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Polymers for designing 3D Printed Pharmaceutical Products

Sanjay Kumar ELISETTI [1], Vimal ARORA [1*], Ram Babu Sharma [2]

1 University Institute of Pharma Science (UIPS), Chandigarh University, Gharuan, Mohali, Punjab, 140413, India.

2 Himalayan Institute of Pharmacy, Kala Amb, Himachal Pradesh, 173030, India.

* Corresponding Author. E-mail: drararavimal@gmail.com (V.A.); Tel. +91 8725861761.

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ABSTRACT: Computer-aided pharmaceutical product manufacturing is the process of creating three-dimensional drug products for a given API in a layer-by-layer process using a suitable binder solution; the process is commonly known as 3D printing. Earlier conventional pharmaceutical methods like tablet compression were utilized in combination with the well-established new procedural advancements for years. These systems are very well accepted. but they are challenging in terms of capability of fabrication flexibility, especially in the cases where there is a very narrow window for selection of excipients for product manufacturing due to incompatibility of API and an excipient. Ease of design and fabrication of complex structures is the key benefit of 3D printing along with the capability of customized product manufacturing for a specific patient or class of patients in the segment of personalized medicine concept. These benefits open the door to new ways to improve drug stability, efficacy, and accessibility. 3D printing technology for manufacturing solid oral dosage forms differs from traditional manufacturing methods and offers an extra benefit of possibility to create risk-based products. In this innovative approach of product development the biocompatible and biodegradable polymers play a very important role as it directly influences the product utilization and efficacy parameters. This article emphasizes polymers that can help in the designing of an automated process of manufacturing the pharmaceutical products using this tool of 3D printing.

KEYWORDS: 3D printing; formulation design; pharmaceutical product; Polymers.

1. INTRODUCTION

Artificial intelligence (AI) based computer assisted, totally automated, product manufacturing techniques are leading to a new era of technological development resulting in better accuracy and efficiency in the quality of the product. There is certainly ongoing drive to produce brand new drug design concepts, and a better understanding of product fabrication, manufacturing and processes technologies that ensure the highest product quality dosage forms.[1] Selection of Active pharmaceutical ingredients (APIs) should be done on the bases of diverse, biopharmaceutical features and auxiliary substances, which needs to be considered and research at each stage of development. Over one decade, lots of emphasis has been shifted on patients-centric drug development. It had formerly concentrated on novel dosage forms and operations that are technical. The assembly of little series of individually-selected doses and prostheses being tailor-made meet patients' anatomical needs drives the most critical improvements in personalized medicine, as evidenced by the assembly of little series of individually-selected doses and tailor-made prostheses to generally meet patients' anatomical needs.[2] Three-dimensional printing (3DP) is widely regarded one of the many revolutionaries and powerful technical breakthrough in the pharmaceutical and biomedical areas. This method is well-known for its flexibility in the manufacturing of a wide array of devices. It is a

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technology that allows for the development of novel dosage forms, cells, and organs, as well as illness modelling.[3]

In this emerging technological era, a new science fact article has made the printing of an organ possible. The growing popularity of three-dimensional (3D) bioprinting has prompted new developments in the field. Researchers are working to create a future in which a fully functioning heart can be printed using a process called as 3D Bioprinting. It's also comparable to additive manufacturing technologies, except that instead of 3D printing, it employs the patient's own cells and biomaterials to solve the problems of organ rejection and long donor waiting lists that affect existing surgical procedure techniques like organ transplantation. [4] One disadvantage of artificial hearts is that metal and plastic mechanisms can be difficult to integrate with tissue and may cause blood vessel damage due to their unnatural movement. A small group led by scholarly individual student Nicholas Cohrs at ETH Zurich/ Swiss Federal Institute of Tech Zurich (German: Eidgenössische Technische Hochschule Zürich) has generated the globe's first soft implant, with its pumping mechanism attained by pushing the silicone polymer ventricles to pump like real a heart that is real.[5] However, instead of a wall separating the two additional chamber that is deflated and inflated by pressurised air to mimic contractions and pump blood separates them. Another Chicago based company BIOLIFE4D is going to create a full-size human heart that can be transplanted.[6] It is undeniably a promising invention with the potential to change people's lives, but it is still a long way from completion. According to a series of tests, this silicon printed 3D heart is heavier than a normal heart, weighing approximately 390 grammes (approximately 0.86 pound or 13.8 ounces). Its latest version is the only one that exists for 3,000 beats, enough to keep someone alive for thirty to forty-five minutes.[7] 3D bioprinting is a game-changing technology that has the potential to improve medical care efficiency, cost-effectiveness, and personalization in the future. This simple technique can be used by researchers to generate geometrically well-defined 3D scaffolds seeded with cells in a quick, low-cost, high-throughput manner. The application of bioprinting to produce organs and tissue patches from a patient's own cells reduces the need for organ donors and also lowers the risk of rejection. Another application of 3D printing is to produce 3D printed tablet, the conventional tablet manufacturing process is very effective in large-scale production. However, when API dosages must be adapted as in clinical studies or any tablet batch production in smaller volumes, then the conventional process consumes both time and money. In such cases we can use the 3D printing technique; nowadays, we are developing a GMP compliant solution that uses additive manufacturing technology (3D printing), combined with a powder and excipients. Laser sintering technology will help simplify the tablet manufacturing process resulting in significant savings in clinical development time and money.[8] One of the most innovative and viable methods for personalizing and customizing pharmaceutical products is to use 3D printers, bearing a range of advantages over conventional tablet manufacturing methods. Pharmaceutical firms will provide drug stores and healthcare offices with outlines for their pharmaceutical information. [6] [9]

2. 3D PRINTING IN FORMULATION DESIGN

2.1. Applications of 3D printing in pharma:

To create artefacts through 3D printing, layers of material are sequentially deposited one upon another. Computer-aided design software (CAD) may be used to produce a variety of structures of various sizes and shapes. Industrial manufacturing, personalized biomaterials i.e., 3D bioprinting is also a similar to additive manufacturing but in this patient's own cell and biomaterials used as bioink for printing, it mainly helps to overcome the organ rejection. Many researchers have succeeded in bioprinting of the organs like 3D bio-printed heart ,ears and kidneys, and medical devices have all used this process.[10] 3D printing can be utilized to make patient-specific items based on the biology of the patients. Joint replacements, cranial implantation, and dental work are few other examples.[11] Despite the fact that certain major manufacturers produce and market these products; point-of-care manufacturing incorporates this level of personalization during patient care. The imaging data from a patient is used to create on-demand 3D-printed medical items.

