wjpmr, 2023, 9(10), 80-93

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

3-D TECHNIQUES IN PHARMACY: A STATE-OF-THE-ART REVIEW

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Article Received on 09/08/2023 **Article Revised on 30/08/2023** **Article Accepted on 20/09/2023**

ABSTRACT

3-Dimensional techniques for drug dosage design and development have potential applications in pharmaceutical industries and patient co-centric problems. It is a forecast for the way of manufacturing and reshape the way of designing the medicines. The 3-Dimensional techniques give us innovative solutions to prepare and develop drug dosage design, especially in oral dosage form, the utilization of these techniques facilitates the fast disintegration time, low volumes with higher accuracy, preparation of these dosage form layer by layer, spatial arrangement produces highly porous yet fast oral dispersible tablets, wide range of taste masking capabilities cause ease of swallowing. These techniques facilitated the drug designing by methods like Stereo lithography (SLA), Selective Laser Sintering (SLS), Direct Metal Laser Sintering (DMLS) and Fused Deposition Modeling (FDM). Development of drug dosage designing, patient centric drug problems (such as can be resolved by the help of 3-Dimensional techniques, the oral dosage form prepared by these 3-dimensional technique are Implant Tablets, ODT (oral disintegration tablets), bilayer tablets, capsules and tablets. Here we will accentuate the challenges, advantages, disadvantages, types of medicines, pharmaceutical application (dosage form design and development), comparison (between the 3-dimensional techniques and other oral dosage form manufacturing techniques) and make a conclusion about the 3-dimensional techniques.

KEYWORDS: 3-Dimensional techniques, Oral dosage design, Dosage development, Challenges, Comparison.

INTRODUCTION

Three-dimensional (3D) techniques have become increasingly important in the field of pharmacy as they offer a range of benefits, including improved drug design and deliver.[7] 3D techniques can also use for creation of tissues and organs for the study in a simulated environment. One of the most important parts of 3D techniques is computer-aided drug design (CADD). CADD involves the use of computer readable models to predict the interactions between drugs and their targets[1], enabling researchers to design more effective drugs with fewer side effects.[10] CADD techniques can also be used to identify potential drug targets and to optimize drug delivery. Another important 3D technique is 3D printing, which enables the production of complex drug delivery systems and personalized medicine. With 3D printing, it is possible to create customized drug according to patient centric problems, improving safety, treatment efficacy and reducing side effects. Additionally, 3D printing can be used to create drug reducing on set of action.[6,8,9] 3-D techniques also used for diagnosis of diseases, 3D imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) have revolutionized the diagnosis and treatment of diseases in pharmacy. These techniques enable the visualization of internal structures of body in three dimensions, helps physicians to diagnose diseases earlier and more accurately.[2] Overall, 3D techniques are a state-of-the-art approach in pharmacy that offer dozens of advantages in drug design, delivery, and diagnosis. Continued advancement in 3-D techniques by research community gives adaptation of 3-d technique by pharmacy.

History: 3-D Printing was first introduced by Charles Hull and gave term Stereo-Lithography (SLA), In year between 1983-1986. Hull issued patent for this technique in year 1986, under which they explained the plausible process about liquid polymers subjected to hard on exposure to UV- light. This act as lead in future for SLA machinery. At the same time another technology was introduced named selective laser sintering (SLS), powder-based solidification process using a laser beam. Consecutively Hull discovered these techniques to be computer oriented. After all this the first commercial printer was released in year 1988. In year 1993, Carl Deckard originated Sinter-station 2000, which industrialized the SLS technology.

Later in 1989, Electro Optical System (EOS) was developed to be worked with Direct Metal Laser Sintering (DMLS) that prints from computer design models, which today is being recognized as industrial prototyping. From 1990`s 3d printing started the

complex fabrication for medical.[64] Food and Drug Administration approved the 3-D techniques on August 2015.

Pros and cons

Before diving into the present-day fragment, let's have a look on positives and negatives of these 3-D Printing Techniques.

Table 1.

Pros	Cons
• 3-Dimensional techniques are utilized to fabricate the drug delivery system and their development with the help of layer-by-layer design.	• Machinery required very high cost, makes it less feasible.
• This technique is potential to dispense low volume preparations and higher efficacy, safety and accuracy.	• Skilled/Professional/Trained individual is required.
• It reshapes the drug customization as required by the patient-centric Problems.	• In case of CADD, time taking process to know how to operate or run the software.
• 3D printed poly-printlet, can also improve treatment efficacy while reducing the risk of adverse effects owing to inaccurate dosing.	• Work can be lost because of the sudden breakdown of computers.
• CAD software enables developers to work more quickly, cut production costs and, ultimately, complete projects more quickly.	• As traditional drafting skills become obsolete, they will be lost.
• The use of CAD allows design teams to control the quality of the final engineered product.	• CAD software requires knowledge and skill. You may need to teach CAD or other digital modeling software to all your designers. Time and money are required for training.
• Auto-Dock (a CAD Software) It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure.	• 3D printers used in enclosed places such as homes can generate potentially toxic emissions and carcinogenic particles.

Rationale

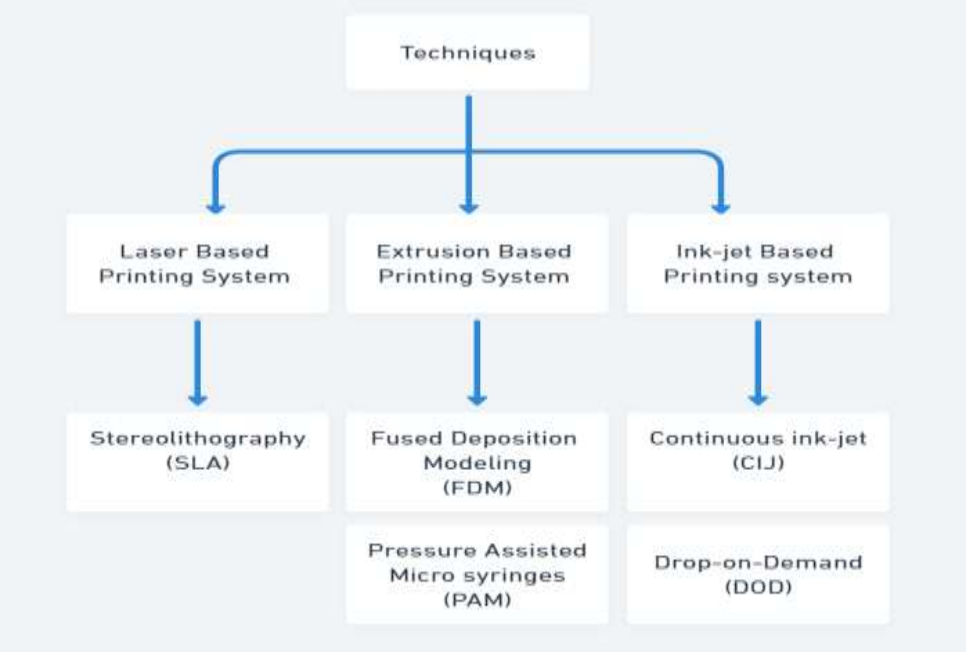
As this article holds "A State-of-the-Art-Review" for 3-D techniques in Pharmacy.

With this review work, this article could become the reference for future research work. After being recognized by the USFDA (US food and drug administration) in year 2015 This article has potential to spark a new wave in research of 3-d techniques. Yet now there is some challenges that are being faced that could inform the key future developments in 3-D printed pharmaceuticals.

Techniques

These 3-D techniques help and plays a vital role in various sectors, especially in medical sector giving a wide variety of resources. Let's have a detailed overview on the techniques that helps to make these rarefied innovations. There are several techniques that helps us to manufacture pharmaceutical preparations, those are:

Flowchart 1.



