

3D PRINTING IN PHARMACY SECTOR: A REVIEW ON RECENT ADVANCE TECHNOLOGY

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Abstract: Researchers from various fields have shown interest in three-dimensional printing because of its wide range of applications. The primary aim of incorporating 3D printing technology within the pharmaceutical sector is to develop customized delivery systems tailored to individual patients. This would allow for easy customization of the form, size, and rate of administration of different medications. The most extensively studied aspect of this technology is the drug delivery mechanism, which includes controlled release, polypills, gastrofloating, orodispersibles, and microneedles. Additionally, 3D printing has facilitated the development of pharmaceutical devices such as pharmacy dispensing aids, drug eluting scaffolds, and combinatorial products that serve as drug delivery systems or medical devices. The utilization of 3D printing technology has the capacity to facilitate the creation and manufacturing of adaptable formulations that can be tailored to specific dosages, forms, sizes, and drug release mechanisms. Additionally, this technology enables the combination of multiple drugs within a single formulation. Consequently, the potential benefits of 3D printing extend to patients, pharmacists, and the pharmaceutical industry as a whole. This provides a broad overview of the evolution of 3D printing technology, from its initial stages to the creation of finished products.

Keywords: 3D printing technology, Drug delivery system, Medical devices, Personalised medicine.

INTRODUCTION

A technique for creating objects involves the process of adding layers of material through three-dimensional printing. A computer-aided design (CAD) program may be used to create buildings of different sizes and forms. This approach has been used in a variety of fields, including industrial engineering, customized biomaterials, and medical devices. Small quantities of pharmaceutical items with customized doses, forms, sizes, and release characteristics may be created using 3D printing in the industry. [Angeliki Siamidi *et al*, 2019]. A manufacturing process called 3D printing involves building up an object layer by layer. Fused deposition modeling (FDM), hot melt extrusion (HME), solid state extrusion (SSE), stereolithography apparatus (SLA), digital light processing (DLP), selective laser sintering (SLS), vat polymerization, and binder jetting are just a few of the processes it uses. [Lifeng Kang *et al*, 2020]. The US Precisions Medicine Initiative was created in 2015 with the aim of understanding how a person's genetic composition, surroundings, and way of life can impact the most suitable approach for preventing or treating illnesses. The UK healthcare agenda has also elevated the practice of personalized medicine to the forefront. A paper titled "Improving outcomes through personalized medicine" was released by the NHS in 2016; In recent times, the UK government has published the "UK Genome Strategy 2020" and the "Life Sciences Vision 2021," both of which give priority to personalized medicine as a crucial aspect of healthcare provision. In February 2021, the FDA granted approval for a clinical study involving the use of a

3D-printed drug for individuals suffering from rheumatoid arthritis. [Abdul W Basit *et al*, 2022]. Three-dimensional (3D) printing technologies are generating a lot of attention in both the academic and industrial sectors. This technology is in no way unaffected by industries like aircraft, engineering, FMCG, architecture, the military, the fashion sector, the chemical business, or the medical area. Applications for 3DP include designing tissues, printing organs, performing diagnostics, producing biomedical equipment, and designing medication and delivery systems for the medical industry. Additional applications of this technique include the replacement and repair of damaged organs like the kidney, heart, etc., as well as the creation of a whole new organ that performs the same tasks as the original organ. Examples of everyday items that can be produced using this technology include clothing, eyeglasses, jewellery, auto parts, and pharmaceuticals. These items can be printed in various shapes and geometries to meet the user's specific requirements. [Asad Ali *et al*, 2020]. Pharmaceutical formulation development is paying more and more attention to 3D as a practical solution to several problems with traditional pharmaceutical unit operations. The conventional manufacturing procedure involving milling, mixing, granulating, and compression has the capability to generate final products with diverse drug loading, drug release, drug stability, and pharmaceutical dosage form stability. The design and manufacture of complex items with previously unheard-of flexibility thanks to 3D printing technology may now be employed in customized and programmable medicine. Multiple dosage forms with active components can greatly benefit from 3D printing, whether it is a single mixture or multi-layer

printed tablets that have sustained release properties. As a result, the patient consumes less dosage form units regularly and less often. The polypill idea, which involves creating customized dose forms, has great promise for 3D printing technology. This presents the possibility of consolidating all the necessary medications for the treatment into a single dosage form. [Dr. Shaikh Siraj *et al*, 2019]. The initial pharmaceutical product to be granted FDA approval for 3D printing technology was SPRITAM, a pill containing the active ingredient levetiracetam. The Zip Dose technology, which relies on a layer-by-layer powder bed fusion mechanism, was used to create the product. [Shankhadip nandi *et al*, 2020]. In the inkjet printing sector, UV curing is frequently employed to quickly firm materials as needed. In this approach, the ink contains cross-linkable functional groups that are designed to be stimulated by light, often in conjunction with a photo initiator. [Elizabeth A. Clark *et al*, 2017]. This method offers several advantages compared to traditional methods of manufacturing pharmaceutical products. These include faster production rates thanks to efficient operating systems, the ability to accurately and precisely load powerful drugs in small doses, reduced material waste leading to lower production costs, and the ability to work with a wider range of pharmaceutical active ingredients that have poor solubility. [Ravikumar Tamil Ponni *et al*, 2020]. This research endeavor seeks to demonstrate the feasibility of employing this technology in routine commercial manufacturing. It

will investigate distinct 3D printing methodologies that are appropriate for pharmaceutical production and their potential application in the creation of pharmaceutical dosage forms. [Byeong Ju Park *et al*, 2018].

HISTORY:

The concept of 3D printing is now widely acknowledged for its expanding applications. In 1983, Charles Hull made a significant contribution to the field of 3D printing by inventing, patenting, and introducing the first-ever 3D printing machinery. This groundbreaking achievement earned him the esteemed title of the father of 3D printing. Hull's innovative technique, known as stereolithography, involved the utilization of a laser to cure a liquid resin and gradually build up layers, ultimately resulting in the desired shape. Subsequently, in 1988, Charles Deckard submitted a patent application for selective laser sintering, a process that employs a laser beam to fuse deposited powder on a bed. This method involves lowering the powder bed, adding fresh powder, and repeating the process to fabricate a solid object. Scott Crump applied for a patent for fused deposition modeling in 1989, which involves layering and solidifying substances to achieve the desired shape. In the year 2015, the Food and Drug Administration (FDA) granted approval for Spritam, a prescription medication that marked a significant milestone as the inaugural pharmaceutical product manufactured through the utilization of 3D printing technology. This groundbreaking development aimed to address specific forms of seizures. The advancements in 3D printing technology continue to progress. [Angeliki Siamidi *et al*, 2019].

Table 1. Pharmaceutical products created using three-dimensional technology. [Asad Ali *et al*, 2020].