Anatomical models that are patient-matched, surgery, and wearing prosthetics, which are surgical devices that direct doctors where to make cuts during an operation, are examples of medical equipment that are printed at the patient care. In the United States, the health care facilities with centralised 3D printing facilities has increased dramatically over the last decade, from three in 2010 to more than 100 in 2019.[12] Other product categories could benefit from 3D printing as well. Studies are being conducted, for example, to determine whether 3D printing can be used to create pharmaceuticals with unique dose forms or formulas, such as those that allow for delayed or rapid absorption. As an example, USFDA has approved an epilepsy treatment in 2015 that was designed to deliver a high dose of active ingredient while rapid dissolving in water.[13] In the next, 3D printing can be used to make customised medicines, such as "polypills," which combine multiple prescriptions into a single pill.[14] In the future, 3D printing could be used to create individualised medicines that mix many pharmaceuticals into a single pill, known as a "polypill. The idea of developing lipid-based formulations for poorly water-soluble pharmaceuticals has aroused interest because it facilitates drug dissolution and improves gastrointestinal absorption.[15] In the pharmaceutical field, it has the ability to provide customised and on-demand medications, avoiding unanticipated side effects and unpleasant reactions during the administration of a medicine[16‑17] It also paves the way for the creation of patient-specific fixed-dose combinations, which would minimise the number of daily doses and increase patient compliance.[18] Moulding is one of the 3D printing processes that has been reported in the literature.[19-22] The pharmaceutical industry's showing interest in 3D printing soared after the US FDA approved the 1st orally disintegrating 3D printed pill, Spritam® (levetiracetam), in the year 2015.[23-24] Spritam®, on the other hand, is a loose compact that is made by spraying a binder solution onto numerous powder beds.[25] The technique requires specialised equipment and is incompatible with small-scale, we can print/produce patient-personalized drug products on patient demand and/or requirement by the patient. Furthermore, because certain printing remnants must be removed or recycled, the generated tablets are soft and porous, therefore powder waste is a possibility. Of the several methods stated above, FDM has proven to be the most extensively used & low-cost additive manufacturing process, and has stimulated substantial research in non-pharmaceutical and pharmaceutical areas, as well as fast prototyping and drug delivery. Geometries that are complex, as well as presentation models, and visual aids are all made with thermoplastic polymers. 3D printing is a technique for creating artefacts by layering materials in a certain order. We can design a wide range of structures of various sizes and shapes by computer-aided design software. Industrial manufacturing, personalised biomaterials, and medical devices have all benefited from this process.[26] Individualized prescriptions are now more accessible thanks to the advantages of 3D printing. The dose must be changed to better suit the patient's needs as the patient's weight ,age, and infection severity change.[27] Patients still prefer orally administered drugs because they are relatively safe, simple, and cost-effective, despite substantial advancements in drug administration techniques. Personalization of oral heavy dose forms could be an advanced for the healthcare system, given predilection for oral solid pharmaceutical forms, specifically tablets.[27]

2.2. Process in 3D printing formulations:

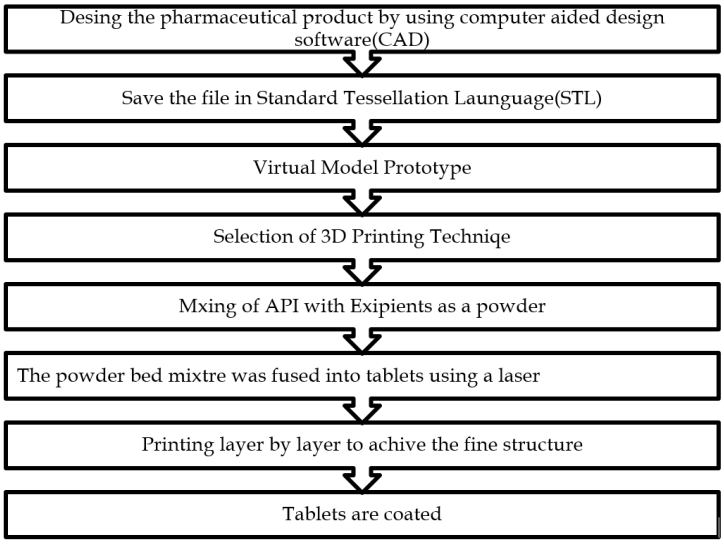


Figure 1. Process of pharmaceutical manufacturing table by using 3D printing

- In the designing of pharmaceutical product (table) researcher should design the virtual product (3D model) in the computer by using the software called auto CAD, which includes shape and size along with the dimensions
- After design of the tablet (3D model) researcher should save the file in the Standard Tessellation Language (STL) format and that file contains the virtual model prototype.
- Now, we need to select the 3D printing Technique (i.e., FDM, HME, SLA) based on the drug, polymers, and requirements. After selection, API should mix with excipients as a powder and need to make into powder bed and that powder bed mixture is given to the 3D printer as feed and it is fused into tablet using a laser and printing makes layer by layer until achieve the fine structure and as per requirements coating may be performed.

2.3. Technologies for manufacturing 3D printed formulations:

There are many numbers of manufacturing technologies present in 3D printing based on categories like prosthetic organs printing, 3D Bio printing.

- ❖ Fused Deposition Modelling (FDM) [28]
- ❖ Hot melt extrusion [29]
- ❖ Inkjet printing [28]
- ❖ Stereolithography (SLA)[28]
- ❖ Selective laser sintering (SLS)[28]

2.3.1. Fused Deposition Modelling (FDM) & Hot Melt Extrusion (HME)

To create drug-absorbent filaments, FDM and HME are two alternative three-dimensional printing methods. The fundamental problem is that printing at high temperatures degrades active medicinal components (APIs).[30] In the FDM (assembly shown in figure 2), thermoplastic polymers are used such as nylon, ABS, PLA and polycarbonates and the starting material is filament and the principle is extrusion and deposition and the resolution is 50-200 (Rapide lite 500). The assembly of an extrusion-based 3D printer is shown in figure 3.

