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3D PRINTING - A NEW TECHNOLOGY FOR THE PHARMACEUTICAL INDUSTRY

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ABSTRACT: Three-dimensional printing (3DP) is an imminent technology used to describe 3D products generated using a digital design platform manufactured layer by layer. This technology appears to be a transformative tool. It has just emerged as a key technological breakthrough, allowing the pharmaceutical sector to develop and generate new pharmaceutical items and equipment. It's a brand-new way to personalize pharmaceutical formulation and design. Spiratam® (levetiracetam), the first commercial 3D tablet, was approved by the FDA in August 2015, sparking a rise in interest in employing this platform for pharmaceutical development. Following the FDA's approval of the first 3D printed tablet, Spritam. The concept can benefit patients, pharmacists, and the pharmaceutical business by enabling the on-demand design and fabrication of flexible formulations with customized dosages, forms, sizes, drug release, and multi-drug combinations. This is a watershed moment in the history of 3D printing in pharmaceuticals, needing the involvement and assistance of healthcare professionals like pharmacists, doctors, nurses, and pharmacy technicians, among others, to enable wider use of the technology. This article summarises current state-of-the-art 3D printing methods and the major benefits and motivations for using 3D printing in pharmaceuticals, emphasizing the critical role that healthcare professionals have played and will continue to play in the future integration of 3D printing into the pharmaceutical sector.

INTRODUCTION: The Mata twins, two sisters, was born in April 2014 into an uncertain future. It was decided to separate the sisters since various common organs joined them from their chest to pelvis. When faced with one of the most difficult conjoined twin separations ever, surgeons at Texas Children's Hospital in Houston, Texas, enlisted the support of an unexpected rookie: A 3D printing device.

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The girls were subjected to a series of computed tomography scans first. This information was utilized to create highly detailed color-coded 3D reconstructions of the girl's organs and skeletons. The separation procedure could be designed and practiced using these models. The girls were separated for 18 hours during a 26-hour operation when they were 10 months old.

At the time, one of their surgeons noted. This is the first time a separation procedure for twins with this unique configuration has been successful'. 3D printing was hailed as a hero alongside the doctors [1]. Three-dimensional (3D) printing, also known as additive manufacturing, is one technique that could meet the demand for tailored therapeutics. It uses a digital model to guide the layer-by-layer production

of a 3D object. It has enormous potential to disrupt the pharmaceutical industry, as 3D printing technologies could enable on-demand production of products with personalized dosages, drug combinations, geometries and release characteristics that are not possible with current conventional manufacturing technologies like tableting and encapsulation [2].

"3D printing can be used to produce prosthetic limbs that are customized [3]."

Pharmaceutical products, including gastrofloating tablets, self-emulsifying drug delivery systems, microneedles and transdermal patches, are used in the pharmaceutical sector [4]. It's important to remember that changing the shape of a capsule doesn't always imply a change in dose or drug attributes like drug release or disintegration rate [5].

"3D printing can potentially change pharmaceutical product manufacturing by enabling decentralized and tailored therapeutic manufacturing".

"According to the International Organization for Standardization (ISO) "The manufacturing of medicines through the deposition of a substance utilizing a print head, nozzle, or other printer technology." Tissue and organ engineering, diagnostics, disease modelling, biomedical device production, and the design and development of novel dosage forms are just a few of the applications [6].

TABLE 1: DEVELOPMENT OF DIFFERENT FORMULATIONS BY USING 3-D PRINTING [7-36]

Manufacturing method	Formulation/ Effect	API	Reference
Fused deposition method	Tablet	Hydrochlorothiazide	07
Fused deposition method	Caplet	Caffeine	08
Extrusion based method	Tablet	Paracetamol	09
Sls	Orodispersible tablets	Paracetamol	10
Liquid, Solidification stereolithography	Microneedles/ Insulin Skin Delivery	Insulin	11
Fused deposition modelling	Tablet/ Immediate Release	Theophylline	12
Extrusion at room temperature	Floating tablet/sustained release, gastro floating dosage form	Dipyridamole	13
Thermal inkjet	Oral films	Salbutamol sulfate	14
Stereolithography	Hydrogel	Ibuprofen	15
Drop on drop	Tablet/Fickian diffusion API release mechanism	Ropinirole hcl	16
Drop on drop	Tablet/ Fickian diffusion API release dosage form	Fenofibrae	17
Fused deposition modeling	Orodispersible Film/ Fast disintegration and dissolution	Aripiprazole	18
Liquid solidification stereolithography	Controlled release tablet	Paracetamol 4-amino salicyclic acid	19
Inkjet 3D printing	Nanosuspension	Folic acid	20
Extrusion at room temperature	Multi-compartment tablet/ Controlled release tablet	Nifidipine, Captopril, Glipizide	21
Drop-On-Powder	Tablet	5-Fluorouracil	22
Thermal Inkjet spray freeze drying	Inhaler	Excipient free salbutamol sulphate	23
Hot melting extrusion	Floating pulsatile drug delivery	Theophylline	24
Stereolithographic printing	Ibuprofen-loaded hydrogels	Ibuprofen	25
Pressure-assisted microsyringes (PAM)	Tablet Controlled release oral drug delivery	Levetiracetam/	26
Semi-solid extrusion		polyvinylpyrrolidone-vinyl acetate copolymer (PVP-PVAc) Ramipril	27
FDM	Tablet/ Rapid Drug Release	Haloperidol	28
	Intravaginal ring	Clotrimazole	29
	Tablet/ Controlled drug release	Isoniazid (INZ) and rifampicin (RFC)	30
	Tablet/fabrication of modified-release tablets	4-amino salicylic acid (ASA) or 5-ASA	31
Semisolid extrusion	Tablet/ High drug loading levetiracetam	Levetiracetam	32

