of flexible polymers that may act as toughening agents, such as elastomers containing PLA, particularly degradable natural rubber; this technique gets rid of this flaw in PLA's mechanical properties. Combining PLA and rubber is a more practical and cost-effective way to enhance certain properties (18).

LIMITATIONS OF PLA

The excessive rigidity, poor impact resistance, ductility, low temperature resistance, and low elongation at break of PLA are only a few of its drawbacks. It is resistant to brittleness, crystallises slowly, and is permeable to gases. Due to its low melt flow index, PLA is also classified as having Newtonian behaviour, which makes it challenging to manage viscosity during processing. The mobility of PLA molecules increases during processing when the temperature rises from a lower level (19).

POLY PROPYLENE

PP, a homopolymer member of the polyolefin family, is one of the most popular low-density, low-cost thermoplastic semi crystals. In contrast to other technical plastics (PC, PA, etc.), PP has poor thermal, electrical, and mechanical properties and a high coefficient of friction in dry shear circumstances. Inorganic nanoparticle fillers are used with polypropylene to enhance its mechanical characteristics. For the same printing conditions, glass fibres enhance Young's modulus and ultimate tensile strength by around 40%. Similar improvements in modules were seen in studies of improving PP compounds that contain spherical microspheres for FDM application by maximising matrix-filler compatibility that influences printability, properties' pull, and toughness, as well as 3D-printed PPs filled with cellulose nanofibrils (20).

Type of Polymers	Processing temperature
Polylactic acid	175-195°C
Acrylonitrile Butadiene Styrene	165-185°C
Polypropylene	204-240°C

SELECTIVE LASER SINTERING (SLS)

SLS is a powder-based layer-additive manufacturing process that is commonly used for rapid prototyping and rapid tooling. As a heat source, laser beams in either continuous or pulse mode are used to scan and join powders in predetermined sizes and shapes of layers (21). SLS creates 3D objects by using laser energy to selectively heat powder particles, resulting in fusion. The fused particles then solidify to form a three-dimensional structure. The SLS system is made up of three major components: a spreading platform, a powder bed, and a laser system (laser and scanner). Utilizing a spreading device with a slot feeder and a roller or scraper blade to disperse powder evenly throughout the building platform, the surface is leveled. Every plane in the system's 3D processing, which represents the fundamental vectors used in laser scanning, is treated as a separate 3D object. The scan pattern of these vectors is predesigned and depends on the final product's qualities. By laser sintering or melting between the particles, the material is heated to a temperature below its melting point, which is necessary to induce fusion. The powder bed's height is changed to focus the laser on the freshly produced surface as the scanner moves the laser in a two-dimensional plane. The process is supported by loose powder particles that are present on the construction platform. A second layer of powder is deposited and fused by the laser as the powder bed surface is lowered by a height equal to one layer thickness. Up until the completion of the object, this process is repeated (Fig 3). Inside the printer, the finished product is given time to cool. Selective laser sintering has been used to create small batches of functional parts, investment casting patterns, and models for design testing. Injection molding, quick tooling for electrode electrical discharge machining, polymer molding, sand casting molds, and other processes have also utilized this method (21). SLS printing can be utilized to create customized pharmaceuticals (22).

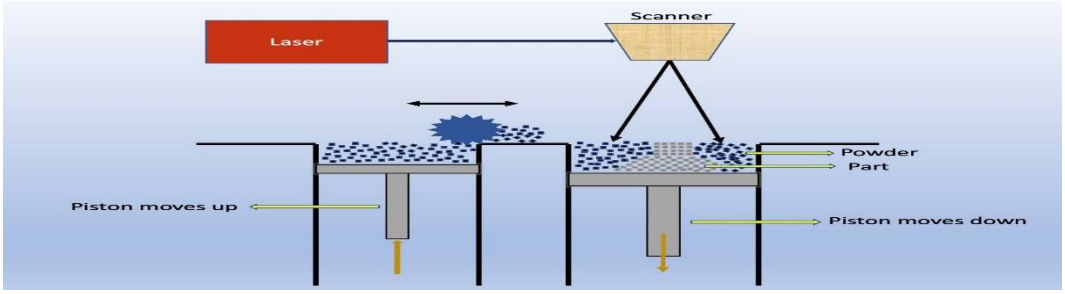

Fig. 3 Selective Laser Sintering

STEREOLITHOGRAPHY (SLA)