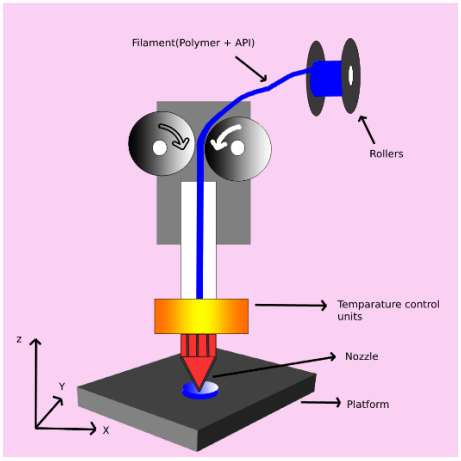


Figure 2. Fused Deposition Modelling (FDM) [28]

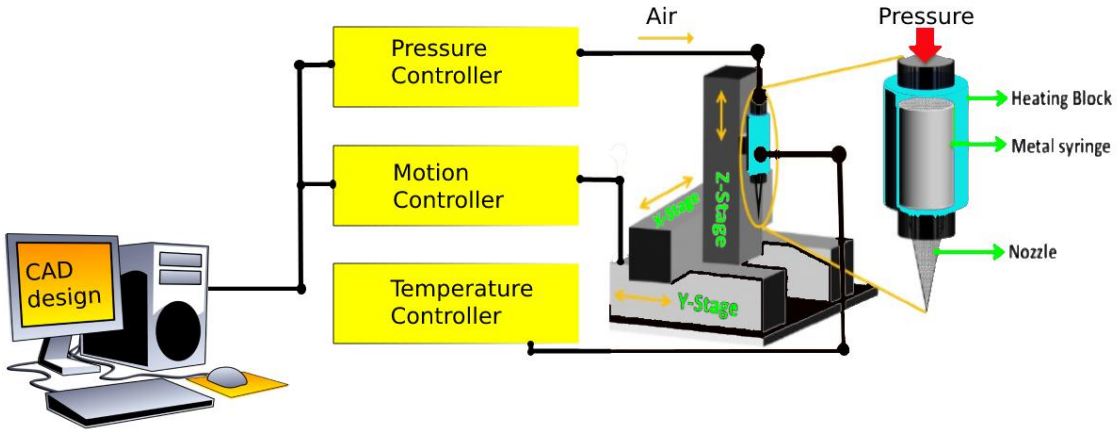


Figure 3. This picture showing the system assembly of extrusion -based 3D PRINTER [29]

2.3.2. Inkjet Printing

An inkjet printer creates three-dimensional objects by spraying various combinations of complicated fixes and excipients (inks) beyond a nozzle. Layer by layer, the medicament fixing is gathered, resulting in a three-dimensional pill. The schematic diagram of an inkjet printer is shown in figure 4.

Captopril was mixed with maltodextrin and maltitol, a sedative carrier, in one study. Water-based inks were used to bind the powders at the time. [31] In the Inkjet printing, any polymer that may be given as a powder is utilised as the starting material. The premise is drop-on-demand binder printing, with a resolution of 100-250. (Plan B,Ytec3D).

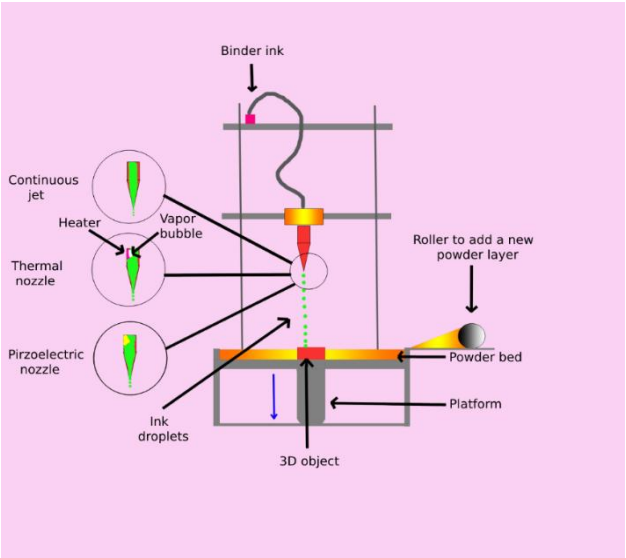


Figure 4. 3D inkjet-based printer's schematic diagram. [28]

2.3.3. Stereolithography (SLA)

Another exciting technology for making drug-loaded tablets is stereolithography (SLA). SLA works by photopolymerizing monomers with a laser beam. [30] The schematic diagram of SLA is shown in figure 5.

A team from London used SLA to deliver a resin-based pill by combining a medicate monomer with a photoinitiator. [32] In the SLA, epoxy or acrylate based resin are used as the starting material is liquid photo polymer and the principle is laser scanning and UV induced, having the resolution of 10 (DWSLAB XF AB).

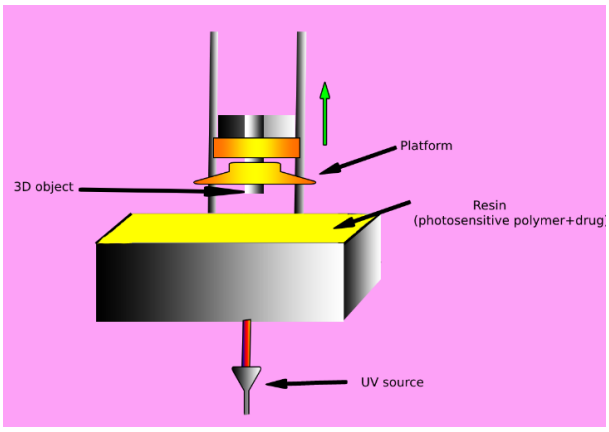


Figure 5. stereolithography (SLA) [28]

2.3.4. Selective laser sintering (SLS)

Drug release dosages with faster release rates have been created using SLS (selective laser sintering). Combining active chemicals with complicated copolymers and laser fusing is carried out at the end to give the resultant powder. In the SLS, [28] PCL and polyamides are used the Starting material is powder and the principal Laser scanning and heat induced with a resolution of 80 (Spo230 HS). The schematic diagram of SLS is shown in figure 6.