The utilization of three-dimensional (3D) printing technology	Formulations	API
Semi-solid extrusion (SSE)	Bi-layered tablets (polypill)	Guaifenesin
	Multiactive tablets (polypill)	Nifedipine, Glipizide, and captopril
Stereolithography (SLA)	Hydrogels	Ibuprofen
	Facial mask	Salicylic acid
Selective layer sintering (SLS)	Tablets	Paracetamol
	Drug delivery device	Progesterone
Fused deposition modeling (FDM)	Tablets	Hydrochlorothiazide
	Oral films	Aripiprazole
	Caplets	Caffeine
Binder jet printing	Tabular devices	Methylene blue and alizarin yellow (dyes)
	Cubic tabular devices	Pseudoephedrine
	Tablets	Chlorpheniramine maleate and fluorescein
	Orodispersible tablets	Levetiracetam
Inkjet 3D printing	Implant	Levofloxacin
3D printing machine	Multidrug implant	Rifampicin and isoniazid
Inkjet 3D printing	Nanosuspension	Folic acid
Thermal inkjet (TIJ) printing	Solution	Salbutamol sulfate
Inkjet 3D printing	Nanoparticle	Rifampicin

ADVANTAGES OF 3D PRINTING:

1. Manufacturing oral dosage forms using 3D printing (3DP) techniques offers numerous benefits, particularly in the context of personalized medication delivery. This approach allows for the incorporation of the active ingredient into the dosage form based on the specific needs of each patient, enabling the attainment of a customized dose and release profile.
2. The utilization of 3D printing has been employed in the production of pharmaceutical combinations with intricate release profiles, encompassing multiple active substances. This innovative technology enables the fabrication of personalized products with distinctive geometries and designs, a feat that would prove challenging to accomplish through conventional tablet manufacturing techniques.
3. 3D printing technology has demonstrated superior efficiency compared to traditional manufacturing methods, particularly in the fabrication of implants and prosthetics. Moreover, it presents advantages such as enhanced resolution, consistency, accuracy, and reliability.
4. One of the revolutionary benefits of this technology is the ability to produce specialized medical items and equipment. Tailored surgical instruments, implants, prosthetics, and fixtures can greatly assist both patients and doctors.
5. 3D printing allows for cost-effective production of objects, making it beneficial for small-scale manufacturing operations.
6. 3D printing technology enables the attainment of meticulous regulation over droplet dimensions, intricate drug release patterns, dosage potency, and the capacity to administer multiple doses. [Asad Ali *et al*, 2020].
7. Small-scale production is feasible, and the entire process can be accomplished in a single operation.
8. Three-dimensional (3D) printers are readily available and occupy a small footprint.
9. Prevents batch-to-batch variability found in traditional dosage form manufacture in bulk.
10. Because of the versatile design and production of this dosage form, it makes it easier to choose the appropriate treatment regimen for a particular patient because immediate and controlled release layers may be mixed.
11. Treatment can be tailored in cases of multiple medication therapy with multiple dose regimens to increase patient adherence.
12. High medication filling capacity compared to dose forms with known composition.
13. Accurate and accurate administration of strong medications that are given in tiny amounts.
14. Reduces production costs by reducing material waste.
15. Appropriate drug delivery for active components that are difficult to manufacture, such as those with low water solubility and medications with a narrow therapeutic window.
16. Based on the genetic variations, ethnic diversity, age, gender, and environmental factors, it is possible to tailor medical treatments to suit individual patients in specific circumstances.
17. The usage of 3D printing for low stability pharmaceuticals, transportable military installations, and hospitals may be appropriate.
18. When creating dose forms for clinical studies, 3DP might be quite helpful.

19. Improved methods are used for poorly soluble API dissolution.
20. The contact surface area can be enhanced through the implementation of various techniques such as printing structures with hollowed or highly porous characteristics, which can lead to increased rates of disintegration and dissolution. Additionally, the utilization of 3DP extrusion techniques allows for the filling of internal holes with loose powders, further augmenting the contact surface area. [Dr. Shaikh Siraj *et al*, 2019].

DISADVANTAGES OF 3D PRINTING:

1. Some 3D printing methods can produce structures with many holes and inconsistent shapes for medication.
2. Using only stable medications and easily available excipients is a constraint when using the fused deposition modeling method.
3. UV light-induced polymerization in stereolithography can potentially lead to drug degradation. [Angeliki Siamidi *et al*, 2019]. Inkjet printing requires ink with a particular thickness in order to achieve the correct ink flow.
4. The ink's composition should allow it to adhere to itself but not to other parts of the printer. If the ink lacks the ability to bind to itself or if it binds to other printer components, the resulting formulation will not have the required level of hardness.
5. The rate at which medication is released may be affected by the way ink binds with other printer materials. [Asad Ali and others, 2020].
6. When choosing raw materials, it is crucial to conduct a comprehensive assessment of their printability, physicochemical properties, thermal conductivity, print fluid characteristics, and viscoelastic material. Furthermore, it is essential to evaluate the appropriateness of the raw materials for human consumption.
7. Powder-based 3D printing necessitates a more specific or exclusive area due to the potential danger of powder spillage, which can present occupational risks. The material utilized for creating the ink must possess the capability to adhere to itself while avoiding bonding with other parts of the printer.
8. If the ink in a specific formulation lacks sufficient self-binding capability or fails to bond with other printer components, it will create foam.
9. In 3D dosage forms, particularly those utilizing powder-based methods, there is an increased susceptibility to friability. The manufacturing technique employed plays a crucial role in determining the strength of the dosage form.
10. Compared to conventional tablet compression techniques, the range of materials, color choices, and surface finishes accessible for 3D printing is relatively restricted.
11. The dosage form's layers are formed through 3D printing with a nozzle mechanism. The printer head pauses and resumes to ensure a steady flow of printing material during the creation of each layer.
12. In certain situations, it may be necessary to use post processing methods like hot air drying, microwaves, or infrared sources to remove any remaining solvents from the final product.
13. Boundaries become a significant consideration when considering polypills, particularly with regards to the quantity

of active pharmaceutical ingredients (APIs) employed and the overall dimensions of the end product. [Dr. Shaikh Siraj *et al*, 2019].

Principle of 3d Printing:

A 3D printer operates in a similar way to a standard printer. It uses an extruder to build the foundation of an item, which moves horizontally on one axis and back and forth on two other axes. The printer's base moves vertically to construct layers on top of the item. The extruder remains at the top and prints the first layer in 2D. The base then gets shorter to add the next layer. This process continues layer by layer, guided by computer-aided drawing instructions. It is also known as rapid prototyping, solid freeform technology, and additive manufacturing. 3D printers can create different porous scaffolds with specific chemistry, porosity, and shapes. These prints are biodegradable and have been found to be effective in drug delivery. This technology is increasingly used in cancer treatment to create complex structures with live cells. Various drug delivery systems, such as oral controlled release systems, micropills, microchips, drug implants, quickly dissolving tablets, and multiphase release dosage forms, have been developed using 3D printing technology. [Dr. Shaikh Siraj *et al*, 2019].

Different methods employed in the process of 3D printing

Whatever the 3D printing method used, the process has three fundamental steps: the creation of a computer-aided design file, its conversion to a rapid prototyping stereolithography file (stl), which describes the surface geometry of the 3D object, and finally its conversion to a machine specific code (gcode), which is recognized by the 3D printer machine and produces the finished object. [Angeliki Siamidi *et al*, 2019].

Classification of 3d printing:

1. Inkjet printing method
2. Fused deposition method
3. Direct inkjet writing method
4. Zip dose method
5. Thermal inkjet printing method
6. Binder deposition method
7. Material jetting method
8. Extrusion method
9. Powder bed fusion method
10. Photo polymerisation method
11. Pen based 3DP method
12. Direct energy deposition method
13. Sheet lamination method

Several types of 3D printing technologies employed in the field of pharmaceutical drug delivery.