Stereolithography (SLA) 3D printing is the most popular resin 3D printing technique and has gained enormous popularity for its capacity to create high-accuracy, isotropic, and waterproof prototypes and end-use components in a variety of sophisticated materials with fine details and a smooth surface finish (23). The stereolithography method uses a localized photo polymerization process that is sparked by ultraviolet (UV) light and occurs in a bath of liquid monomers, oligomers, and photo initiators. Since stereolithography is adaptable enough to produce a variety of highly complex 3D structures with high precision and an affordable cost, more and more materials have been developed for a wide range of applications, including soft robotic actuators, sensors, medical implants, microfluidic devices, and energy storage components (24).

PROCESS

A standard tessellation language (STL) file, which is currently the starting point for every AM process, is used in stereolithography. The STL file is used to slice a 3D model, turning it into 2D slices that provide cross-sectional data. These 2D slices can be used to create the physical model layer by layer (Fig 4). The STL format's 3D model is depicted using a lot of tiny triangular facets. Each triangular facet is characterised by the coordinates of three vertices and a unit vector pointing away from the facet to denote the normal direction (24). The exothermic polymerization process known as the curing reaction of resins, which is characterised by chemical cross-linking reactions, is the basis of stereolithography. Two transitions, gelation and vitrification occur during the curing reaction process, which is started by delivering UV light energy. The transition from liquid to rubber, known as gelation, results in a significant rise in viscosity. During this transition, the system's gel phase and sol phase coexist. A slow, thermo-reversible process called vitrification transforms liquid or rubber resin into a glassy, solid resin (24).

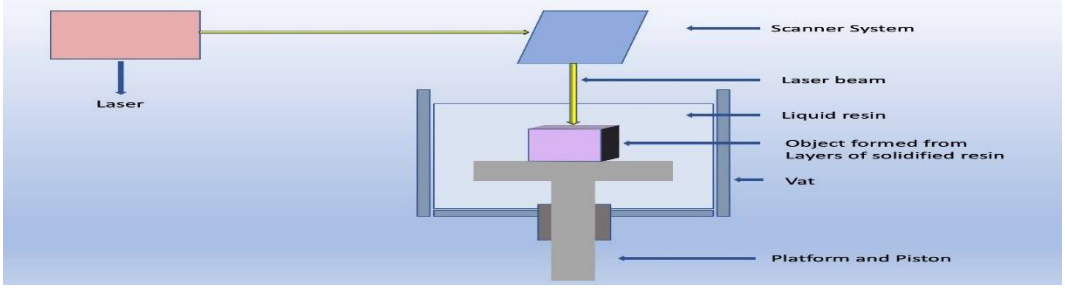

Fig. 4 Stereolithography

INKJET PRINTING (IJ)

The term "inkjet printing" refers to a wide range of techniques for digitally generating and placing tiny liquid droplets. The two innovative inkjet printing methods, continuous inkjet (CIJ) and drop-on-demand (DOD) are separated by the way drips are created physically. In contrast to DOD printing, which only ejects liquid from the print head when a drop is needed, CIJ printing involves the discharge of a persistent stream of fluid through a nozzle with a diameter of 50–80 mm and a high-pressure pump, which then fragments into a stream of drops under the influence of surface tension forces**.** DOD technology includes the subcategories of drop-on-drop deposition and drop-on-solid deposition. Drop-on-drop deposition, which is how the printer head ejects the droplets onto one another, creates a solid layer with excellent resolution. Drop-on-powder or drop-on-bed sedimentation, binder jetting, plaster printing, or powder bed 3DP is one of the more common names for the drop-on-solid deposition process, because it spreads a liquid link, the binder, on the powders and spreads solid powder on top of a platform. This method uses an ink-jet head to dispense a liquid binder solution over a powder bed that has been flattened. Due to adhesion forces or the hydraulic cement setting process, binders (organic or inorganic) can bind powder carrier particles together to form an agglomerated result. Drop-on-demand (DoD) inkjets can be

delivered in a variety of ways. Thermal and piezoelectric techniques are the most commonly used ones. In thermal DOD, also known as bubble jet printing, the ink is heated locally, causing bubbles to form that eject ink (Fig 5). The fast volume change brought on by the piezoelectric crystal's quick change in shape produces an acoustic pulse that is sufficient for ink ejection in piezoelectric DOD. The piezoelectric DOD method can be used with any substance, but the thermal DOD methodology is limited to volatile liquids. Numerous liquids can be used with the piezoelectric DOD technique. Inkjet printing demonstrates product transition via the innovation pipeline and demonstrates a wide range of applications, where it can successfully enable continuous and semi-continuous manufacturing as well as a faster feed of the innovation pipeline. Pharmaceutical inkjet printing applications utilizes a variety of formulations, polymers or APIs (25).