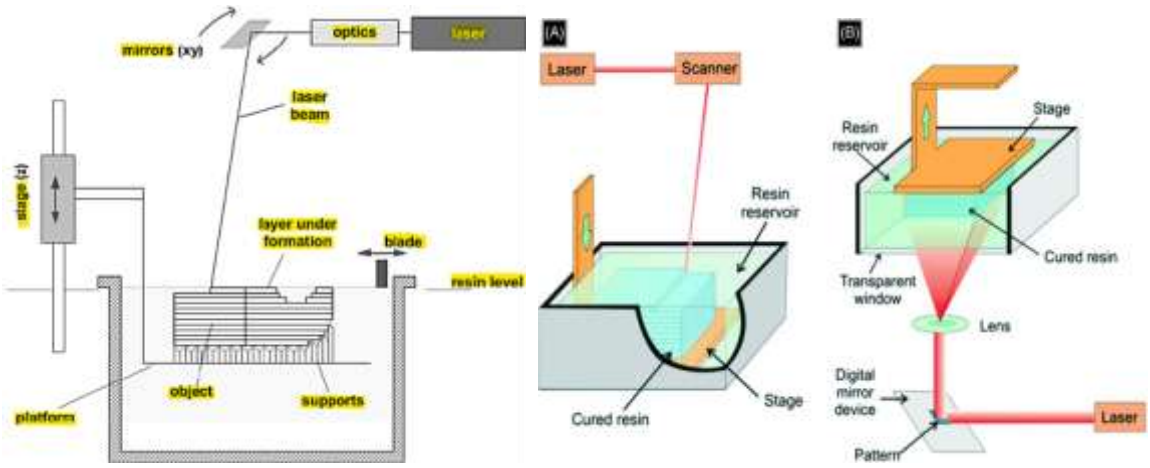
- **Laser Based printing system**: Laser-based printing systems operate on the principle of using laser beams to create patterns or images on a substrate.[2]

Table 2.

Printing System	Technique	Pros	Cons
Laser Based printing system	SLA, SLS	• This technique prints object with high resolution (~10–300 μm) and highest accuracy. • Best suited for complex and micro- delivery devices. • Minimum chance of drug decomposition and minimum mechanical anisotropy.	• Limited availability of drugs and excipients that are suitable for the technique. • Process is slow (printing speed between 1 and 5 cm/s). • High input energy of laser may degrade starting material.

1. SLA: (Stereolithography) First ever technique to be discovered by Charles Hull yet the most reviewed and used technique. Also known as vat photopolymerization.[8] This technique can be easily explained by figure, in this technique a thick resin liquid is rapidly passed through a nozzle and exposed from a UV-Light spectrum which hardens the resin liquid and turns into hard object.[7] Based on this principle this technique revolutionizes the industrialization, provide ease to build one-of-kind 3-d objects. After this technique the other techniques develop drastically, so its not wrong to say that SLA is the mother technique.

Figure for SLA
Figure 1.[45]



- **Extrusion Based printing system**

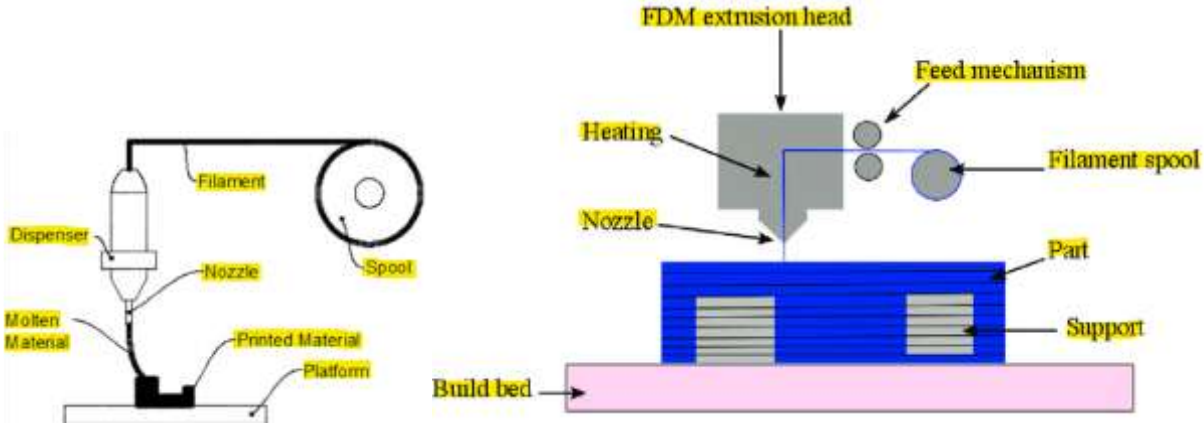
Extrusion-based printing systems in pharmacy are a type of 3D printing technology that allows for the fabrication of pharmaceutical products using a layer-by-layer extrusion process.[9] There are different technique as follows.

Table 3.

Printing System	Technique	Pros	Cons
Extrusion-based printing systems	FDM, PAM	High equipment diversity (multiple nozzles) Low equipment price Good mechanical properties of printed dosage forms	Difficult to scale up Low drug loading

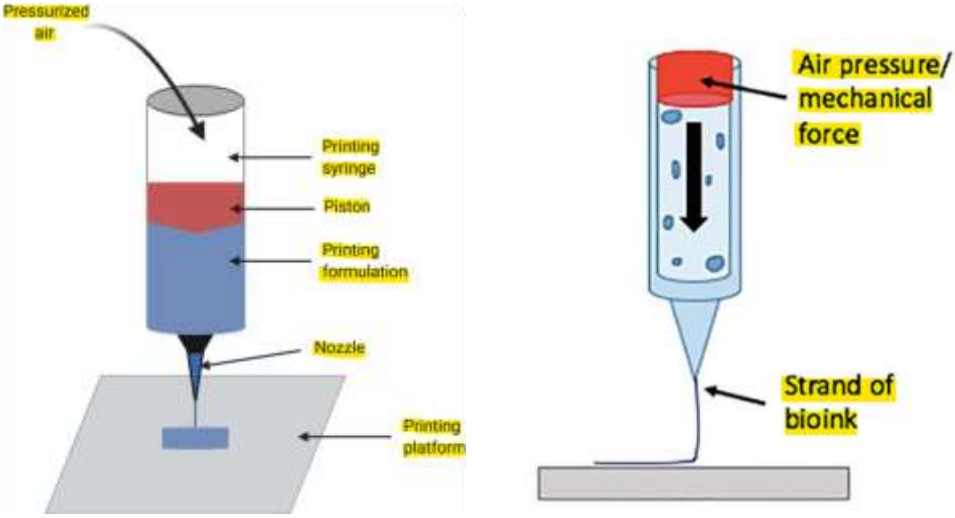
1. FDM: This technique is also known as Fused Filament Fabrication (FFF) and Fused Deposition Modeling (FDM). This technique resembles to the extrusion-based-printing technique/system. However, it was originated for non-pharmaceutical use of printing but further developed for custom solid dosage forms. It includes some of the crucial yet important pieces to produce one-of -the-kind dosage form those are: (filament, roller, heat extrusion head, heating nozzle, solid dosage form) the following equipment are ease available and in-expensive.[8][9] Now through process a thermosetting filament is used to pass through two heated rollers and melted extrusion is passed through nozzle to produce a layer-by-layer design using a CAD model (Computer-based-software) and thus print a 3-D structured solid dosage form.[7]

Figure 2.[44]



2. PAM: This technique also resembles to the extrusion-based-printing technique/system. It is known as Pressure Assisted Micro syringes, typically these techniques extrude the material from a moving nozzle, through a pressure-controlled air pump. With the help of air pump, the material is extruded from nozzles of different size and shapes.[9][5] Then the printer head moves to form a design pattern. This technique also follows CAD software and STL format to print the 3-d printing tablet (on demand manufacturing with immediate release) and encapsulated medicines (poly-vinyl alcohol PVA and polymer PLGA).[2] This technique uses non gritty extrude material such as viscous and semi-liquid material which can be extruded with the pressurized air.