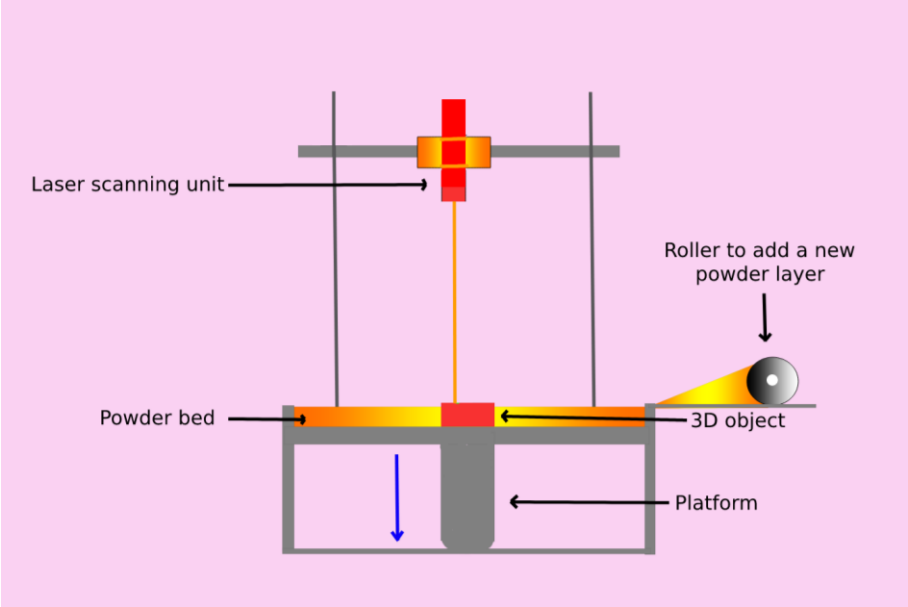


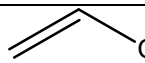
Figure 6. Selective laser sintering (SLS) [28]

3. POLYMERS USED IN 3D PRINTING FOR MEDICAL APPLICATIONS

3D printing technology is developing day-by-day as one of the novel technologies. The production rate and real stability for the active pharmaceutical ingredients (APIs). In this 3DP technology, for the formulations associated with the dosage fabrication, polymers are playing an important role and those would be the backbone because they are helping in the molding intended materials or structures. There are numerous polymers (natural and synthetic) that have been used in the 3D printing for biomedicines. Natural polymers such as collagen, chitosan, gelatin, alginate frequently necessitates use of cross-linkers that are not cytotoxic. Due to this drawback now a days synthetic polymers are having limited use. [33 -38]

3.1. Polyvinyl alcohol (PVA)

PVA is a thermoplastic synthetic polymer soluble in water and reported to be odorless polymer with excellent mechanical properties. It is made by partially or completely removing the acetate groups from polyvinyl acetate.[39-40] The degree of hydrolysis affects the polymer's mechanical, chemical, & physical properties. The melting point of PVA varies and depends on the degree of acetate group hydrolysis, starting from 180 °C (partial hydrolyzed) to 220 °C (completely hydrolyzed) (fully hydrolyzed). The degree of hydrolysis determines the viscosity scale of the polymer from 3.4 to 52 mPas for in partial hydrolyzed PVA to 4 to 60 mPas for fully hydrolyzed PVA. [39] [24] [40] Water solubility, Crystallization, molecular weight possess inverse relationship with degree of hydrolysis. PVA must have a glass transition temperature of 85°C and then degrade at temperatures ranging from 350 to 450 °C. The chemical structure of PVA is shown in figure 7.



Polyvinyl alcohol
Chemical Formula: C_2H_4O
Exact Mass: 44.03
Molecular Weight: 44.05
m/z: 44.03 (100.0%), 45.03 (2.2%)
Elemental Analysis: C, 54.53; H, 9.15; O, 36.32

Figure 7. Poly (vinyl alcohol)

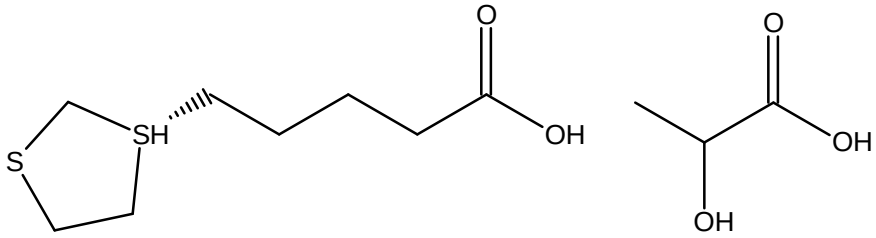
It has several applications in 3D printing, for example PVA has been used in inkjet printing to create polymer multilayers for additive manufacturing (XYPrint100Z Hybrid printer with Konica Minolta KM512 print head). To prevent nozzle clogging, aqueous PVA solutions containing humectant (glycerin or mono-propylene glycol) and pigment were used (duasyn acid violet). PVA with high and low molecular weights are combined to make other inks; because of the viscosity of the ink, the molecular weight has an impact on inkjet printability. PVA inks with a high molecular weight did not acquire color as well as PVA inks with a lower molecular weight did not stay stable for six months. After six months, inks developed lower molecular weight PVA gels with a milky appearance, indicating that the prerequisites for inkjet printing had not been reached. At low shear rates, all of the inks demonstrated a combination of pseudoplastic as well as thixotropic behavior, whereas, at high shear rates, most of the inks demonstrated Newtonian behavior.[41]

PVA has been recently utilized successfully in both FDM (Fused Deposition Modelling) and inkjet printing. When using this method, the density of the infill (which varies from 0% for hollow structures to 100% for completely cores) speed of the extruder, with layers, as well as the temperature of the nozzles and building dish must all be carefully controlled.[24]

PVA filaments also have been found to be used in several experiments to accommodate up to 10% drug content. In one of the studies reported by Goyanes et al. (2014), researchers have used hot-melt load extrusion of paracetamol and caffeine loaded with PVA filaments at a temperatures of 200 °C, infill percentages of 100%, and extrusion speeds of 90 mm/s to get ready solid dosage forms with medication loadings in the range of 4 to 10%. Drug launch has been lower in filaments with lower API loading.[42]

3.2. Poly Lactic Acid (PLA)

The US Food and Drug Administration (USFDA) has classified poly lactic acid as safe (GRAS) chemical, rendering it suited to a wide range of medical applications such as tissue engineering, regenerative medicine, excipient for drug delivery systems, wound dressing, stent applications, orthopedic and fixation devices. Direct but also ring-opening polymerization are the primary methods for the manufacture of this polymer.[43] PLA's properties (Heat Deflection Temperature (HDT), Density, Tensile Strength, Flexural Strength, Impact Strength, Shrink Rate) are influenced by its isomer ratio, which in turn depend up on processing temperature, molecular weight, and crystallinity. Hardness, melting temperature, stiffness, and tensile strength are all affected by the percentage of amorphous and crystalline areas in a polymer. The melting point of PLA homopolymer is 150–175 °C, with a Tg of 55 °C.[8] [43] PLA has to have an observed melt viscosity of 1000 Pas at 200°C, though under shear stress and also at high temperatures, it can reach 5100 Pas. The chemical structure of PLA is shown in figure 8.