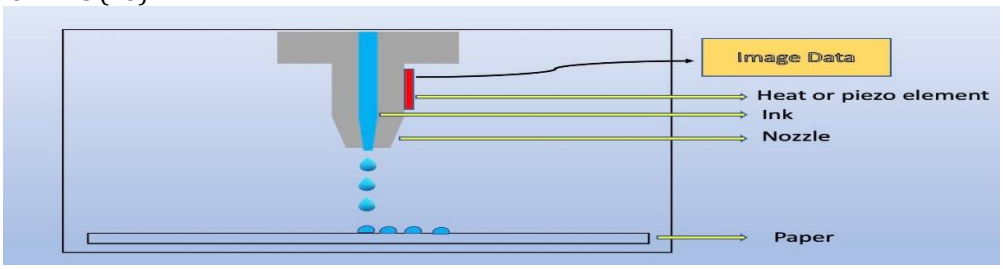

Fig. 5 Inkjet printing

HOT MELT EXTRUSION (HME)

Beginning in the 1970s, the usage of HME in the pharmaceutical sector increased, and it was used in product development, formulation, and manufacturing. Molecular level mixing of the active compounds and thermoplastic binders, polymers, or both is achieved by pumping polymeric materials with a rotating screw at temperatures above their glass transition temperature and occasionally above the melting temperature. This continuous pharmaceutical process is known as HME. The components are combined molecularly to create an amorphous product with a consistent shape and density, which improves the drug's weak water solubility and its dissolution profile. Additionally, HME has been used to distribute medications that are soluble in water for a variety of purposes, including taste obliteration. This innovative but difficult technique may have a number of advantages over traditional pharmaceutical manufacturing procedures, including a quicker and more effective final product and a more effective medication delivery to the patient. HME has thereby become a platform technology that can be used as a substitute for other conventional methods for producing pharmaceutical dosage forms, such as tablets, capsules, films, and implants, for drug delivery via oral, transdermal, and transmucosal routes (26).

WORKING PROCESS OF HME

Extrusion is the controlled process of driving a substance through a die or orifice to modify its physical properties. The screw extruders play a crucial role in the pharmaceutical sector since they continuously transform raw materials into final products like rods, tubes, and films (Fig 6). The feed material is propelled forward towards the die by the rotating screws and softened by frictional heat generated via the barrel wall. When the feed reaches the screw's end, it is in a viscous state that can be forced through an aperture (or die) and shaped into the appropriate shape (27).

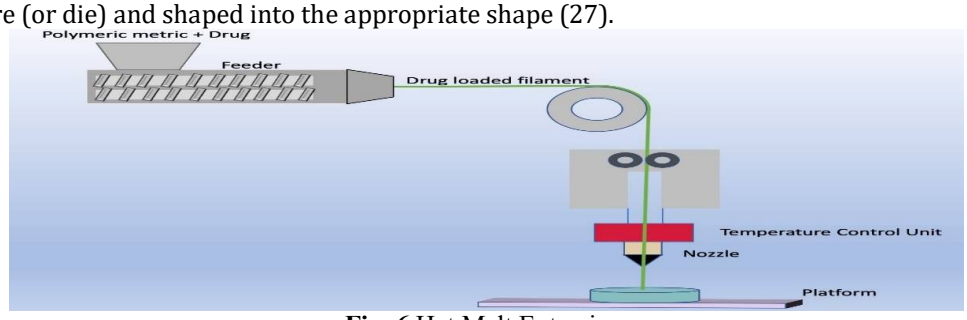

Fig. 6 Hot Melt Extrusion

CHALLENGES

Due to the different printing principles used by each type of 3D printing technology, there are specific requirements for the properties of the excipients during the preparation process. It is crucial to choose a good drug carrier because the printing process for 3D Printing technology involves heating and melting phases.Some of the challenges are discussed below.