Figure 3.[43]



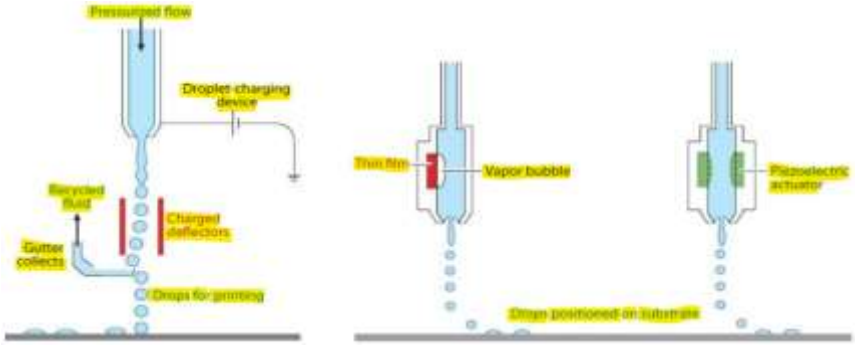
- **Inkjet based printing system**: The fundamental principles of inkjet printing, including droplet formation and deposition mechanisms, as well as there are different types of inkjet printing technologies currently in use.[5][9] The formulation of the ink or "solution" is a crucial step in inkjet printing. A solution contains the active pharmaceutical ingredient (API), excipients, and other additives necessary for the desired pharmaceutical application. The inkjet printer is programmed to deposit the solution onto the substrate (powder bed or droplet). The printer applies precise control over droplet size (through a nozzle), enabling the creation of intricate patterns or coatings. Multiple layers or different formulations can be printed to achieve specific drug release. There are two types of printing techniques which works on this principle.

Table 4.

Printing system	Technique	Pros	Cons
Inkjet based printing system	CIJ, DOD	• Simple application procedure • High dose flexibility • Choice from wide range of starting material • Easier production of porous structure	• Limited availability of solvent based inks • High amount of ink and unbound powder are wasted • Nozzle clogging leading to inaccurate jetting and subsequent dropping • Low drug loading attained in case of poorly soluble drugs

1. CIJ Which is also known as Continuous inkjet printing system, which consist the continuous flow of the solution on to substrate surface through a nozzle consisting piezoelectric transducer.[9]

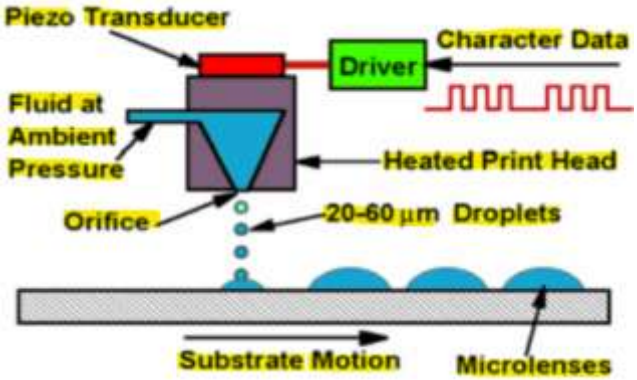
Figure 4.[46]



2. DOD Also known as Drop-on-Demand printing system, with controlled release of the solution through a nozzle consist thermal head and piezoelectric printheads, gives less amount of solution to be used. This technique further divides into different types: those are

- Drop-on-liquid
- Drop-on-solid.

Figure 5.[47]



Comparison of Traditional method, Old 3-D techniques and New 3-D techniques

Table 5.

Traditional method:	Old 3-D Technology: (Stereolithography)	New 3-D Technology (FDM)
1: More time consuming.	1: Fast as compare to traditional method but slow compare to new	1: It follows layer-by-layer design yet fast among all.
2: Leads to wastage of material.	2: It is compressed form of drug leads to less waste.	2: Produces more efficacy with less volume.
3: Required high man power.	3: High power consumption required by this technique.	3: Less power consuming but require skilled man power.
4: Chances of contamination are high as compare to others.	4: Chances of contamination is low.	4: Also having less contamination chances

CAD: A CAD model refers to a Computer-Aided Design model. CAD is a technology used in various industries, including pharmacy, to create detailed and precise digital representations of dosage and formulation. In pharmacy, CAD models can be utilized for various purposes[1][8], such as:

- Drug formulation: CAD models can assist in the design and development of new drug formulations. Pharmacists and researchers can use CAD software to create 3D models of drug molecules and analyze their chemical properties, structure, and interactions with receptors.
- Packaging design: CAD models can be employed to design pharmaceutical packaging, such as blister packs, bottles, and containers. With CAD software, pharmacists can create virtual prototypes, test different designs, and assess their functionality and compatibility with the medication.
- Equipment design: CAD models are used in the design and development of pharmaceutical equipment and machinery. For example, in the manufacturing of tablets or capsules, CAD models can aid in designing the equipment responsible for the production process.
- By leveraging CAD models in pharmacy, professionals can visualize and simulate different aspects of drug development, packaging, equipment, and pharmacy design. In practical terms, this means that person can produce practically anything that can be designed using a Computer-Aided Design (CAD) software in a digital platform.[1]

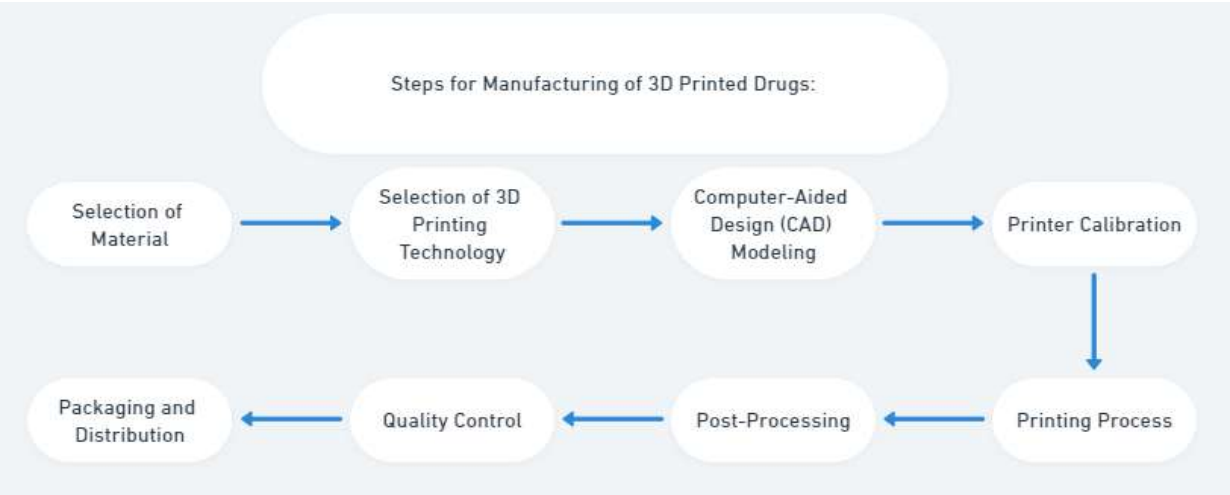
Up to this date there are multiple options available for designing. Those are.

Table 6.