Inkjet Printing:

The method entails the precise application of small droplets of active ingredient and excipient mixtures (ink) onto a non-powder substrate. The ink is sprayed onto a powder foundation, which solidifies to form a solid dosage form. This technique is commonly referred to as powder-based 3D printing.

Fused deposition method:

Various pharmaceutical formulations, such as implants, zero-order release tablets, multi-layered tablets, and fast-dissolving devices, incorporate polymers as integral components of their structural composition. The manufacturing process entails melting the

desired polymer and extruding it through a heated nozzle that is in motion. The polymer is typically dispensed layer by layer along the x-y-z axis, subsequently solidifying to assume the predetermined shape as determined by computer-aided design models.

Direct inkjet writing method:

The process involves the utilization of a computer-controlled translational stage to manipulate a pattern-generating tool, enabling the sequential fabrication of a three-dimensional microstructure layer by layer.

Zip Dose method:

This method enhances the delivery of a substantial amount of medication by incorporating a modified dosage into a highly porous material, resulting in increased rates of disintegration and dissolution.

Thermal inkjet (TIJ) printing method:

The thermal inkjet (TIJ) system utilizes a micro-resistor to generate heat, which in turn warms a small amount of ink fluid stored in the ink reservoir. This heating process leads to the formation and expansion of a vapor bubble, ultimately resulting in the ejection of an ink droplet through a nozzle. The TIJ system offers the potential to administer spontaneous medication preparations or solutions onto 3D scaffolds.

Binder deposition method:

Using a method called binder jetting, the printers lay down layers of a binder until the item is finished on a bed of sand. The final component is then created by pouring molten metal into the 3D-printed sand item. The sand is broken up after cooling to reveal the necessary metal component.

Material jetting method:

The procedure of fabricating objects through material jetting bears resemblance to that of a 2D inkjet printer. In this process, material is propelled onto a construction platform employing either a continuous or drop-on-demand technique. The sculpture is constructed incrementally as the material is dispersed onto the build surface or platform and subsequently undergoes solidification.

Extrusion method:

The procedure entails the sequential deposition of heated material layers through a nozzle, with horizontal movement of the nozzle and vertical movement of the platform occurring after each layer is added. This technique is frequently employed in cost-effective, domestic, and recreational 3D printing devices.

Powder Based fusion method:

This method involves using powder jetting and a powder bed to evenly distribute thin layers of powder, while inkjet printers are used to instantly add liquid binder droplets. In the context of a two-dimensional (2D) manufacturing process, the deposition of ink, comprising binders and APIs or binder solutions, onto a powder bed is employed to fabricate the end product in a sequential layer-by-layer manner. Given the prevalent use of powders and binder solutions in the pharmaceutical sector, this method exhibits greater feasibility and versatility for pharmaceutical manufacturing when compared to alternative approaches. However, there are some drawbacks to this approach, such as the need for additional drying to remove solvent residues, the accumulation of excess powder during printing leading to waste, and the potential for insufficient

mechanical strength in the drug delivery system due to the porous nature of the powder. [Ravikumar Tamil Ponni *et al*, 2020].

Photo polymerisation method:

The application of ultraviolet (UV) light to induce the solidification of photosensitive resin is a widely employed technique in various 3D printing technologies, such as Stereolithography (SLA), Multijet printers, and 3D Digital Light Processing (DLP).

Pen based 3DP method:

Using a PLA filament that has been softened, a 3D printing pen can create solid 3D objects. PLA is a thermoplastic polymer that melts between 170 and 210 degrees Celsius. It is a biodegradable polymer that has just lately been more well-known in the medical community and has been proven to have no negative effects on the body. [Sarah J. Trenfield *et al*, 2018]

Direct energy deposition method:

The material is available in either wire or powder form, and it is subsequently melted through the use of a laser, electron beam, or plasma arc after deposition. To enhance or restore desired properties of an existing object, additional material is applied in a sequential manner and undergoes solidification.

Sheet lamination method:

In the sheet lamination technique, multiple thin sheets of material are adhered together in a sequential manner, resulting in the formation of a unified structure. This composite structure is subsequently divided into a three-dimensional object through slicing.

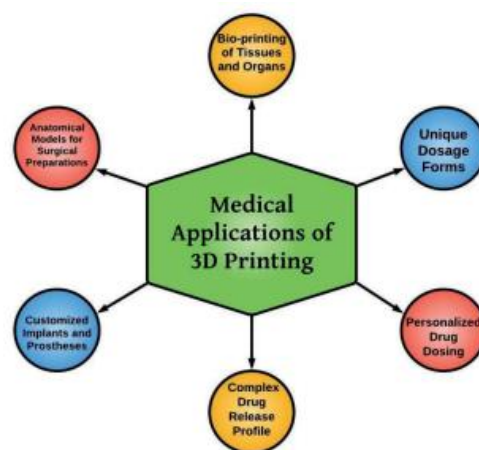
Medical applications of 3D printing:

Personalized drug dosing:

Therapeutic development should focus on enhancing therapeutic efficacy while simultaneously lowering the likelihood of adverse reactions, which can be done by creating customized pharmaceuticals utilizing 3D printing. Tablets are the most commonly used form of medication because they are easy to prepare, patients find them easy to take, they provide accurate dosing, and they do not cause any discomfort. In the production of oral tablets, a process is employed where in powder ingredients are combined, ground, and granulated. Subsequently, these granules are compressed to yield the final tablet form. However, there is currently no means for creating individualized solid dose forms like tablets. If suitable procedures are not followed while making tablets the conventional method, medicines can readily degrade, changing the end product's medicinal usefulness. Additionally, these traditional techniques cannot be utilized to create bespoke dosage forms with new drug release profiles, long-lasting stability, and precise geometries. Utilizing 3D printing, it is simple to create medications with narrow therapeutic indices. The ideal dosage may then be administered to the patient by taking into account their pharmacogenetic profile as well as other factors like age, race, and so on. Another important use for 3D printing is the creation of brand-new formulations, such as printed tablets with many reservoirs or pills with a combination of several active medicinal ingredients. Consequently, individuals suffering from multiple ailments can have their medication compounded into a single multi-dosage form directly at the healthcare facility. This approach allows for the provision of a personalized and precise dosage, thereby enhancing patient adherence and compliance.

Bioprinting of tissues and organs:

Failure of organs and tissues due to accident, congenital flaws, age, etc. is one of the most serious medical problems, and the current cure is organ transplantation from deceased or live donors. Only a select few fortunate individuals obtain organs, while the majority pass away from lack of donors. Additionally, the costs associated with organ transplant treatments put them beyond the means of the average person. The challenge of finding tissue-matched donors poses a significant obstacle in the field of transplant surgery. However, this issue can potentially be addressed through the creation of tissue or organs using the patient's own cells. This approach would not only decrease the likelihood of tissue or organ rejection but also reduce the reliance on immunosuppressant drugs. One prominent technique in tissue engineering involves the extraction of stem cells from a small tissue sample, which are then combined with growth factors and multiplied in a laboratory setting. These cells are subsequently placed onto scaffolds that regulate cell division and proliferation, ultimately leading to the development of functional tissue. Compared to traditional tissue engineering methods, 3D bioprinting offers advantages such as precise cell placement, digital control of various parameters including speed, drop volume, precision, concentration, and diameter of printed cells. The choice of materials for scaffold construction depends on factors such as porosity, intended tissue support, and required strength. Hydrogels are considered particularly suitable for constructing soft tissues. While organ printing is still in its early stages of development, several studies have provided supportive evidence for its potential. Using 3D printers, scientists have created prosthetic heart valves, cartilage, and bone. Wang *et al.* created an artificial liver by depositing diverse cells into various biocompatible hydrogels using 3D bioprinting technology. Due to the immense potential of this technology and the growing attention of researchers and academics, it may reveal new possible medicinal medications, drastically reducing the cost and time of research.