	Suppositories/Self-Emulsified Drug Delivery System	Tacrolimus	33
	Tablet/ Controlled-release	Glipizide	33
Stereo lithography (SLA)	Novel indwelling bladder devices/Site specific drug delivery	Lidocaine hydrochloride	34
	Controlled release Antihypertensive polyprintlet	Hydrochlorothiazide, Amlodipine, atenolol, Irbesartan	35
Direct powder extrusion (DPE)	Tablet/ Modified release	Tramadol	36

Printing a range of pharmaceutical formulations made up of poorly water-soluble substances and proteins showed 3D printing to be a potential method.

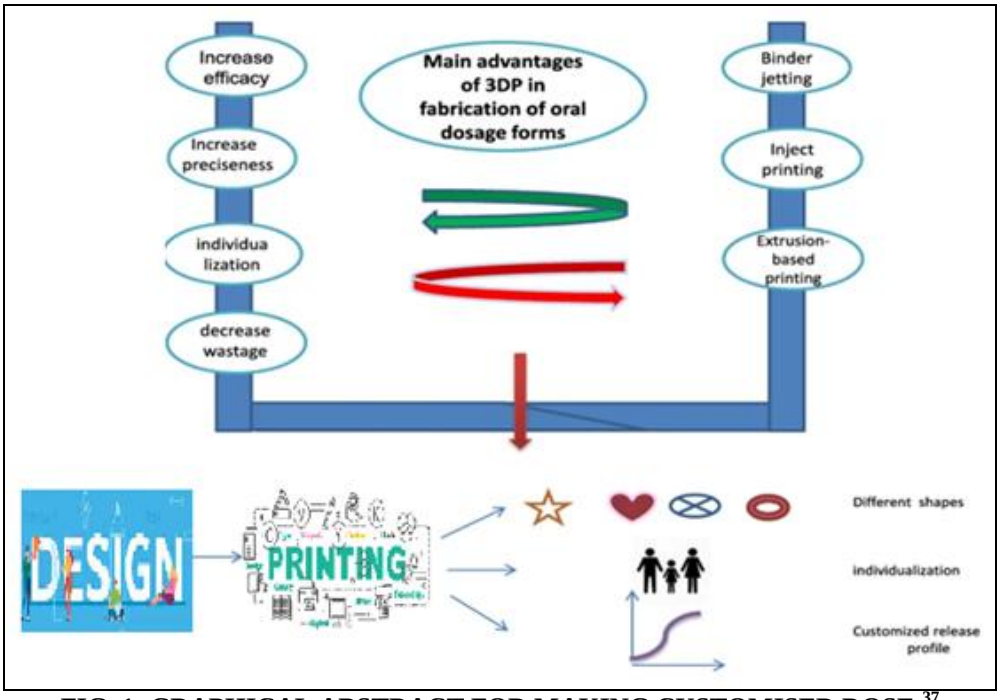

FIG. 1: GRAPHICAL ABSTRACT FOR MAKING CUSTOMISED DOSE [37]

Additive manufacturing, often known as 3D printing, encompasses a wide range of techniques that are divided into several categories, although only three of them are commonly employed in medicine 3D printing: Inkjet printing systems, nozzle-based deposition systems and laser-based writing systems are all examples of printing-based inkjet systems [38]. Since, then, a variety of technologies and materials have been researched and proved to be effective for this purpose.