Sr no.	Tools/ Software	Name of Designer	Approach/ Application	Reference
1.	Flex X	T. Lengauer and M. Rarey BioSolveIT	Incremental Construction	[14]
2.	Glide	Schrödinger Inc	Monte Carlo Sampling	[15]
3.	DOCK	I. Kuntz University of California, San Francisco	Shape fitting (sphere sets)	[13]
4.	GOLD	Cambridge Crystallographic Data Centre	Genetic Algorithm	[16]
5.	Ligand fit	Accelrys Inc.	Monte Carlo Sampling	[17]
6.	Auto Dock	D. S. Good sell and A. J. Olson The Scripps Research Institute	Genetic Algorithm Lamarckian Genetic Algorithm Simulated Annealing	[12]
7.	Rhinoceros 3d, Free CAD, Fusion 360.	Robert McNeel & Associates	CAD softwares	[18]
8.	ZMorph 2.0SX, RegenHU Benchtop, Carbon M2.	Z Morph Company	3D printer softwares	[18]
9.	3D Systems ProJet 6000, Z Corporation Spectrum Z510	ProJet Series	Packaging design, 3D modeling for equipment design	[18]
10.	Osirix, 3D Slicer Blender, 3 Mtic, and MakerBot print	By Antoine Rosset, Charles Marion	Digital Imaging and Communication in Medicine	[18]

Procedure for Manufacturing of 3D Printed Drugs.

Flowchart 2.



Selection of Material

- Select the active pharmaceutical ingredient (API) for the drug. Determine the appropriate excipients (inactive ingredients) such as binders, disintegrants, and fillers. Formulate the drug by combining the API and excipients in specific ratios to achieve the desired properties.

Selection of 3D Printing Technology

- Evaluate different 3D printing technologies such as powder bed fusion, stereolithography, or extrusion-based printing. Consider factors such as the drug's characteristics, required dosage form, printing speed, and resolution to choose the most suitable technology.

Computer-Aided Design (CAD) Modeling

- Create a digital model of the desired drug dosage form using CAD software. Specify the dimensions, shape, and geometry of the drug product in the CAD model (Rhinoceros 3d, Free CAD, Fusion 360).[1][10]

Printer Calibration

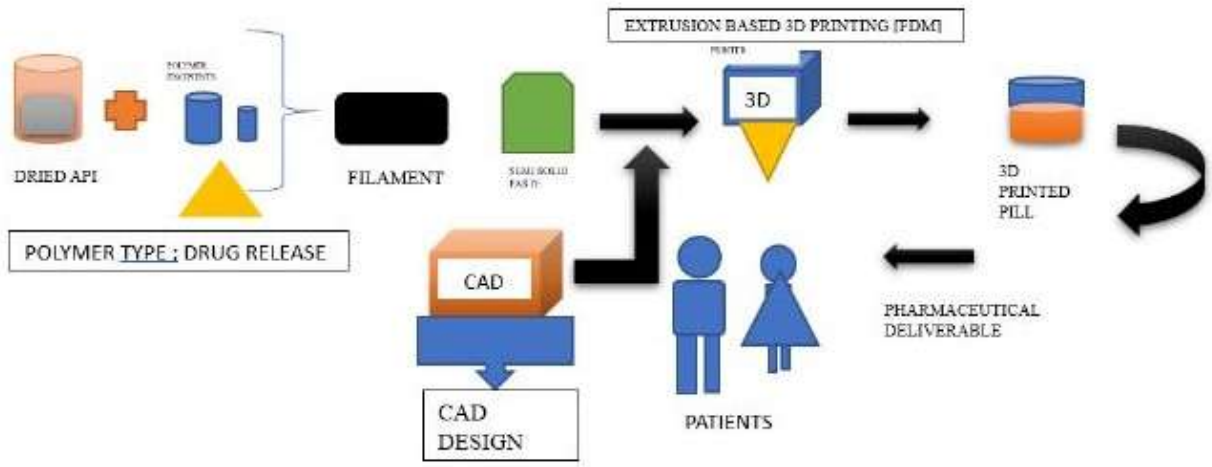
- Calibrate the 3D printer according to the manufacturer's instructions. Adjust parameters such as temperature, speed, and resolution to ensure accurate and precise printing.[3]

Material Preparation

- Prepare the drug formulation for 3D printing. Depending on the chosen 3D printing technology, prepare a specialized ink, filament, or powder mixture that includes the drug formulation and other additives if required.

Printing Process

As shown in **Figure 6.**



Example of 3-D Printed Drugs

- In Pre-Clinical Research.
- Load the prepared drug formulation into the 3D printer.
- Initiate the printing process, which involves depositing or fusing the material layer by layer based on the CAD model.
- The printer may use a nozzle or laser to precisely place the material and solidify it if necessary.[1]

Post-Processing

- After printing is complete, perform post-processing steps to enhance the properties of the 3D printed drug product.
- This may include drying, curing, or additional treatments such as heat or light exposure.

Quality Control

- Conduct rigorous quality control tests on the manufactured drug products to ensure they meet safety, efficacy, and quality standards.
- Perform analytical testing to verify the drug's identity, purity, and potency.
- Conduct dissolution testing to assess how the drug dissolves and releases in the body.
- Conduct stability studies to evaluate the shelf life and storage conditions of the 3D printed drugs.

Packaging and Distribution

- Package the 3D printed drug products in suitable containers, ensuring proper labeling and instructions for use.
- Comply with regulatory requirements for packaging and distribution.
- Distribute the drugs to pharmacies, hospitals, or other healthcare providers.[18]

Table 7.

Sr. No.	Formulation/Dosage	3D Technology	Drug	Animal	Aim	Reference
1	Capsule	FDM	Lamivudine	Beagle dog	Thicknesses to modulate Drug Release	[10,29]
2	Capsule	FDM	Radiotracer	Rat	Medical Imaging	[10,28]
3	Capsule	FDM	Octreotide, sodium caprate and paracetamol	Beagle dog	Release in upper gastrointestinal tract	[10,27]
4	Tablet	FDM	Isoniazid and rifampicin B	Rat	Dual-compartmental dosage unit	[10,30]
5	Tablet	FDM	Sodium warfarin	Rat	Alternative to splitting marketed tablets	[10,26]
6	Tablet	FDM	Diltiazem	Rat	Pulsatile and Chrono controlled-release tablets	[10,25]
7	Tablet	SSE	Efavirenz, tenofovir and emtricitabine	Pig	Controlled release tablets	[10,24]
8	Gastro-floating tablet	FDM	Domperidone	Rabbit	Determination of their gastric residence time	[10]
9	Gastro-floating tablet	FDM	Amoxicillin	Rabbit	Prolong the gastric residence time	[10,23]
10	Gastro-floating tablet	FDM	Acyclovir	Beagle dog	Determination of the residence time	[10,22]
11	Gastric resident device	FDM	Doxycycline and levonorgestrel	Pig	Development of a gastric resident electronic device	[10,21]
12	Gastric resident device	VAT photo polymerization	Ivermectin	Pig	Ultra-long-acting Drugs	[10,20]
13	Suppository	SSE	Tacrolimus	Rat	Therapeutic activity of lipid-based tacrolimus suppositories	[10,31]