Customized implants and prostheses:

The utilization of MRI, CT scan, and X-ray images, along with their conversion into stl 3D print files, enables the creation of implants and prostheses in various shapes. This technology allows for the rapid production of prosthetic limbs and surgical implants within a 24-hour timeframe. While the development of hip and spinal implants has already been achieved, the validation process

requires additional time. Previously, medical professionals had to fabricate customized metal and plastic components, perform bone grafting procedures, or modify implants using drill machines in order to achieve the precise shape and size required. However, with the aid of MRI, CT scan, and X-ray images, and their subsequent conversion into stl 3D print files, implants and prostheses of any shape can now be conceptualized and manufactured. It is possible to create prosthetic limbs and standard or sophisticated surgical implants in as little as 24 hours. Although hip and spinal implants have already been created, validating them takes time. Previously, doctors had to create custom metal and plastic parts, perform bone grafting, or alter the implants using drill machines in order to acquire the required shape and size that fits precisely. Given the individuality of each person's ear canal, this technology offers an optimal solution for every user, while also enabling efficient and cost-effective production. The significance of this technological advancement in the realm of hearing aids is such that presently, 3D printers are employed to fabricate nearly all personalized hearing aids. [Ali, A, Ahmad, U *et al*, 2020].

Unique dosage forms:

The application of 3D printing technology in the pharmaceutical industry allows for a wide range of dose formulations to be produced. Inkjet-based and inkjet powder-based 3D printing are the main techniques employed in this field. Notable examples of novel dosage forms created through 3D printing include microcapsules, micropatterns of antibiotics, scaffolds made of mesoporous bioactive glass, nanosuspensions, and synthetic extracellular matrices based on hyaluronan.

Complex drug release profile:

In conventional compressed dosage forms, a uniform blend of active components typically results in a straightforward medication release profile. However, 3D printed dosage forms offer a more intricate drug release profile, allowing for the creation of complex structures with pores and the incorporation of multiple medications. These structures are surrounded by barrier layers that regulate the release of the drugs. For instance, a bone implant can be 3D printed with alternating release profiles of rifampicin and isoniazid, resulting in a pulse release mechanism. In another application, 3D printed antibiotic micropatterns on paper have been utilized as implants to eradicate *Staphylococcus epidermidis*. Moreover, the application of 3D printing technology to deposit chlorpheniramine maleate onto a cellulose powder substrate in minute quantities has exhibited the capability to achieve controlled release of medication at predetermined intervals. This enables the investigation of drug release kinetics. Comparing this study's findings to those of drugs that are typically made, it showed better precision for the release of extremely tiny pharmacological dosages.

Anatomical models for surgical preparations:

Due to variances in unique and complicated human anatomy, understanding of patients' personal anatomy prior to medical surgery is crucial for effective medical treatments. In this regard, 3D printed models have been quite helpful, turning them into a crucial tool for surgical techniques. The human skull is one of the body's most intricate structures, and 3D printed neuroanatomical models are quite useful to neurosurgeons. Even a minor error during a medical procedure can have severe consequences due to the complex relationships between brain structure, cranial nerves, and arteries that are difficult to discern from 2D radiography

images alone. To address this challenge, the use of 3D models has become crucial. These models provide a more realistic representation and allow for a detailed comparison between a normal brain structure and one with lesions, enabling surgeons to adopt safer techniques. For instance, Kobe University Hospital in Japan utilized 3D printed liver transplant models to investigate the most precise method of creating a donor liver with minimal tissue loss. Similarly, surgeons employed a 3D printed model of a calcified aorta to plan their surgical procedures for plaque removal. Using 3D printing technology, the airways of preterm newborns were recreated in order to evaluate the administration of aerosol drugs to the lungs. [Asad Ali *et al*, 2020].

Oral Solid Dosage Forms:

Controlled Release:

A drug's release from its dose form is crucial to its subsequent absorption and therapeutic impact. The majority of oral dose formulations require immediate release (IR) for the medicine to be absorbed. Contrarily, sustained release enables the gradual release of medicinal substances, minimizing changes in drug level brought on by taking various IR dosage forms on a regular basis. This could aid in healing or be convenient for the patient. The absorption process occurring in the gastrointestinal tract can lead to a reduction in the surface area of conventional sustained release tablets, resulting in inconsistent release of the drug. To address this issue, additive manufacturing (AM) techniques can be employed to produce tablets with complex shapes that facilitate consistent and sustained drug release profiles, as well as customized release profiles. In a study conducted by Zhao *et al.*, poly (vinyl alcohol) (PVA) was utilized to print a spherical shell with an empty interior tetrahedron hollow using a fused deposition modelling (FDM) printer. Subsequently, the PVA shell was filled with a combination of PVA and medication. Upon contact with water, the tablet eroded from the four corners inward, gradually revealing a larger portion of the tetrahedral-shaped core. This erosion process accelerated the breakdown of the drug over time. This accelerated drug release may be advantageous for certain conditions, such as hypertension, where patients can take the pill at night and experience the highest concentration of medication in their blood in the morning. Another example of AM application is demonstrated by Kadry *et al.*, who used an FDM printer to create tablets with varied infill patterns. By extruding a powdered combination of diltiazem and hydroxypropyl methylcellulose (HPMC), drug-impregnated filaments were successfully produced. The results of the study indicated that tablets with hexagonal infill designs exhibited a faster disintegration rate. This finding aligns with the research conducted by Yang *et al.*, who also observed that the pattern of tablets influenced the rate of medication release. In their study, tablets were produced using an FDM printer with ethyl cellulose and ibuprofen filaments. Furthermore, it is well-established that the relationship between surface area and drug release rate allows for the development of tablets with different release profiles. Khaled *et al.* printed tablets of various shapes using a 3D extrusion printer, with the printing ink consisting of a combination of paracetamol and excipients. Their findings demonstrated that tablets with larger surface areas released the medication at a faster rate. Similarly, Cui *et al.* utilized a mixture of glipizide, poly (vinyl pyrrolidone) (PVP), and HPMC to create a paste, which was then printed at room temperature to produce tablets with varying grid widths. These tablets exhibited a consistent pattern of drug release.