5-[(3R)-dithiolan-3-yl]pentanoic acid;2-hydroxypropanoic acid

Chemical Formula: $C_{11}H_{22}O_5S_2$

Exact Mass: 298.09

Molecular Weight: 298.41

m/z: 298.09 (100.0%), 299.09 (11.9%), 300.09 (9.0%), 299.09 (1.6%), 300.10 (1.0%)

Elemental Analysis: C, 44.27; H, 7.43; O, 26.81; S, 21.49

Figure 8. Poly Lactic Acid

PLA and its own derivatives are readily soluble in dioxane, acetonitrile, chloroform, methylene chloride, 1,1,2-trichloroethane, and in dichloroacetic and poorly soluble throughout cold ethylbenzene, toluene, acetone, as well as tetrahydrofuran. However, their solubility increases whenever the solvents have been heated to boiling temperatures. Water, alcohol (e.g., methanol, ethanol), propylene glycol, and unsubstituted hydrocarbons such as hexane & heptane have been discovered to have low solubility .[43]

PLA breaks down into α-hydroxy acid when it enters the human body. The identical product then goes through the tricarboxylic acid cycle before being excreted.[43] Three factors influencing the rate of degradation of a polymer are, crystallinity, molecular weight, and stereochemistry. Aside from that, there are some other factors that can affect the rate of breakdown like water migration into the polymer, distribution, and shape. PLA degrades slowly in general, giving it a lengthy in-vivo life. [43] In a saline environment at 37 °C, it can take up to 3–5 years for polymer mass to approach zero, and between 6 and 12 months for PLA tensile power to reach 50%. Breakdown of PLA may be expedited by co-polymerizing with PLLA. Because D-lactic acid is difficult to degrade by enzymes in the human body PLA and PLLA combine to extend the degradation time. [44]

Thermal degradation of the polymers can be caused by hydrolysis, lactide reformation, oxidative scission of the major chains. At 325 °C, the degradation is a simple one-step process that culminates in a 5% mass polymer loss and at 500 °C polymers mass will completely loss. It's also more brittle than many other polymers.[43] PLA has been effectively used in medical devices utilizing a selection of 3D publishing techniques, including FDM (Fused Deposition Modelling) and laser-based approaches.[10]

3.3. Poly lactic-co-glycolic acid (PLGA)

PLGA is an FDA-approved biodegradable co-polymer that is used to make a number of drug delivery systems.[45] In one of the study, 3D-printed patches of fluorouracil were prepared utilizing the blend of PLGA/PCL for the controlled drug delivery. Patches are made by melting PLGA/PCL/5-FU and depositing them using the printing head of an extrusion-based 3D printer outfitted with a multi-head deposition system (MHDS). The MHDS consists of a printing head connected with a pneumatic pressure controller, and three axis-linear motion controllers. The material is extruded from the reservoir at around 140 °C and pressure of around 600 kPa and then permitted to cool to ambient temperature on the stage.[29] The chemical structure of PLGA is shown in figure 9.

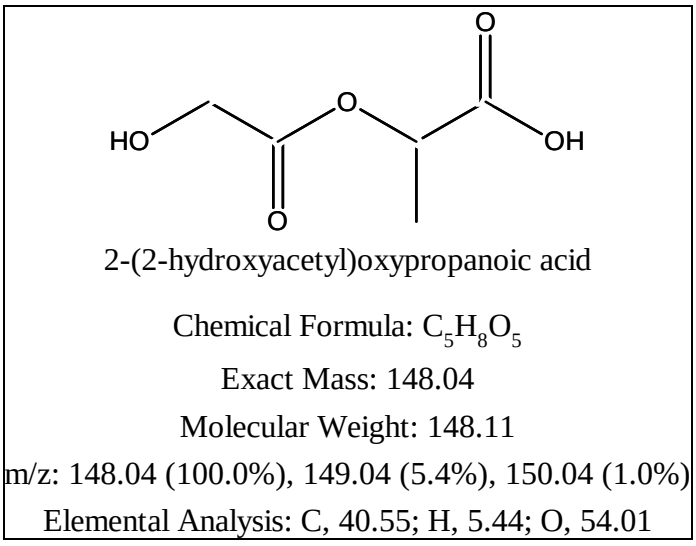


Figure 9. Poly (lactic-co-glycolic acid)

3.4. Poly Caprolactone (PCL)

According to the USFDA, polycaprolactone is really a hydrophobic semi-crystalline polymer and its crystallinity increases while the molecular weight decreases. It exhibits glass transition temperature of 60 °C and melting is reported in range 59–64 °C.[44] It has solubility in chloroform, dichloromethane, carbon tetrachloride, benzene, toluene, cyclohexanone, and 2-nitropropane at room temperature and insoluble in alcohol, petroleum ether, and diethyl ether very slight soluble in acetone, 2-butanone, ethyl acetate, dimethylformamide, and acetonitrile.[46] Physicochemical properties are impacted by isomer ratio, processing temperature, molecular weight, and crystallinity. Poly (vinyl chloride), poly(styrene-acrylonitrile), poly (acrylonitrile butadiene styrene), and poly (acrylonitrile butadiene styrene) are other polymers that PCL mixes well using bisphenol-A. The chemical structure of PCL is shown in figure 10.