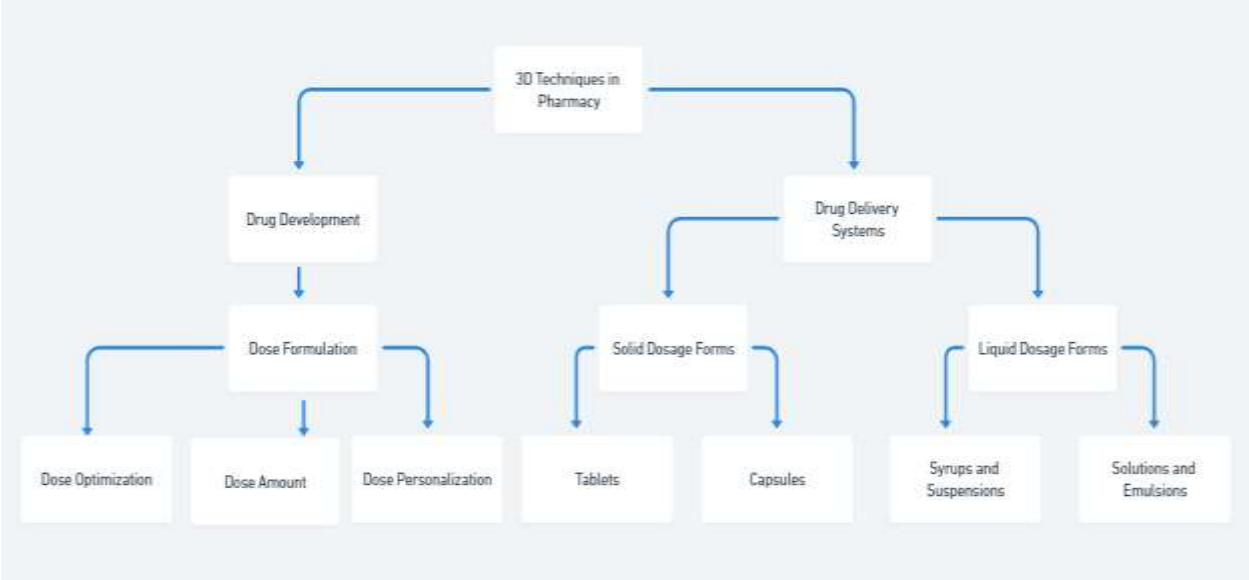
- Drugs approved and Marketed

Table 8.

Sr No.	Formulation/Dosage	3d Technology	Drug	Aim	Reference
1	Disintegrating Tablet	DoP ink-jet based	Levetiracetam Spritam®	High porosity, Disintegration time around 5s	[8]
2	Tablet	PAM Extrusion based	Captopril/Glipizide/Nifedipine	One tablet containing various APIs, displaying different release profiles	[32]
3	Biodegradable implant	FFF extrusion based	5-fluoruracil	Tailored biodegradable implants that deliver high amounts of API locally	[33]
4	Oral dose	Fused Deposition Modelling (FDM)	Theophylline	New dose morphology, improved drug dissolution and release rate	[34]
5	Tablet	Water-based inkjet	Thiamine (Vitamin B1)	Application of the printing system without toxic solvents or high temperatures	[35]
6	Tablet	FDM extrusion based	Ibuprofen	Excipient adaption to produce a sustained drug release	[36]
7	orodispersible film	FDM	Aripiprazole	Alternative method to orodispersible film production	[37]
8	Vaginal rings	FDM	Progesterone	The vaginal rings showed the long-term sustained release of progesterone for more than 7 days	[38]

9	Microneedle patch	Piezoelectric inkjet printing technique	Seasonal influenza vaccine	The 3D printing technique was utilized to precisely fabricate bilayer dissolvable microneedle	[39]
10	Coating shell to encapsulate tablet	PAM	Propranolol HCl	3D printed coating shell to control the drug release of encapsulated immediate-release tablets.	[40]
11	Tablet	FDM and injection modeling (IM) technique	Caffeine	The drug release profile exhibits both immediate and sustained release characteristics	[41]
12	Intrauterine device (IUD)	SLS	Progesterone and 5-fluorouracil	The 3D printed IUD exhibited zero-order release kinetics throughout the dissolution profile for progesterone while 5-fluorouracil exhibited initial burst release followed by a sustained release	[42]
13	Solution	Thermal Inkjet (TIJ) Printing	Salbutamol sulphate	Treatment of asthma	[9]
14	Nanoparticles	Inkjet 3DP	Rifampicin	Absorbs from gastrointestinal tract inhibit DNA dependent RNA polymerase	[9]
15	Tablet	(FDM) and Hot Melt Extrusion (HME)	Domperidone, hydroxypropyl cellulose (HPC)	Gastric muscle contraction stimulation, inhibit effect of dopamine	[9]

Application of 3D Techniques in Pharmacy
Flowchart 3.



Majorly the 3D techniques help in Pharmacy by two ways as shown in above Flowchart

- **Drug Development (Dose Formulations):** Drug development is a complex process that involves the discovery, design, testing, and development and.[29][59]

1. **Dose Optimization:** Dose optimization through 3D printing technology involves using precise fabrication methods improving treatment effectiveness while minimizing side effects, facilitates combination therapy. While the field is still evolving, further research and regulatory considerations are being addressed to ensure the safety and efficacy of 3D-printed medications.
2. **Dose Amount:** Dose personalization through 3D printing technology involves the creation of customized dosage forms tailored to meet the specific needs of individual patients. This innovative approach allows for the precise fabrication of medication doses based on patient-specific

characteristics such as body weight, age, and medical condition. 3D printing enables the production of dosage forms with personalized drug concentrations, release profiles, and even shapes and sizes.

3. **Dose Personalization:** Dose amount customization through 3D printing technology involves the fabrication of dosage forms with precise and specific drug concentrations.[5][20] With 3D printing, medication doses can be tailored to meet the individual needs of patients. This technology allows for the creation of dosage forms with accurate and personalized drug amounts, ensuring optimal therapeutic effect while minimizing the risk of adverse reactions.

- **Drug Delivery system:** A drug delivery system refers to the methods and technologies used to deliver medications or therapeutic agents to the intended site of action to the patient.

Solid Dosage Form: Solid dosage forms are pharmaceutical preparations that are presented in a solid form for administration. They are designed to deliver a specific dose of medication to patients.

1. **Tablets:** tablets are most widely used dosage forms for the patients which could be comprised of one or more active pharmaceutical ingredient and excipients, by the application 3DP technologies for the betterment of drug delivery.[25][29]
   For Example: Immediate release tablets (theophylline with polymer poly vinyl pyrrolidone)[18], dissolution rate (polyethylene glycol 6000 and 20000), modified release tablets (theophylline) and tablets containing multiple API (metformin and glimepiride).
2. **Capsules:** these are also the solid dosage forms which encapsulate the drug in shell to limit the site of release. The techniques are used to build these encapsulated shells is fused deposition modelling. For example.

Amoxicillin is encapsulated in SiaMox® (a commercial capsule).[18]

Liquid Dosage Form: Liquid dosage forms are pharmaceutical preparations that are presented in a liquid form for administration. They are designed to deliver a specific dose of medication to patients.

1. Syrups and Suspensions: The application of 3D printing (3DP) technique to the production of syrups and suspensions offers several advantages.[4][26] On-demand production reduces waste and ensures freshness and potency. However, further research is needed to optimize formulation, printing processes, regulatory considerations, and quality control for safe and effective 3D-printed syrups and suspensions.
2. Solutions and Emulsion: The application of 3D printing (3DP) technique to the formulation of solutions and emulsions offers unique advantages for drug delivery. Customized Solutions, Complex Formulations, Enhanced Drug Stability, Precise Emulsion Design, Tailored Drug Release Profiles.[8][10]

- It can low the cost of production, decrease production time and allow new product design with complex and unique drug release profile. Ability to fabricate complex geometrics of the drug releasing kinetics with rapid production, used to scale the model object in lesser time.[9] Using CAD software complex structures are built and printed in such time lowers the risk of damaging, wastage in production and health of patient.[1][30] With these applications 3D techniques Optimize the health care system.

Challenges

One of the major issue/ challenges is potential high cost. Limited supply of Pharmacy compounding. Design has minimum availability. Custom design can cause heavy work load that can lead to high cost. Difficulty to maintain viscosity of semisolid formation yet it takes long post printing time.