Increasing the surface area has previously been employed to enhance medication release. Isreb et al. developed a unique radiator-like structure that possesses a surface area to mass ratio 7-8 times greater than that of conventional tablets. The thin plates of this "radiator" design were maintained to minimize the thickness of the gel layer formed upon contact with water, thereby facilitating drug release. In a separate study conducted by Fina et al., a bi-layer tablet was developed consisting of both an exposed lattice structure and a conventional infilled tablet. The lattice layer possessed a large surface area, enabling rapid release of the medication within a 30-minute timeframe. The researchers also investigated tablets with distinct drug release patterns. One such tablet, referred to as the "chrono-tablet," featured an inner core filled with the drug and an outer layer that delayed the release of the medication until a later time. Another tablet, known as the "pulsatile tablet," consisted of three layers, with the drug being carried by both the innermost and outermost layers. The middle layer, devoid of the drug, created a drug-free interval that could be adjusted between the release of the outermost and innermost drug-containing layers. The researchers also noted that excipients, in addition to the tablet's geometry, were found to influence the rate of medication release. In a separate study conducted by Tagami et al., Naftopidil tablets were produced using a semi-solid extrusion printer. The printing inks were created by combining varying amounts of HPMC, naftopidil, and different excipients. The tablets demonstrated an inverse relationship between the percentage of HPMC content and the rate of medication release. Furthermore, in a different trial, low dosage pramipexole tablets exhibited comparable release patterns to those of regular tablets, even without the inclusion of fillers or disintegrating agents. This new technology has also led to advancements in medication release theories. For instance, certain substances like cellulose are commonly used as carriers for medications in additive manufacturing. However, the Higuchi equation, derived from Fickian diffusion laws, cannot be applied to study drug release from these materials due to their expansion and resulting non-Fickian diffusion. Consequently, an extension of the Higuchi equation has been proposed to predict drug dissolution from such materials.

Polypills:

A growing number of patients, particularly elderly ones, are taking many medications, raising worries about medication mistakes because of the intricacy of the regimen. It's conceivable that some

illnesses, including cardiovascular disease, may call for the administration of many drugs. An individual's health results may be adversely affected by taking more drugs because of decreased adherence. Therefore, a polypill should potentially make a person's medication schedule simpler, resulting in improved patient convenience and adherence. A polypill with six active components was developed by Wald and Law in 2003 as a prophylactic measure to lower cardiovascular illnesses by more than 80%. The fact that it failed to take into account the various dose or combination requirements of various persons, or how such needs can change over time, as well as worries regarding chemical incompatibility between components, led to harsh criticism at the time. These concerns can be effectively addressed through the advancements in 3D technology. The mixture of medications in a polypill and their precise quantities can be customized to a person's present treatment regimen. Dosing accuracy is a minimal problem because 3D is an accurate procedure. Additionally, concerns with incompatibility can be resolved by compartmentalizing each medicine to a distinct section of the tablet or separating the pharmaceuticals with an excipient that is chemically compatible. Two-compartment capsular device made using FDM by Maroni et al. Different drug formulations or chemically incompatible medications can be delivered using this device. The dissolving profile was influenced by the thickness of the capsule. In a study conducted by Christos et al., the concept of compartmentalization was employed to create a tablet containing two anti-diabetic medications, namely metformin and glimepiride. This was achieved through the use of two nozzles in FDM printing, which generated two drug load filaments that effectively segregated the medications within the tablet. Pereira et al. took a more advanced approach by developing two variations of polypills, each containing four components: amlodipine, rosuvastatin, indapamide, and lisinopril. These polypills were designed with four layers, each layer serving a distinct purpose. Additionally, a third polypill was created by combining all four elements. The researchers reached a conclusion that the combination pill has the potential to save time and money by utilizing a single filament. However, concerns were raised regarding its stability. In contrast, the multilayered polypill showed the capability to accommodate various doses and allowed for the modification of the release profile by rearranging the layers in the stack.

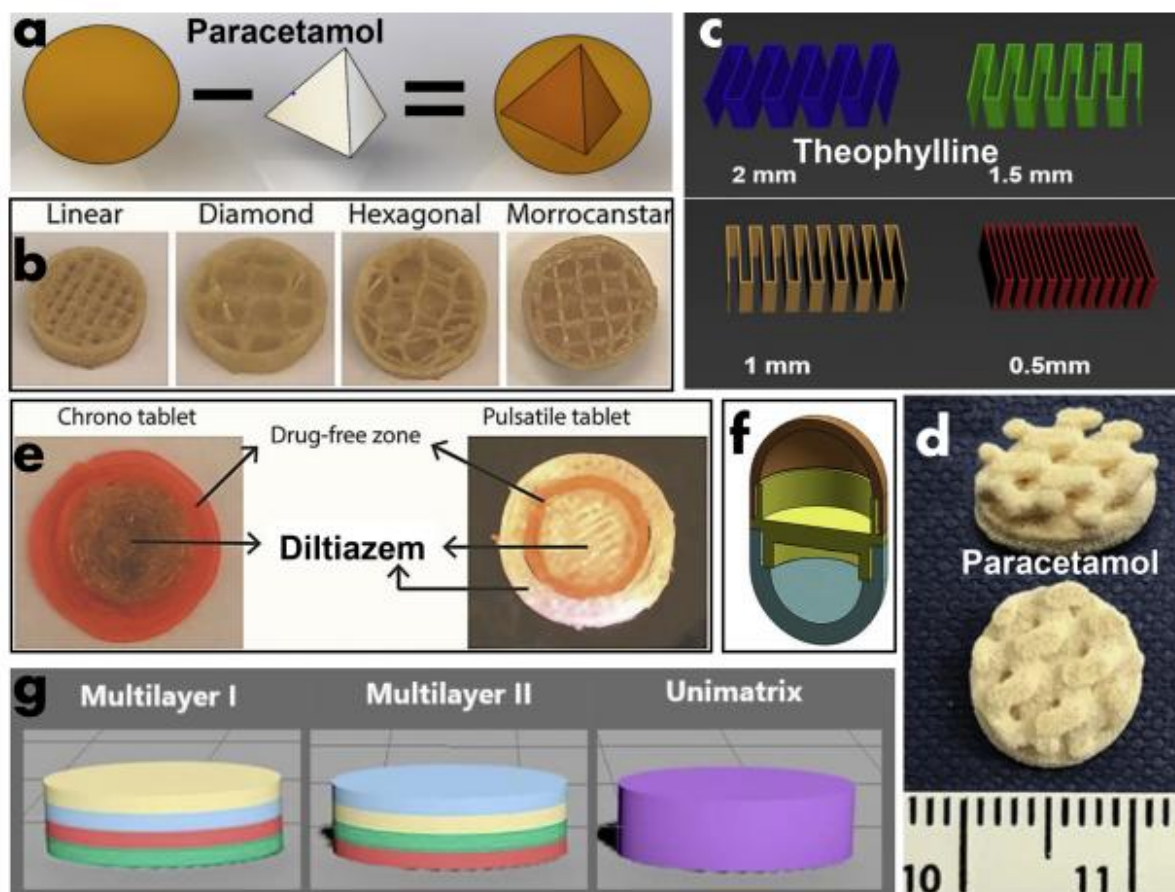


Figure 1 illustrates different oral dosage forms produced through 3D Manufacturing a) 3D printed shell b) Different infill patterns c) Radiator-like design d) Bilayer tablet with Different release profiles e) Chrono tablet and pulsatile tablet f) Polypill capsule

Gastrofloating:

Drugs taken orally are better absorbed in various parts of the gastrointestinal system depending on their chemical and solubility qualities. Dipyridamole is a medication that exhibits limited solubility, a characteristic that is influenced by the pH of its surroundings. Consequently, it is absorbed within the acidic milieu of the stomach. As a result, the primary determinant of its absorption is the stomach retention period. In order to prolong the duration of stomach retention, there exist two main categories of gastric floating devices. The two types of systems are non-effervescent systems that minimize bulk density to float and effervescent systems that employ CO₂ to sustain buoyancy. By altering the infill density parameter, AM can construct low density objects with ease. A method created by Huan Butta and Sangnim utilized a 3D-printed housing for a drug-loaded tablet core. The container's porosity made it easier for the drug to be released. Another method was utilized by Li et al., who created a number of lattice-filled dipyridamole tablets. HPMCs as hydrophilic matrices and microcrystalline cellulose as the extrusion moulding agent are

combined to create the printing ink, which is printed at room temperature using an extrusion-based printer. To examine the features of buoyancy and medication release rates, different infill rates were employed. Similar to the findings of Huan Butta and Sangnim, when lattice density grew, the rising weight caused the tablet to sink, which in turn led to an enhanced drug release rate. Chai et al. used hydroxypropyl cellulose (HPC), a cellulose-based substance, to produce hollow tablets based on FDM using an FMD printer. the medication, specifically. A hot melt extruder was used to integrate the medication, domperidone, into HPC filaments. The observed extended floating and release was caused by the low density and stiff shells. In a different investigation, tablets with various interior architectures were created using the pressure-assisted microsyringe (PAM), a unique AM technology. A range of typical pharmaceutical excipients, including lactose, microcrystalline cellulose, PVP, and HPMC, may be printed using PAM. The fact that these excipients are governed by laws for pharmaceutical uses makes it advantageous to utilize them as printing inks.

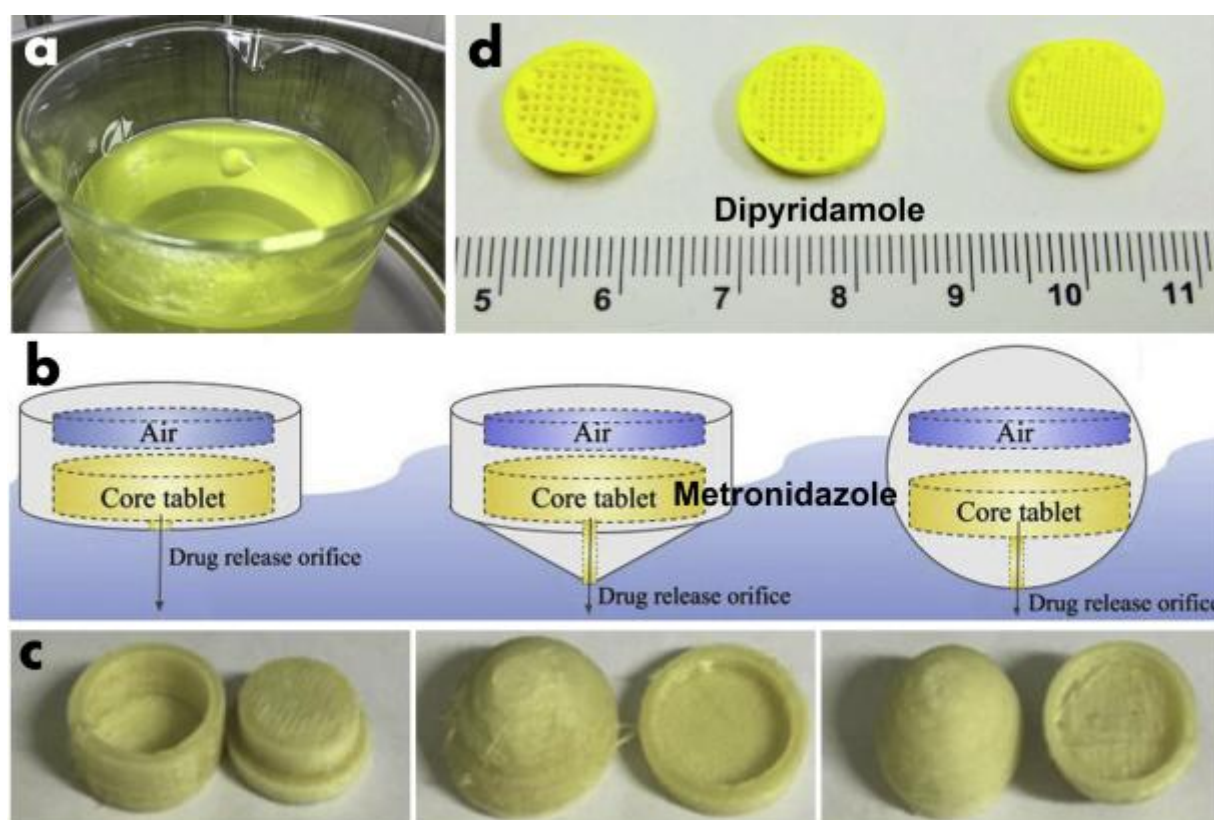


Figure 2 illustrates gastro retentive tablets a) Floating tablet b) Floating tablet with zero-order drug release c) 3D printed pockets for these tablets d) Different in fill percentages of 3D printed tablets containing Dipyridamole

Oro-Dispersible:

Oral kinds of medicine are the most popular and widely used by patients. However, certain people, especially children, the elderly, and those with dysphagia, may find it difficult to take oral forms such as tablets, capsules, and liquids. Oro-dispersible pills can be consumed without water since they are made to dissolve in the mouth. Oro-dispersible tablets often have a porous structure, leading to a rapid dissolving profile. By avoiding the high compression pressures required in traditional manufacturing, additive manufacturing (AM) creates a final structure that is much more porous and disintegrates more quickly. Spritam™, the first and only AM drug approved by the US Food and Drug Administration (FDA), was made using binder jetting and dissolves within 2-27 seconds. Tian et al. also used the same technique to produce oro-dispersible warfarin tablets, which disintegrated within one minute. Additionally, selective laser sintering (SLS) has been shown to successfully create orodispersible paracetamol tablets with varying dissolution rates.

Paediatric Preparations:

The pharmacokinetic and pharmacodynamic characteristics of the juvenile population are unique from those of adults. As a result, doses for this demographic must be carefully optimized to avoid severe side effects. Syrups can be used as pediatric formulations and can be dose-adjusted, although many of them have disagreeable flavors and are prone to dosing errors. A mini printlet, a 3D-printed little tablet, is a creative solution to this issue. A micro tablet may be simpler to give than syrups because of its smaller size and milder flavor. Furthermore, by regulating the quantity of

material utilized, AM may be used to modify doses. SLS or FDM have been used to demonstrate its viability. To make administration even simpler, it is also feasible to mix many prescriptions into a single mini printlet. The swallowing motion is also influenced by the tablet's form. This might be modified for usage in groups like children, the elderly, those with dysphagia, etc. who have trouble swallowing conventional pills. Scoutaris et al. suggested another dose form for young children, which consisted of fun-shaped chewable tablets with a masking flavor. In this work, hot melt extrusion was used to promote H-bonding interactions between the medication and polymer, which helped to hide indomethacin's unpleasant taste. To appeal to younger children, interesting forms were printed using the drug-loaded filament that had been created in a 3D printer.