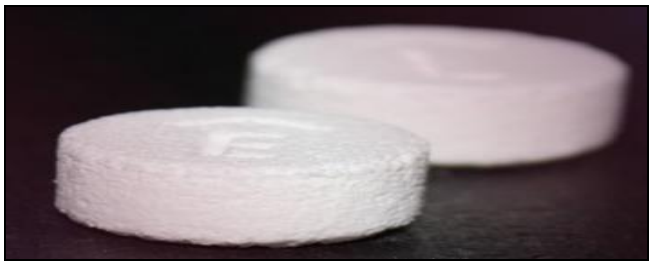

FIG. 2: SPRITAM, THE WORLD'S FIRST FDA APPROVED 3D PRINTED DRUG. PHOTO VIA APRECIA [39]

SLS stands for selective laser sintering, similar to powder pressing in that it uses the loose powder that is bonded together to form a solid item. Binder deposition is a powder-based process in which a liquid binding solution is printed onto a powder bed. Inkjet printing provides a high level of resolution [40]. Stereolithography, the first commercially available technology created by Chuck Hull, was stereolithography (SLA).

It takes advantage of the photopolymerization principle, which causes the release of free radicals after ultraviolet (UV) rays contact with a photoinitiator. When exposed to UV light, a specific patch of photosensitive liquid resin is treated to localized polymerization in a stereolithography apparatus (SLGA). Here, as the z-axis gradually changes throughout construction, UV rays pass over the surface of the liquid resin to expose the x/y axis of each separate layer. New

layers of liquid resin are layered on top of each other once a particular layer solidifies to create the final result. When a part is created, the supporting structures are physically removed, and the excess resin is rinsed away [41]. It is a type of lithography that uses (SLA). Because it is the oldest rapid prototyping technique, it is frequently used to create idea models or as a master pattern for moulding procedures. It is the selective solidification of a pool or bed of photosensitive material, and it can be utilized to make drugs. CAD data is first divided into cross-sections or layers, then transmitted to a SLA AM system with a UV-curable photopolymer vat [40]. The liquid material hardens on contact when the laser impinges on the cross-section of the resin. The build platform is indexed once each layer is done so that the next layer can be deposited. Using a bottom-up strategy, the layers are created one by one on top of each other [42].

Printing Procedure: Modeling, Printing and Finishing. Before employing a 3D printer to manufacture a product, creating a virtual model of the object is necessary using computer drug design software (CAD). A 3D modelling application or a 3D scanner was used to create this CAD file. A 3D scanner can create a 3D digital duplicate of the thing from an existing virtual model. The object model is saved as a stereolithography (STL) or additive manufacturing file (AMF) format once this process is completed. 3D printing is also ideal for creating complexity, making it ideal for rapid prototyping. Pharmaceutical drugs are also manufactured using CAD to gain maximum flexibility, time savings, and superior quality [40].

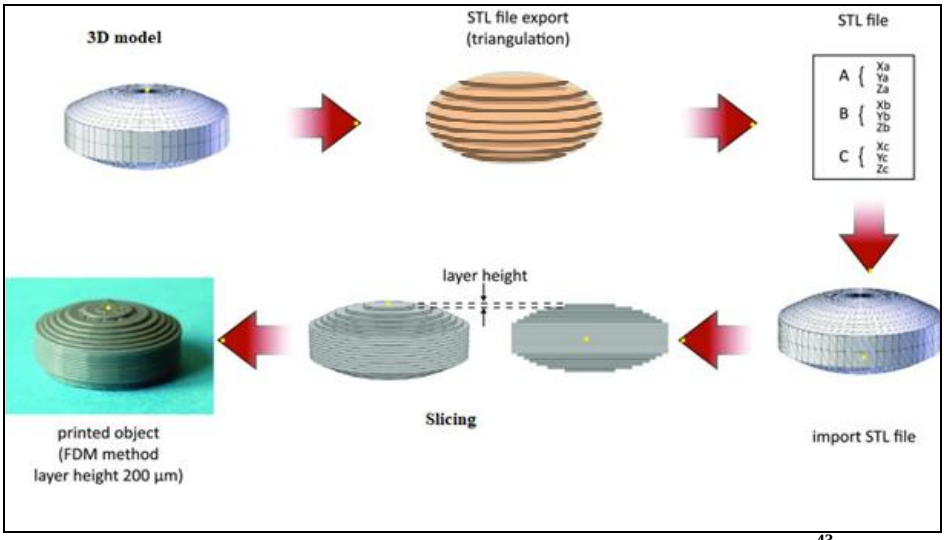

FIG. 3: THE DEVELOPMENT OF 3D PRINTED OBJECTS [43]

- A three-dimensional pharmaceutical product is created using computer-aided design.
- The design is transformed into a machine-readable format, such as STL or AMF, representing the 3D dosage form's external surface.
- This surface is then sliced into multiple unique printable layers by the computer program, which is then transferred to the machine layer by layer [44].

Advantages of A 3D Printed Drug Delivery:

1. Medication can be adjusted to a patient's specific needs based on genetic differences, ethnic differences, age, gender, and the patient's surroundings.
2. Treatment can be tailored to promote patient adherence in the event of multi-drug therapy with numerous dose regimens.
3. Because of the variable design and fabrication of this dosage form, instant and controlled release layers can be integrated, it aids in the selection of the optimal treatment regime for an individual [2, 4].
4. When compared to traditional dose forms, this dosage form has a high drug loading ability [4].
5. The quickest design cycle [5].