CONCLUSION

In conclusion, the ongoing development of drug dosage design techniques holds the promise of significantly benefiting mankind in the future. The continuous refinement and discovery of new improvements have the potential to reshape treatment systems, leading to better patient outcomes. With each advancement, drug dosage design techniques will become more sophisticated and targeted, revolutionizing the pharmaceutical industry, hospitals, and medical institutions. As these techniques gain FDA approval, their credibility and effectiveness will be solidified, paving the way for their widespread adoption and integration into mainstream medical practices. The future of drug dosage design is bright, offering the potential for personalized and precise therapies that can address complex medical challenges. Patients can look forward to improved treatments with reduced side effects, shorter recovery times, and better overall care. Furthermore, pharmaceutical industries will witness a transformation, focusing on developing innovative medications that align with these advanced drug dosage design techniques. This shift in approach will drive research and development towards finding solutions for previously untreatable conditions, leading to a healthier and more hopeful future for all. Embracing these techniques and fostering further research will undoubtedly reshape the landscape of healthcare, ushering in a new era of medical advancements that benefit humanity in myriad ways.

REFERENCES

1. SHARMA, A., KUNWAR, S., VAISHALI, AGARWAL, V., SINGH, C., SHARMA, M. D., & CHAUHAN, N. (2021). Molecular Docking: an Explanatory Approach in Structure-Based Drug Designing and Discovery. *International Journal of Pharmacy and Pharmaceutical Sciences*, *January*,

6–12. https://doi.org/10.22159/ijpps.2021v13i6.40830.
2. Mohapatra, S., Kar, R. K., Biswal, P. K., & Bindhani, S. (2022). Approaches of 3D printing in current drug delivery. In *Sensors International* (Vol. 3). KeAi Communications Co. https://doi.org/10.1016/j.sintl.2021.100146.
3. Okafor-Muo, O. L., Hassanin, H., Kayyali, R., & ElShaer, A. (2020). 3D Printing of Solid Oral Dosage Forms: Numerous Challenges With Unique Opportunities. In *Journal of Pharmaceutical Sciences* (Vol. 109, Issue 12, pp. 3535–3550). Elsevier B.V. https://doi.org/10.1016/j.xphs.2020.08.029.
4. Tracy, T., Wu, L., Liu, X., Cheng, S., & Li, X. (2023). 3D printing: Innovative solutions for patients and pharmaceutical industry. *International Journal of Pharmaceutics*, *631*. https://doi.org/10.1016/j.ijpharm.2022.122480.
5. Mohammed, A. A., Algahtani, M. S., Ahmad, M. Z., Ahmad, J., & Kotta, S. (2021). 3D Printing in medicine: Technology overview and drug delivery applications. *Annals of 3D Printed Medicine*, *4*. https://doi.org/10.1016/j.stlm.2021.100037.
6. Zhu, X., Li, H., Huang, L., Zhang, M., Fan, W., & Cui, L. (2020). 3D printing promotes the development of drugs. In *Biomedicine and Pharmacotherapy* (Vol. 131). Elsevier Masson SAS. https://doi.org/10.1016/j.biopha.2020.110644.
7. Beg, S., Almalki, W. H., Malik, A., Farhan, M., Aatif, M., Rahman, Z., Alruwaili, N. K., Alrobaian, M., Tarique, M., & Rahman, M. (2020). 3D printing for drug delivery and biomedical applications. In *Drug Discovery Today* (Vol. 25, Issue 9, pp. 1668–1681). Elsevier Ltd. https://doi.org/10.1016/j.drudis.2020.07.007.
8. Souto, E. B., Campos, J. C., Filho, S. C., Teixeira, M. C., Martins-Gomes, C., Zielinska, A., Carbone, C., & Silva, A. M. (2019). 3D printing in the design of pharmaceutical dosage forms. In *Pharmaceutical Development and Technology* (Vol. 24, Issue 8, pp. 1044–1053). Taylor and Francis Ltd. https://doi.org/10.1080/10837450.2019.1630426.
9. Godge, D. G. R., Ghume, V. K., Bidave, B. B., & Golhar, A. R. (2021). 3D Printing Technology in Pharmaceutical Drug Delivery. *International Journal of Pharmaceutical Sciences Review and Research*, *68*(1). https://doi.org/10.47583/ijpsrr.2021.v68i01.003.
10. Seoane-Viaño, I., Trenfield, S. J., Basit, A. W., & Goyanes, A. (2021). Translating 3D printed pharmaceuticals: From hype to real-world clinical applications. In *Advanced Drug Delivery Reviews* (Vol. 174, pp. 553–575). Elsevier B.V. https://doi.org/10.1016/j.addr.2021.05.003.
11. Choudhury MD. In silico study for identification of drug like inhibitor from natural compounds against INHA reductase of Mycobacterium tuberculosis. Int J Pharm Pharm, 2015; 7: 232-7.
12. Goodsell DS, Olson AJ. Automated docking of substrates to proteins by Simulated Annealing. Proteins, 1990; 8: 195-202.
13. Jha N, Kumar P. Molecular docking studies for the comparative analysis of different biomolecules to target hypoxia inducible factor-1α. Int J Appl Pharm, 2017; 9: 83-9.
14. Choudhury MD. In silico study for identification of drug like inhibitor from natural compounds against INHA reductase of Mycobacterium tuberculosis. Int J Pharm Pharm, 2015; 7: 232-7.
15. Brindha DP, Kanakam CC, Nithya G. Docking studies for various antibacterial benzilate derivatives. Asian J Pharm Clin Res, 2017; 10: 268-71.
16. Hamsa NS, Nair VP, Chandramohan V, Patel SJ. Pharmacophore elucidation and docking studies on anti-inflammatory compounds of medicinal plants for ulcerative coloitis. Asian J Pharm Clin Res, 2013; 6: 56-61.
17. Venkatachalam CM, Jiang X, Oldfield T, Waldman M. Ligand fit: a novel method for the shape-directed rapid docking of ligands to protein active sites. J Mol Graph Model, 2003; 27: 289-307.
18. Parhi, R. (2021). Journal of Drug Delivery Science and Technology A review of three-dimensional printing for pharmaceutical applications : Quality control , risk assessment and future perspectives. *Journal of Drug Delivery Science and Technology*, *64*(February), 102571. https://doi.org/10.1016/j.jddst.2021.102571
19. Rezaei Nejad, H., Oliveira, B. C. M., Sadeqi, A., Dehkharghani, A., Kondova, I., Langermans, J. A. M., Guasto, J. S., Tzipori, S., Widmer, G., & Sonkusale, S. R. (2019). Ingestible Osmotic Pill for In Vivo Sampling of Gut Microbiomes. *Advanced Intelligent Systems*, *1*(5): 1900053. https://doi.org/10.1002/aisy.201900053.
20. Bellinger, A. M., Jafari, M., Grant, T. M., Zhang, S., Slater, H. C., Wenger, E. A., Mo, S., Lee, Y. A. L., Mazdiyasni, H., Kogan, L., Barman, R., Cleveland, C., Booth, L., Bensel, T., Minahan, D., Hurowitz, H. M., Tai, T., Daily, J., Nikolic, B., … Traverso, G. (2016). Oral, ultra-long-lasting drug delivery: Application toward malaria elimination goals. *Science Translational Medicine*, *8*(365). https://doi.org/10.1126/scitranslmed.aag2374.
21. Kong, Y. L., Zou, X., McCandler, C. A., Kirtane, A. R., Ning, S., Zhou, J., Abid, A., Jafari, M., Rogner, J., Minahan, D., Collins, J. E., McDonnell, S., Cleveland, C., Bensel, T., Tamang, S., Arrick, G., Gimbel, A., Hua, T., Ghosh, U., … Traverso, G. (2019). 3D-Printed Gastric Resident Electronics. *Advanced Materials Technologies*, *4*(3): 1–11. https://doi.org/10.1002/admt.201800490.
22. Shin, S., Kim, T. H., Jeong, S. W., Chung, S. E., Lee, D. Y., Kim, D. H., & Shin, B. S. (2019). Development of a gastroretentive delivery system for acyclovir by 3D printing technology and its in vivo pharmacokinetic evaluation in Beagle dogs.