Transdermal Microneedle (MN) Patches:

Transdermal drug delivery involves administering medication through the skin. Transdermal distribution is restricted mostly by the skin's own stratum corneum. MNs are an effective method for delivering medicines through the skin by creating tiny passageways through the skin using an array of needles that are a few hundred microns in diameter. Traditional manufacturing processes, including microfabrication or molding, are intricate and need several stages. In order to do this, AM technologies, particularly SLA and DLP, provide MN production alternatives. Biocompatible liquid resin was printed using a SLA printer into MN patches, and any leftovers were subsequently cleaned off with alcohol. After that, inkjet printing was used to place tiny layers of insulin-sugar onto the MN surface. A SLA printer was used by Uddin et al. to

create polymeric MNs, which were subsequently coated with cisplatin formulations. The mechanical strength, buckling load, and force necessary to puncture human skin have all been demonstrated to be crucial for producing MNs using SLA printers. MNs can be tailored to fit curved surfaces through the process of printing, a capability that is not achievable using traditional production methods without the aid of additive manufacturing (AM). In a study conducted by Lim et al., a DLP printer was utilized to create MN patches with varying curvatures, mimicking specific regions of the human facial structure. By ensuring consistent distribution of the pressures necessary for skin penetration, it was observed that the utilization of curved MNs that conform to facial features resulted in enhanced skin penetration and improved efficacy of drug delivery.

In addition to direct MN production, MN masters printed on DLP printers have been cast with polydimethylsiloxane (PDMS) to produce moulds. A magnesium microparticle-loaded active MN patch was created using the PDMS mold for quicker and deeper intradermal medication administration. This work serves as an illustration of the high resolution—a few microns—a cheap DLP printer is capable of printing utilizing photo cross linkable polymers. SLA may also be used to create hollow MNs in addition to solid MNs. Yeung et al. incorporated hollow MNs in microfluidic designs. The MNs and microfluidic channels were created as a single unit and printed together. The ability of AM to produce functionally disparate pieces collectively without

additional assembly shown by this integrated design. Instead of being connected to a syringe in this instance, the hollow MNs can be utilized directly for injection via the associated microfluidic channels. Liquid pre-polymer solutions that can be crosslinked through photo crosslinking can be utilized for printing microneedles (MNs). In order to achieve high resolution, the pre-polymer solutions contain macromers and photo initiators such as methacrylic oligomer, glycol methacrylate, pentamethyl piperidyl sebacate, and phosphine oxide. Moreover, riboflavin-sodium persulfate-hydroquinone, a combination of initiator, catalyst, and inhibitor, has been identified as a potential photosensitive composition for keratin printing. This composition can be employed for topical applications utilizing hydrogels, as an alternative to microneedles.

Regarding MN printing technology, it should be remembered that vat printing, or the exposure of liquid polymers to ultraviolet or visible light to transform them into solids, is a widespread technique that prints 3D things. High resolution, which is required to produce MNs with pointed ends for skin penetration, is a benefit of vat printing. Vat printing, however, also has drawbacks in comparison to molding. A variety of materials can be employed for the molding procedure, although the candidate materials are only allowed to be photocrosslinkable polymers. Second, photo initiators are present in the photocurable polymer solutions, which raises questions due to their possible toxicity.

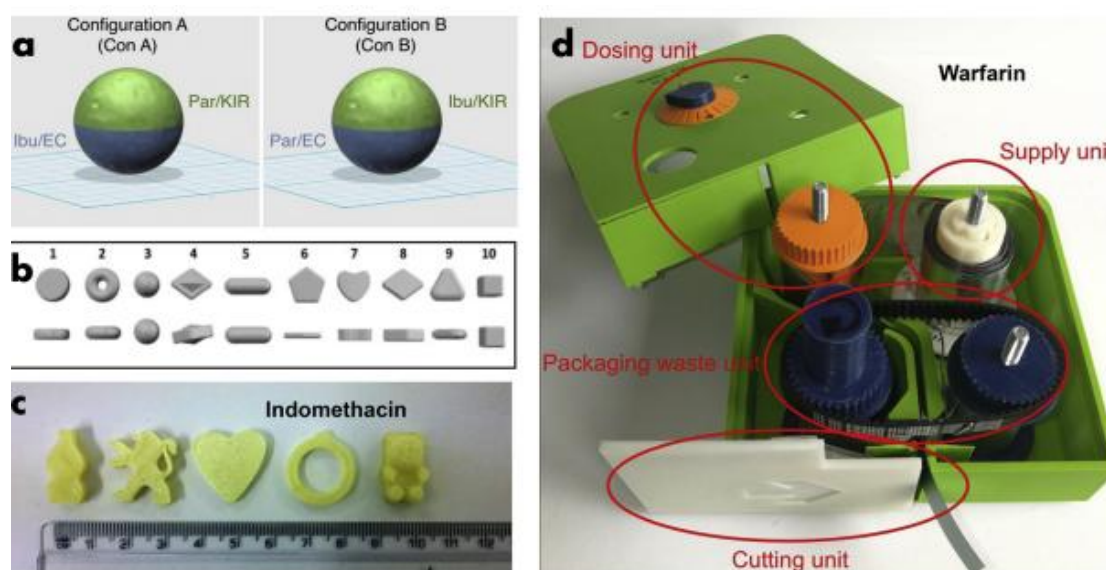


Figure 3 illustrates various designs that can assist in medicine dispensing. (a) Combination pill with ibuprofen and paracetamol. (b) Various tablets shapes (c) Three-dimensional chewable tablets for paediatrics (d) A three-dimensional printed warfarin film dosing tool

Pharmaceutical Devices

Dose Dispensing Aids:

AM is commonly used for creating prototypes, especially outside of the pharmaceutical industry. In the past, prototyping required expensive and time-consuming custom-made dies or moulds. However, AM allows for the rapid and simple creation, modification, and reprinting of highly customized models. It is a cost-effective method that does not require specialized equipment. Furthermore, there are now biodegradable and environmentally friendly materials readily available, reducing the environmental

impact. AM has also become a powerful tool for developing prototypes of pharmacy dispensing equipment for individualized treatment. Niese et al. created a prototype of a pharmacy dispensing system that utilized a continuous film filled with an active substance. The prototype included various components such as a dosing dial unit, cutting unit, supply unit, and waste packing unit, all manufactured in accordance with the European Pharmacopoeia. The device allowed for variable dosage and individualized treatment, with the supply unit rolling out the dosage as directed by the dosing dial. The strip containing the drug

was distributed through a designated opening, while the packaging waste was enclosed separately. This device is categorized as Class 1 based on its cost-effectiveness, lack of electrical elements, and ability to accommodate a wide range of dosages.

Drug Eluting Devices:

The necessity for frequent dosing in patients is decreased by drug eluting dosage forms, which enable the sustained release of a therapeutic agent for a significantly longer time than oral dosage forms. This significantly reduces issues with non-adherence, whether deliberate or not. This local delivery method can lessen the exposure of healthy tissues to the medication as compared to systemic distribution, lowering the likelihood of negative consequences. When compared to alternative delivery methods, employing an implanted device might sometimes offer more advantages. For instance, sustained release devices are not linked with the consequences of intraocular injections, which include increased ocular pressure. Currently on the market, drug eluting implants can be used for a variety of conditions, including opioid addiction, cardiovascular illness, ocular delivery, peritoneal delivery, and contraception. The shapes, components, and doses of the formulations that are readily accessible are, however, constrained. By adjusting the dose, shape, and drug release profile of the dosage forms, AM can be employed to get around this. The most recent advancements in this field include drug-eluting catheters, cancer therapy implants, hormone-containing dose forms for gynaecological purposes, and implants for cancer therapy.