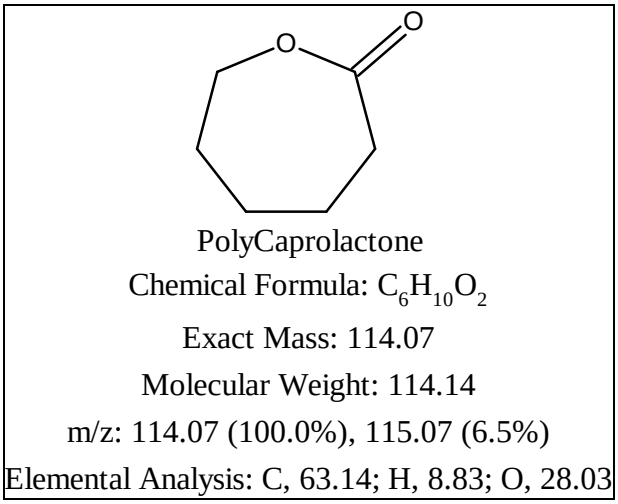


Figure 10. Poly (Caprolactone)

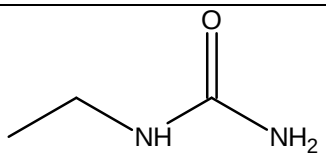
Bacteria and fungi can degrade PCL in the environment; however, it cannot breakdown in a human due to lack of enzymes required for biodegradation. [44] [46] This is one of the popular product for long term application in drug delivery due to longer degradation time i.e., 2-3 years. This polymer could be utilized in a number of biomedical applications due to its broad blend compatibility, low melting

temperature, and solubility, in tissue engineering, wound dressings, [47] or drug delivery systems(DDS).[44] [46]

Berck, R.C.R. et al. (2017) formulated 3D printed polymeric nanocapsules with PCL and Eudragit RL100 using an FDM printer. Extrusion temperatures for Eudragit and PCL were maintained at 110 °C and 65 °C, respectively. Eudragit filaments were set at printing temperature of 170 °C, while maintaining 95 °C for PCL filaments. Parameters which were controlled on FDM printer were extruding speed 90 mm/s and infill percentage (100%), as well as some Eudragit filaments having a 50% infill percentage, were found to be developed to test the effect of filling on the tablet quality. Because of their higher swelling indices Eudragit tablets accommodate higher drug loading than PCL tablets. Eudragit tablets outperformed PCL tablets in terms of release profile also.[47]

3.5. Polyurethane (PU)

Polyurethane is a linear polymer that is thermoplastic, highly biocompatible and has potential to mimic tissue characteristics. This polymer is made up of two independent components; the hard and soft section ratio can easily be changed to alter the mechanical properties.[48] Waterborne polyurethane is typically synthesized by including an ionic part (PLLA-PEO blocks) that converts polyurethane to an ionomer and permits it to disperse in water. When compared to standard polyurethane, which offers several advantages, such as an environmentally benign synthesis method and non-flammability. Drug transporters, surgical sutures, and wound dressings are just a few of its biological applications. Using widely available hydrophobic and hydrophilic Polyurethane (PU), the FDM technology was used to produce considerable medication loading (>30%) in 3D printed tablets (Tecoflex and Tecophilic ™). In a study, theophylline and metformin were used as model pharmaceuticals, with extrusion temperatures ranging from 100 to 180 °C. However, up to 60% of the drug was deposited in filament, with rough surfaces on the filament's surfaces. 3DP tablets made from PU polymer showed sustained drug release for up to 24 hours without bursts, but they were found to be faster than tablets made with hot molding (HME/IM) technology. This behavior was considered to be caused by the porosity of 3D printed tablets, and use of hydrophobic PU.[49] A thermos-responsive PCL-based PU that is waterborne exhibits a sol-gel transition at body temperature while remaining less viscous at normal temperature was also developed. The thermos-responsive PU developed was supposed to be used being a bio-3D printing ink as well being an hydrogel that is injectable.[50] The chemical structure of PU is shown in figure 11.



Polyurethane

Chemical Formula: $C_3H_8N_2O$

Exact Mass: 88.06

Molecular Weight: 88.11

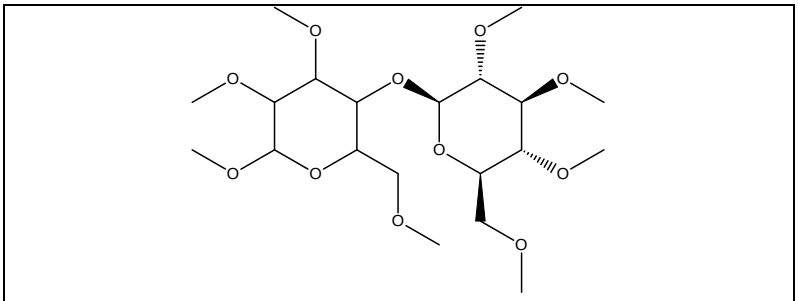
m/z: 88.06 (100.0%), 89.07 (3.2%)

Elemental Analysis: C, 40.90; H, 9.15; N, 31.79; O, 18.16

Figure 11. Polyurethane

3.6. Hydroxypropyl Methylcellulose (HPMC)

Hydroxypropyl methylcellulose is a polymer that shows an exceptional production of drug-impregnated 3D-printed filaments; in pharmaceutical applications, several grades of HPMC are utilized.[51] In various experimental work the printing temperatures for HMPC and Kollidon® formulations had been set at 135 °C and 100 °C, correspondingly, with a printing laser scanning speed in the range from 100 to 300 mm/s. Based on drug release studies, it may be postulated that increasing the laser rate from 100, 200, and 300 m/s hastens drug release at higher laser rates.[52] A researcher group created tablets with delayed and immediate release profiles using diltiazem-loaded HPMC filaments and a MakerBot Replicator® 2X Desktop 3D printer.[53] In a recent research the SLS procedure was recently used to create new accelerated release solid oral dosage forms using HPMC and a vinylpyrrolidone-vinyl acetate copolymer (Kollidon® VA 64). To improve laser printing and absorption simplicity, 5% paracetamol was mixed with various ratios of HPMC and Kollidon® VA 64, and 3% Candurin® Gold Sheen was included with each formulation. The liquids were fed right into a Desktop SLS printer to create the dental formulations (Sintratec Kit, AG, Brugg, Switzerland).[52] The chemical structure of HPMC is shown in the figure 12.