EXCEPIENTS

Contrasting them with those used in conventional pharmaceutical processes, the excipients that are generally available for 3D printing technology are rather few. Due to their distinctive printing principles,

all types of 3D printing technologies have specific constraints on the qualities of excipients. It is crucial to choose a good drug carrier in the case of FDM technology, as it involves heating and melting phases during the printing process. The most frequently reported carrier excipients are PVA, but due to its high melting point, it is not suited for medications that are thermally unstable, such as levetiracetam. In recent years, some other excipients have also been used, such as HPMC, talc triethyl citrate, and Kollidon. In the case of SLS and SLA technology, photopolymers and laser-sinterable materials are some of the limited excipients, and these polymers are not on the Food and Drug Administration's (FDA's) list of materials that are generally recognized as safe. Only a small number of excipients have been utilized for printing up to this point, and the majority of them are expensive, hazardous, and stinky. They also require protection from light to prevent premature polymerization (28).

SOFTWARE AND EQUIPMENT FOR PRINTING

The four key steps of the 3D printing process are modelling, slicing, printing, and post-processing. Therefore, to satisfy better printing requirements, modelling and slicing software must be continuously updated as the complexity of the desired structure rises. Only a few models and software applications are specifically designed for 3D printing technology. And also, the good manufacturing practises (GMP) standard is not adhered to by the 3D printers used in medicine, so it is necessary to check the production process and the final goods to ensure that they are safe for use (29).

MECHANICAL CHARACTERISTICS

The performance of the items is impacted by elements like surface tension, adhesive viscosity, and nozzle fineness. Additionally, post-printing procedures like drying techniques, drying times, and drying temperatures may also have an impact on the products' appearance and quality. To improve the mechanical behaviour of products, printing equipment must be optimized, including computer control programmes, adhesive nozzles, and printing process parameters.

REGULATIONS

Currently, there are no proper regulations or guidelines for 3D printing medicines. Focusing on the design, production, and usage of the device, the FDA proposed its final advice on technical considerations for the regulation of 3D-printed medical devices in 2017. Although these concepts may not be applied to all 3D-printed medical equipment, a separate evaluation of their usefulness and safety may be necessary, particularly for products that correspond to the patient (30).

RECENT ADVANCEMENTS

The first and only oral drug formulation platform to utilise 3D printing enables disintegration in seconds with a sip of liquid. Spritam, an antiepileptic drug made by aprecia pharmaceuticals using Zip Dose technology, was approved by the FDA as the first 3D-printed drug. Zip Dose technology can create pills that rapidly disintegrate with a sip of liquid and allows a high drug load of up to 1000 mg to be delivered in a single dose.

The world's first 3D printer is FabRx's innovative M3DIMAKERTM, which supports printing with a variety of nozzles. A specialised software platform controls the M3DIMAKER 3D printer, allowing users to select the dose prescribed by the pharmacist and clinician. The software also includes fingerprint access control and a data matrix reader, ensuring dependability and security. In other words, many of the technology's features are only accessible to qualified personnel. In addition, the pharmaceutical 3D printer has advanced in-line quality control procedures, such as camera monitoring for defect detection. The M3DIMAKER can produce 28 printlets in about eight minutes, depending on the type of drug being printed.

CONCLUSION

3D Printing promises a future of drugs and medicines print on demand, personalized medicines with customized dose and able to deliver what you want, how much you want and when you want. This technology definitely helps doctors and pharmacist to provide tailore made medicines for each patient.

ACKNOWLEDGMENTS

The authors thank the Department of Pharmaceutics, SwamyVivekanandha College of Pharmacy, Tiruchengode, Namakkal, Tamilnadu, India, for supporting them in preparing this review.

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CITATION OF THIS ARTICLE

Pydimarri Venkata A S A, Subashini R,Vinutha Sree A.R, Ranjitha P, Senthil Rajan Dharmalingam, Kiruthiga N, AdlinJino Nesalin. 3d Printing Technology: A Novel Breakthrough in the Field of Pharmaceutical Drug Delivery Systems – An Extensive review. Bull. Env. Pharmacol. Life Sci., Vol 12 [7] June 2023: 274-281