FDM has been utilized to create constructions that elute hormones. Utilizing biodegradable polymers of polycaprolactone (PCL), Tappa et al. created adaptable devices. With the use of an extruder, the medications, which included progesterone and estrogen, were enclosed in the filaments. In this investigation, three different dosage form types—subcutaneous implants, intrauterine devices, and pessaries—were created. In spite of the need for elevated temperatures to facilitate the melting of filaments in the printing procedure, research has demonstrated the potential of Fused Deposition Modelling (FDM) for the fabrication of drug-loaded filaments. In a separate study, Fu et al. successfully employed FDM to manufacture programmable progesterone vaginal rings with controlled release properties, varying in shape and dosage. To produce filaments, the pharmaceutical compound progesterone was blended with poly (ethylene glycol) PEG 4000 and subsequently extruded with PCL and poly (lactic acid) (PLA). The resulting vaginal rings exhibited sustained release of progesterone for a duration exceeding seven days. In a separate study, the notion of customized suppositories was advanced through the utilization of a Fused Deposition Modelling (FDM) printer to fabricate water-soluble suppository shells that could be customized to achieve the desired release profile of the active drug. The suppository shells

were created using PVA filament and printed with holes of different sizes and densities before being filled with progesterone-containing drug-laced macrogels. Another sort of formulation created was a suppository in the shape of a matryoshka doll with many layers, each holding a separate medicine. The preparation of suppositories using traditional manufacturing techniques is difficult because different medicines have different release rates. On the other hand, this is simple to do using a 3D printer. A reasonably straightforward tool for manufacturing pharmaceutical preparations is provided by AM technology, which may be utilized to deliver individualized medicine. In addition to gynaecological uses, 3DP implants were created for anti-cancer therapy. To avoid difficulties following surgery, Cho et al. printed a nanogel disc holding medications. To make the printing ink, paclitaxel and rapamycin were combined with a thickening agent called poloxamer 407 to create a sol. After then, a disc-shaped version of the sol was produced. To eliminate any remaining tumour tissues and avoid peritoneal adhesions following surgery, the drug-filled disc can be placed intraperitoneally. Similar to this, Farto-Vaamonde et al. added medications to filaments at various points during manufacturing, such as before printing (resulting in a sustained-release profile) or after printing (resulting in an instantaneous release profile). These two methods were combined to produce a scaffold that was impregnated with two separate medicines, one with a quick release and the other with a long release. Prednisolone has an anti-inflammatory impact in the scaffold, but dexamethasone can stimulate osteogenic differentiation.

Additionally, there have been documented instances of drug eluting devices that are not implantable, such as orthodontic retainers that are loaded with clonidine. In order to create the filaments, the medication clonidine hydrochloride was combined with PEG 4000, PLA, PCL, and a non-ionic surfactant called Tween 80. The filaments were created into a retainer using an FDM printer using the measurements from a 3D scan of a willing human subject. When the retainers were subjected to a rinsing process using a buffered solution in order to eliminate any residual clonidine present on their surface, the initial burst-release followed by a sustained-release pattern of the original 3D-printed retainer was no longer observed. In a further investigation, the idea of producing customized catheters on demand was investigated. FDM was used to create catheters that were filled with methotrexate and gentamycin. Utilizing an extruder, the medicines were combined with PLA to create filaments. Catheters for gentamycin and methotrexate released their drugs continuously for at least five days. It was shown that AM has the ability to create catheters loaded with drugs for localized medication administration, including antibiotics and chemotherapeutics. [Lifeng Kang *et al*, 2020].

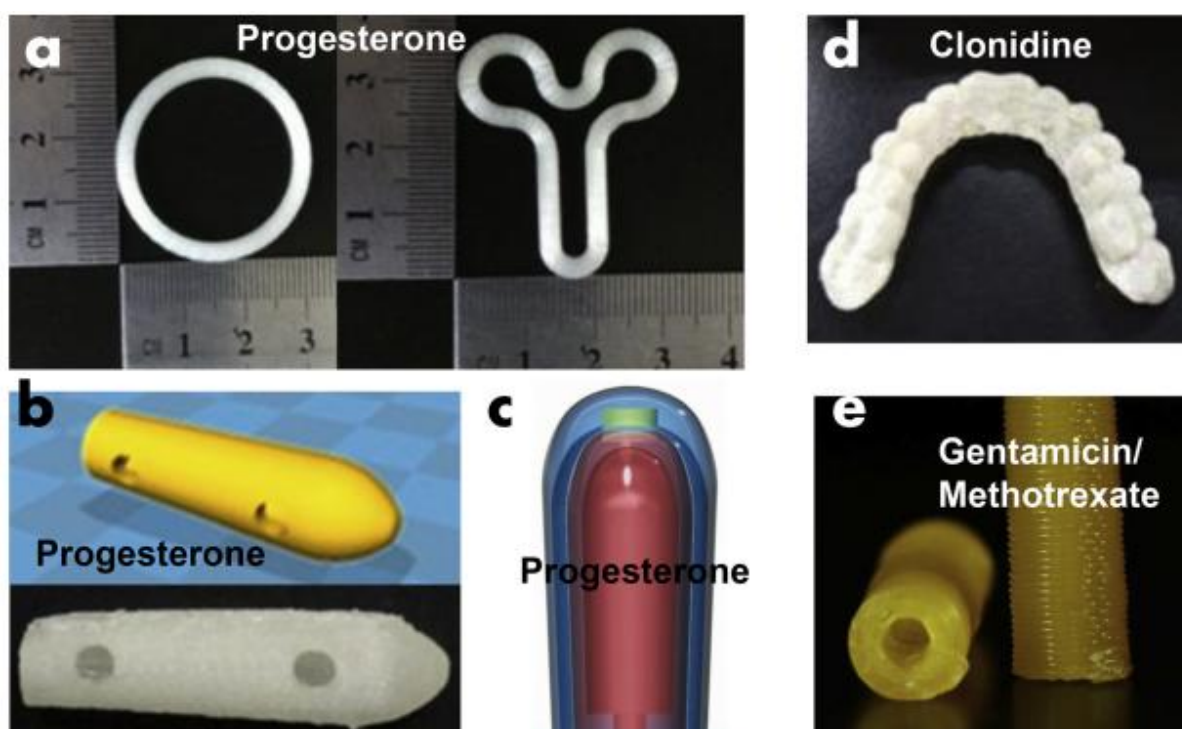


Figure 4 show cases various sustained drug eluting dosage forms created through 3D printing. (a) Personalized vaginal rings (b) A suppository shell designed using CAD software (c) A matryoshka-type suppository shell developed using CAD (d) orthodontic retainers of clonidine hydrochloride. (e) 3D printed catheters for antibiotics and chemotherapeutics.

Conclusion

In conclusion, 3D has enormous potential to revolutionize pharmaceutical practice and production, particularly with regard to individualized medicine. It has significantly improved the creation and characteristics of innovative forms including polypills, gastro floating tablets, and oro dispersible tablets. The ability to quickly create customized models is unique to 3D printing and may be applied to fields like bioengineering models and customized implants. Since the US FDA first approved 3D tablets in 2015, the use of 3D is anticipated to grow in the pharmaceutical business. However, standards and norms must be created in advance of 3D being the new standard to address concerns that are certain to arise. This will be driven by the unmet demands from the pharmaceutical sector and pharmacy practice.

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