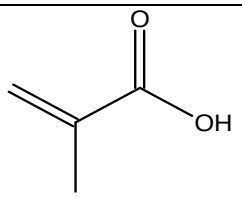


2,3,4-trimethoxy-6-(methoxymethyl)-5-[(2S,3R,4S,5R,6R)-3,4,5-trimethoxy-6-(methoxymethyl)oxan-2-yl]oxyoxane

Chemical Formula: $C_{20}H_{38}O_{11}$
Exact Mass: 454.24
Molecular Weight: 454.51
m/z: 454.24 (100.0%), 455.24 (21.6%), 456.25 (2.3%), 456.25 (2.2%)
Elemental Analysis: C, 52.85; H, 8.43; O, 38.72

Figure 12. Hydroxypropyl Methylcellulose

3.7. Eudragit (Polymethacrylate-based copolymers)



methacrylic acid
Chemical Formula: $C_4H_6O_2$
Exact Mass: 86.04
Molecular Weight: 86.09
m/z: 86.04 (100.0%), 87.04 (4.3%)
Elemental Analysis: C, 55.81; H, 7.03; O, 37.17

Figure 13. Methacrylic acid

Eudragit copolymers are produced from an acrylic acid that is methacrylic and are available in a variety of grades. Acidic groups in dissolvable poly(meth)acrylates, in the polymers grade L, where as eudragit S, FS, and E, provide pH-dependent swelling for medication release. Insoluble poly(meth)acrylates, such as Eudragit RL and RS polymers with alkaline groups and Eudragit NE polymers with neutral groups,

show pH-independent swelling and controlled release of the active moiety .[54] To produce immediate-release tablets containing many different pharmaceuticals, Eudragit EPO filaments and a commercial FDM 3D printer had been used (0.4mm nozzle size) in few studies. Autodesk® 3ds Max® Design 2012 pc software version 14.0 was used to generate the templates for printing the tablets in caplet shape.[55-56] The chemical structure of methacrylic acid is shown in figure 13.

3.8. Polyethylene glycol Diacrylate (PEGDA)

Polyethylene glycol diacrylate is a specific kind of glycol, making use of 3DP technology. It is a short-chain polymer that had been investigated as a monomer and crosslinker in the development of hydrogels. This polymer is a superb candidate for the formation of hydrogels due to its water solubility in addition to the capability of acrylate groups for photopolymerization. Larush et al. (2017) used PEGDA as a crosslinker in pH-sensitive hydrogels, hypothesizing that increasing the total amount of PEGDA, may leads to delayed drug release.[57] Another study used PEGDA and PEG as a monomer and plasticizer to produce a 3DP hydrogel for controlled release of ibuprofen using SLA printing technology.[58] The chemical structure of PEGDA is shown in the figure 14.

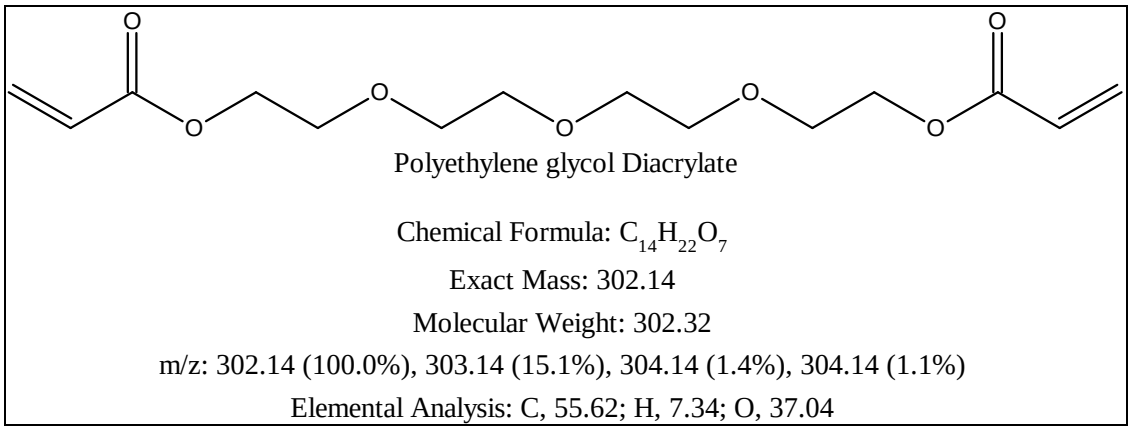


Figure 14. methacrylic acid Polyethylene glycol Diacrylate

4. ADVANCEMENTS

4.1. Spritam® is a commercially available 3D printed Tablet.

Spritam® (Aprecia Pharmaceuticals), which contains the antiepileptic API levetiracetam, it was the first FDA-authorized 3D printed medication in 2015. The pharmacological efficacy was shown to be comparable to that of conventional tablets, with the noticeable improvement that due to the porous and soluble matrix composition, the solubilization period is frequently shortened. Spritam® is a trademark of Aprecia Pharmaceuticals, which is based on powder bed fusion via a layer-by-layer manufacturing system. The active component, as well as most of the excipients required to make the matrix tablet, are found in the first layer. To achieve certain integration and aggregation of all successive and similar layers, a binder liquid is deposited. The ultimate product is an orodispersible tablet that can hold up to 1000 mg of API and dissolves in a matter of seconds with very little water.[59-60] This discovery shows how this technology can be used to create specialised dosage forms with properties that compression or other classic production methods can't give.

4.2. 3D Printing Technology with Melt Extruison Deposition (MED®)

The US FDA has granted Triastek, a Chinese pharmaceutical and 3D printing technology business, IND certification for T19, its first 3D printed drug product is designed by melt extrusion deposition method. T19

was developed in-house to treat rheumatoid arthritis, an autoimmune disease in which the immune system erroneously attacks the cells lining joints, causing them to stiffen and enlarge.[61]

The FDA Emerging Technology Team (ETT) enlisted MED® 3D Printing technology (as shown in figure 15) into the Emerging Technology Program (ETP) in April 2020 based on the following innovative features:[61]

- Manufacturing of modified release solid oral dose form using MED-based 3D printing technology
- PAT and feedback controls are used in a completely automated process.

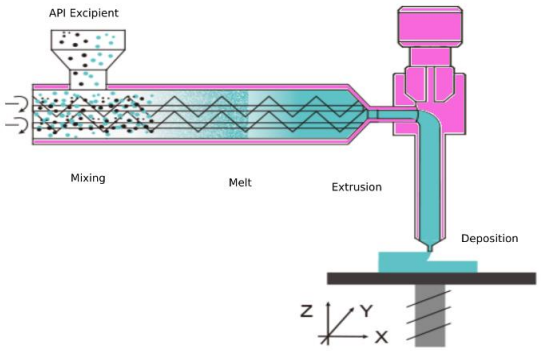


Figure 15. MELT EXTRUSION DEPOSITION (MED®) 3D PRINTING TECHNOLOGY [61]

4.3. Topical Treatment Devices that are Customized

The 3D printing revolution could also be used to create custom, drug-loaded devices that are tailored for every patient's shape and size. There has been rapid and efficient development of nose-shaped masks containing salicylic acid for anti-acne treatments. The face of the patient is scanned, and the image was exported to AutoCAD, where the nose region is picked. The inside section has to be left hollow to ensure flawless adaptation to the patient's face and to build the three-dimensional model with great precision. To see which was better in terms of manufacturing, morphological features of the object, drug release, and printing stability, the geometric model was printed using two different techniques.