PLoS ONE, *14*(5): 1–17. https://doi.org/10.1371/journal.pone.0216875.
23. Charoenying, T., Patrojanasophon, P., Ngawhirunpat, T., Rojanarata, T., Akkaramongkolporn, P., & Opanasopit, P. (2020). Fabrication of floating capsule-in- 3D-printed devices as gastro-retentive delivery systems of amoxicillin. In *Journal of Drug Delivery Science and Technology* (Vol. 55). Elsevier B.V. https://doi.org/10.1016/j.jddst.2019.101393.
24. Siyawamwaya, M., du Toit, L. C., Kumar, P., Choonara, Y. E., Kondiah, P. P. P. D., & Pillay, V. (2019). 3D printed, controlled release, tritherapeutic tablet matrix for advanced anti-HIV-1 drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics*, *138*: 99–110. https://doi.org/10.1016/j.ejpb.2018.04.007.
25. Kadry, H., Al-Hilal, T. A., Keshavarz, A., Alam, F., Xu, C., Joy, A., & Ahsan, F. (2018). Multi-purposable filaments of HPMC for 3D printing of medications with tailored drug release and timed-absorption. *International Journal of Pharmaceutics*, *544*(1): 285–296. https://doi.org/10.1016/j.ijpharm.2018.04.010.
26. Arafat, B., Qinna, N., Cieszynska, M., Forbes, R. T., & Alhnan, M. A. (2018). Tailored on demand anti-coagulant dosing: An in vitro and in vivo evaluation of 3D printed purpose-designed oral dosage forms. *European Journal of Pharmaceutics and Biopharmaceutics*, *128*: 282–289. https://doi.org/10.1016/j.ejpb.2018.04.010.
27. Berg, S., Krause, J., Björkbom, A., Walter, K., Harun, S., Granfeldt, A., Janzén, D., Nunes, S. F., Antonsson, M., Van Zuydam, N., Skrtic, S., Hugerth, A., Weitschies, W., Davies, N., Abrahamsson, B., & Bergström, C. A. S. (2021). In Vitro and In Vivo Evaluation of 3D Printed Capsules with Pressure Triggered Release Mechanism for Oral Peptide Delivery. *Journal of Pharmaceutical Sciences*, *110*(1): 228–238. https://doi.org/10.1016/j.xphs.2020.10.066.
28. Goyanes, A., Fernández-Ferreiro, A., Majeed, A., Gomez-Lado, N., Awad, A., Luaces-Rodríguez, A., Gaisford, S., Aguiar, P., & Basit, A. W. (2018). PET/CT imaging of 3D printed devices in the gastrointestinal tract of rodents. *International Journal of Pharmaceutics*, *536*(1): 158–164. https://doi.org/10.1016/j.ijpharm.2017.11.055.
29. Smith, D., Kapoor, Y., Hermans, A., Nofsinger, R., Kesisoglou, F., Gustafson, T. P., & Procopio, A. (2018). 3D printed capsules for quantitative regional absorption studies in the GI tract. *International Journal of Pharmaceutics*, *550*(1–2): 418–428. https://doi.org/10.1016/j.ijpharm.2018.08.055.
30. Genina, N., Boetker, J. P., Colombo, S., Harmankaya, N., Rantanen, J., & Bohr, A. (2017). Anti-tuberculosis drug combination for controlled oral delivery using 3D printed compartmental dosage forms: From drug product design to in vivo testing. *Journal of Controlled Release*, *268*: 40–48. https://doi.org/10.1016/j.jconrel.2017.10.003.
31. Seoane-Viaño, I., Gómez-Lado, N., Lázare-Iglesias, H., García-Otero, X., Antúnez-López, J. R., Ruibal, Á., Varela-Correa, J. J., Aguiar, P., Basit, A. W., Otero-Espinar, F. J., González-Barcia, M., Goyanes, A., Luzardo-álvarez, A., & Fernández-Ferreiro, A. (2020). 3D printed tacrolimus rectal formulations ameliorate colitis in an experimental animal model of inflammatory bowel disease. *Biomedicines*, *8*(12): 1–19. https://doi.org/10.3390/biomedicines8120563.
32. Khaled, S. A., Burley, J. C., Alexander, M. R., Yang, J., & Roberts, C. J. (2015). 3D printing of tablets containing multiple drugs with defined release profiles. *International Journal of Pharmaceutics*, *494*(2): 643–650. https://doi.org/10.1016/j.ijpharm.2015.07.067.
33. Zhang, C., An, T., Wang, D., Wan, G., Zhang, M., Wang, H., Zhang, S., Li, R., Yang, X., & Wang, Y. (2016). Stepwise pH-responsive nanoparticles containing charge-reversible pullulan-based shells and poly(β-amino ester)/poly(lactic-co-glycolic acid) cores as carriers of anticancer drugs for combination therapy on hepatocellular carcinoma. *Journal of Controlled Release*, *226*: 193–204. https://doi.org/10.1016/j.jconrel.2016.02.030.
34. Pietrzak, K., Isreb, A., & Alhnan, M. A. (2015). A flexible-dose dispenser for immediate and extended release 3D printed tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *96*(August), 380–387. https://doi.org/10.1016/j.ejpb.2015.07.027.
35. Zhai, Y., Yang, X., Zhao, L., Wang, Z., & Zhai, G. (2014). Lipid nanocapsules for transdermal delivery of ropivacaine: In vitro and in vivo evaluation. *International Journal of Pharmaceutics*, *471*(1–2): 103–111. https://doi.org/10.1016/j.ijpharm.2014.05.035.
36. Kitson, P. J., Glatzel, S., & Cronin, L. (2016). The digital code driven autonomous synthesis of ibuprofen automated in a 3D-printer-based robot. *Beilstein Journal of Organic Chemistry*, *12*: 2776–2783. https://doi.org/10.3762/bjoc.12.276.
37. Jamróz, W., Kurek, M., Łyszczarz, E., Szafraniec, J., Knapik-Kowalczuk, J., Syrek, K., Paluch, M., & Jachowicz, R. (2017). 3D printed orodispersible films with Aripiprazole. *International Journal of Pharmaceutics*, *533*(2): 413–420. https://doi.org/10.1016/j.ijpharm.2017.05.052.
38. Fu, J., Yu, X., & Jin, Y. (2018). 3D printing of vaginal rings with personalized shapes for controlled release of progesterone. *International Journal of Pharmaceutics*, *539*(1–2): 75–82. https://doi.org/10.1016/j.ijpharm.2018.01.036.
39. Boehm, R. D., Daniels, J., Stafslien, S., Nasir, A., Lefebvre, J., & Narayan, R. J. (2015). Polyglycolic acid microneedles modified with inkjet-deposited antifungal coatings. *Biointerphases*, *10*(1): https://doi.org/10.1116/1.4913378.
40. Azad, M. A., Olawuni, D., Kimbell, G., Badruddoza, A. Z. M., Hossain, M. S., & Sultana, T. (2020).

Polymers for extrusion-based 3D printing of pharmaceuticals: A holistic materials–process perspective. *Pharmaceutics*, *12*(2): 1–34. https://doi.org/10.3390/pharmaceutics12020124.