In one of the study it is reported that because of the increased device resolution, which allowed for more drug loading, and the minimal degradation of salicylic acid during 3D printing,[62] SLA was the most promising approach for mask manufacturing.

4.4. Cancer Treatment Using 3D Printing

Traditional chemotherapy has a hard time reaching therapeutic levels in the tumour. Traditional approaches, such as intravenous injection or oral delivery, fail to attain the same essential concentrations at the tumour site because most chemotherapy medicines are poorly soluble in aqueous solutions. Additionally, antineoplastics frequently build-up in the important organs such as the liver and heart, resulting in substantial side effects. As a result, local delivery systems would be immensely beneficial in overcoming standard chemotherapy's limitations.

In a research 3D-printed patches containing 5-fluorouracil, poly(lactic-co-glycolic) acid, and PCL were successfully printed and transplanted into a pancreatic cancer patient. The patch geometry and release kinetics have always been tweaked, allowing for a four-week delivery of the medication. The patch biodegraded in the body after that period of time.[63]

4.5. Polypill 3D Printed

A "polypill" is a single tablet that includes a mixture of numerous medications, as shown in figure 16. As a result, it has significant benefits in patients who are poly-medicated, such as the elderly. A variety of polypills have been successfully created using 3D extrusion printing. For example, Captopril, nifedipine, and glipizide, which can be used to deal with hypertension and type 2 diabetes, had been mixed right into a single tablet via 3-D printing. Prototypes of five special kinds of APIs with different release profiles are now under trials, demonstrating how fast and long the technology has advanced.[62] In another research a penetrable membrane of hydrophobic cellulose acetate, actually separating 3 APIs (pravastatin, atenolol, and ramipril) within the prolonged release compartment has been designed.

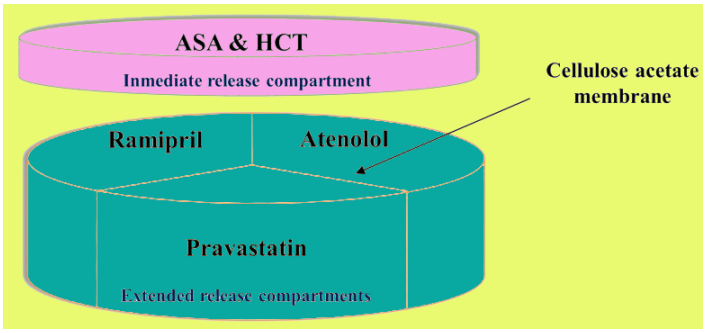


Figure 16..3D printed polypill.[62]

4.6. Aprecia: 3d-printed pills

Aprecia 3D-prints levetiracetam, an epilepsy medication, as a conveniently dispersible (and then swallowable) pill sold under the name 'Spritam' (is the brand name for the product) [13] .

4.6.1. The improved three - dimensional (3D) printing method

Binder jetting would be a popular 3D printing technique used by Aprecia and many other innovators. In this technique, a powder is spread in a thin layer on a platform in conventional binder jetting methods, and an inkjet printer passes over the layer to bond the powder together. This procedure is repeated several times until the required thickness is achieved. For example, Spritam is made by spreading a thin layer of powdered medication and precisely placing tiny droplets of polymer solutions to tie the powder together. Industrial-grade inkjet printer nozzles are used to create these droplets. After printing, the pill is dried at 50–60 degrees Celsius to extract moisture before being packaged in child-resistant blister packaging.[64]

5. ADVANTAGES AND LIMITATIONS

Oral dosage forms made with 3D printing have a number of advantages, especially in terms of drug delivery customization. Active ingredients can be included according to patient's preference or need in order to achieve a customized release pattern and dose. Conventional tablet manufacturing process is very effective in large-scale production, however, when API doses are to be adapted in clinical studies or any tablet batch production in smaller volumes, then the conventional process consumes both time and money, in that case we can use the 3D printing technique. Now a days, we are in the direction of developing a GMP compliant solution that uses additive manufacturing technology (3D printing), using a suitable polymer powder and excipients. Laser sintering technology will help to simplify the tablet manufacturing process

resulting in significant savings in clinical development time and money. In addition to single-drug combinations, 3D printing can be extremely beneficial for multidrug combinations.[65] In the conventional tableting process, complex geometries, styles, and shape changes would be impossible, which can be easily addressed by using 3D printing. Despite extensive studies into how to fix 3D printing's flaws, modern technology still has some limitations. On the other hand a 3D printing process cannot produce porous or uneven dosage forms.[66] A limitation of fused deposition molding makes it a limited use technology for only thermostable drugs and a limited number of excipients. The polymerization reactions caused by UV light in stereolithography also have the potential to degrade the drugs.[8]

6. FUTURE PERSPECTIVES

3D printing is a game-changing technology that can enhance the efficiency, affordability, and personalization of medical care in the future, and by using 3D bioprinting, researchers can create geometrically well-defined 3D scaffolds seeded with cells in a fast, low-cost, high throughput manner using this innovative technique. The use of bioprinting to build organs and tissue patches from a patient's own cells may lead to a reduction in the need for organ donors along with lowering the risk of organ rejection. On the other hand, the 3D printed tablet or other dosage form will lead to the next generation manufacturing of innovative medicinal products, which are otherwise tough to manufacture using conventional manufacturing technologies.

7. CONCLUSION

The content compiled in this manuscript is encompassing the applications of 3D printing in pharmaceutical product development, with a special emphasis on the material properties associated with the polymeric substances employed in 3D printing. It covers the fundamental information about the subject matter and highlights the significance of the selected topic. The manuscript is majorly focusing on customized product development and drug delivery utilizing the 3D printing technology. The facts and information compiled for the polymers used in design and development of 3D printed futuristic pharmaceutical products will help the researchers to traverse the possibilities of designing, developing and utilizing various natural and synthetic polymeric substances for their suitability to be explored as the base material for developing the pharmaceutical products like tablets, capsules, implants, prosthetic organs etc. This approach will in turn lead to the development of new age pharmaceutical products associated with precision and personalized medicine systems, offering a good deal of patient compliance.

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