41. Fuenmayor, E., Forde, M., Healy, A. V., Devine, D. M., Lyons, J. G., McConville, C., & Major, I. (2019). Comparison of fused-filament fabrication to direct compression and injection molding in the manufacture of oral tablets. *International Journal of Pharmaceutics*, *558*: 328–340. https://doi.org/10.1016/j.ijpharm.2019.01.013.
42. Salmoria, G. V., Vieira, F. E., Muenz, E. A., Gindri, I. M., Marques, M. S., & Kanis, L. A. (2018). Additive Manufacturing of PE/fluorouracil/progesterone intrauterine device for endometrial and ovarian cancer treatments. *Polymer Testing*, *71*(August): 312–317. https://doi.org/10.1016/j.polymertesting.2018.09.023.
43. Vaz, V. M., & Kumar, L. (2021). 3D Printing as a Promising Tool in Personalized Medicine. *AAPS PharmSciTech*, *22*(1). https://doi.org/10.1208/s12249-020-01905-8.
44. Surmen, H. K., Akalan, N. E., & Arslan, Y. Z. (2017). Design, Manufacture, and Selection of Ankle-Foot-Orthoses. *Encyclopedia of Information Science and Technology, Fourth Edition*, *July 2017*; 298–313. https://doi.org/10.4018/978-1-5225-2255-3.ch027.
45. Beal, V. E., Ahrens, C. H., & Wendhausen, P. A. (2004). The Use of Stereolithography Rapid Tools in the Manufacturing of Metal Powder Injection Molding Parts. *Journal of the Brazilian Society of Mechanical Sciences and Engineering*, *26*(1): 40–46. https://doi.org/10.1590/S1678-58782004000100007.
46. Shama, A., Pouchon, M. A., & Clifford, I. (2019). Simulation of the microfluidic mixing and the droplet generation for 3D printing of nuclear fuels. *Additive Manufacturing*, *26*(April): 1–14. https://doi.org/10.1016/j.addma.2018.12.011
47. Altman, C. (2007). Microlens array fabrication via microjet printing technologies. *Proc. Workshop Opt. Fabrication Technol*, *May*, 2–7. http://altman.casimirinstitute.net/microlens.pdf
48. "FabRx's pharmaceutical 3D printer for personalised medicines, M3DIMAKERTM, is now available." https://www.fabrx.co.uk/2020/04/06/fabrxs-pharmaceutical-3d-printer-for-personalised-medicines-m3dimaker-is-now-available /(accessed Mar. 10, 2021).
49. Azad, M. A., Olawuni, D., Kimbell, G., Badruddoza, A. Z. M., Hossain, M. S., & Sultana, T. (2020). Polymers for extrusion-based 3D printing of pharmaceuticals: A holistic materials–process perspective. *Pharmaceutics*, *12*(2): 1–34. https://doi.org/10.3390/pharmaceutics12020124.
50. Hsiao, W. K., Lorber, B., Reitsamer, H., & Khinast, J. (2018). 3D printing of oral drugs: a new reality or hype? *Expert Opinion on Drug Delivery*, *15*(1): 1–4. https://doi.org/10.1080/17425247.2017.1371698.
51. Awad, A., Trenfield, S. J., Gaisford, S., & Basit, A. W. (2018). 3D printed medicines: A new branch of digital healthcare. *International Journal of Pharmaceutics*, *548*(1): 586–596. https://doi.org/10.1016/j.ijpharm.2018.07.024.
52. Samiei, N. (2020). Recent trends on applications of 3D printing technology on the design and manufacture of pharmaceutical oral formulation: a mini review. *Beni-Suef University Journal of Basic and Applied Sciences*, *9*(1): https://doi.org/10.1186/s43088-020-00040-4.
53. De Gans, B. J., Duineveld, P. C., & Schubert, U. S. (2004). Inkjet printing of polymers: State of the art and future developments. *Advanced Materials*, *16*(3): 203–213. https://doi.org/10.1002/adma.200300385.
54. Goyanes, A., Buanz, A. B. M., Basit, A. W., & Gaisford, S. (2014). Fused-filament 3D printing (3DP) for fabrication of tablets. *International Journal of Pharmaceutics*, *476*(1): 88–92. https://doi.org/10.1016/j.ijpharm.2014.09.044.
55. Jennotte, O., Koch, N., Lechanteur, A., & Evrard, B. (2020). Three-dimensional printing technology as a promising tool in bioavailability enhancement of poorly water-soluble molecules: A review. *International Journal of Pharmaceutics*, *580*: 119200. https://doi.org/10.1016/j.ijpharm.2020.119200.
56. Mohammed, A. A., Algahtani, M. S., Ahmad, M. Z., & Ahmad, J. (2021). Optimization of semisolid extrusion (pressure-assisted microsyringe)-based 3D printing process for advanced drug delivery application. *Annals of 3D Printed Medicine*, *2*: 100008. https://doi.org/10.1016/j.stlm.2021.100008.
57. Lu, A., Zhang, J., Jiang, J., Zhang, Y., Giri, B. R., Kulkarni, V. R., Aghda, N. H., Wang, J., & Maniruzzaman, M. (2022). Novel 3D Printed Modular Tablets Containing Multiple Anti-Viral Drugs: a Case of High Precision Drop-on-Demand Drug Deposition. *Pharmaceutical Research*, *39*(11): 2905–2918. https://doi.org/10.1007/s11095-022-03378-9.
58. Ong, J. J., Castro, B. M., Gaisford, S., Cabalar, P., Basit, A. W., Pérez, G., & Goyanes, A. (2022). Accelerating 3D printing of pharmaceutical products using machine learning. *International Journal of Pharmaceutics: X*, *4*(May). https://doi.org/10.1016/j.ijpx.2022.100120.
59. Zheng, Y., Deng, F., Wang, B., Wu, Y., Luo, Q., Zuo, X., Liu, X., Cao, L., Li, M., Lu, H., Cheng, S., & Li, X. (2021). Melt extrusion deposition (MED^{TM}) 3D printing technology – A paradigm shift in design and development of modified release drug products. *International Journal of Pharmaceutics*, *602*(April): 120639. https://doi.org/10.1016/j.ijpharm.2021.120639
60. Trenfield, S. J., Awad, A., Madla, C. M., Hatton, G. B., Firth, J., Goyanes, A., Gaisford, S., & Basit, A.

W. (2019). Shaping the future: recent advances of 3D printing in drug delivery and healthcare. *Expert Opinion on Drug Delivery*, *16*(10): 1081–1094. https://doi.org/10.1080/17425247.2019.1660318.

61. Khaled, S. A., Burley, J. C., Alexander, M. R., & Roberts, C. J. (2014). Desktop 3D printing of controlled release pharmaceutical bilayer tablets. *International Journal of Pharmaceutics*, *461*(1–2): 105–111. https://doi.org/10.1016/j.ijpharm.2013.11.021.
62. Allen, E. A., O'Mahony, C., Cronin, M., O'Mahony, T., Moore, A. C., & Crean, A. M. (2016). Dissolvable microneedle fabrication using piezoelectric dispensing technology. *International Journal of Pharmaceutics*, *500*(1–2): 1–10. https://doi.org/10.1016/j.ijpharm.2015.12.052.
63. Algahtani, M. S. (2021). Assessment of Pharmacist's Knowledge and Perception toward 3D Printing Technology as a Dispensing Method for Personalized Medicine and the Readiness for Implementation. *Pharmacy*, *9*(1): 68. https://doi.org/10.3390/pharmacy9010068.
64. Su, A., & Al'Aref, S. J. (2018). History of 3D printing. In *3D Printing Applications in Cardiovascular Medicine*. Elsevier Inc. https://doi.org/10.1016/B978-0-12-803917-5.00001-8.