6. Dosing of strong medications in small doses in an accurate and precise manner

7. Reduces production costs by reducing material waste.

8. Suitable drug delivery for active components that are difficult to manufacture, such as those with low water solubility or medicines with a limited therapeutic window [5, 6].

9. 3D printers use up little space and are inexpensive.

10. Because water may be entrapped in these matrices, it is possible to construct pre-wetted, drug-loaded hydrogels and devices.

11. Stereolithographic (SLA) printing has the unique advantage of being able to fabricate objects by cross-linking resins to form networked polymer matrices [38].

12. It creates multidose or multi-drug pharmaceutical products [40].

13. Set yourself apart from the competition by putting superior products on the market first.

14. Stereolithography prototypes are machine-able and can be utilized as master patterns for injection moulding, thermoforming, blow moulding, and various metal casting methods [45].

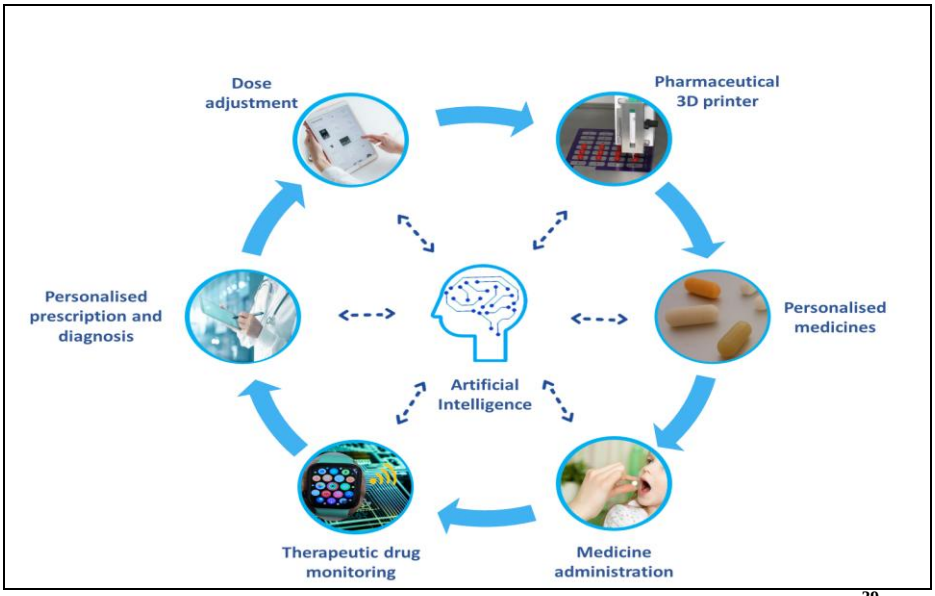

FIG. 4: THE VIRTUOUS CYCLE OF PERSONALIZED MEDICINE [39]

Disadvantages:

Product Liability: Pharmaceutical firms can authorize pharmacies and healthcare professionals to use their designs via 3D printing. As a result, they can now print medications quickly and easily on the spot [46].

Cyber risk: The proliferation of counterfeit pharmaceuticals is likely the most serious problem for the pharmaceutical business when it comes to 3D printing. Printers are far more vulnerable to hackers than traditional manufacturing methods, and the extremely quick production time increases the potential of counterfeiting.

Safety and Efficiency of 3D Printers: Traditional mass-manufacturing facilities are subject to strict regulatory control, keeping products safer and providing tranquility to insurers that cover them. However, because the FDA is unable to oversee every aspect of 3D printing, evaluating the safety of items generated and who is responsible for bad events remains a gray area. Importantly, 3D printing companies must thoroughly vet their suppliers, as tainted or defective materials might result in a flawed output, posing an even greater risk [47].

Types of 3D Printing:

Binder Jet 3D Printing: In 1993, Sachs *et al.* at the Massachusetts Institute of Technology (MIT) invented and patented binder jet printing. Binder jet printing is an inkjet printing technique commonly

known as drop-on-powder printing. The print head, which can be thermal or piezoelectric, is the most important component of a binder jet printer. A binder jet printer is made up of a powder bed linked layer by layer. A printer nozzle containing the binder (and/or medication) fluid is programmed to move along an x-y axis and jet the liquid onto the loose powder bed. The liquid drops moisten the powder, which causes the layer to harden and solidify, as illustrated in diagram [48].

Step-by-Step Binder Jetting: A roller is used to disseminate powder material throughout the build platform. The print head places the binder glue on top of the powder where necessary. The layer thickness of the model lowers the build platform.

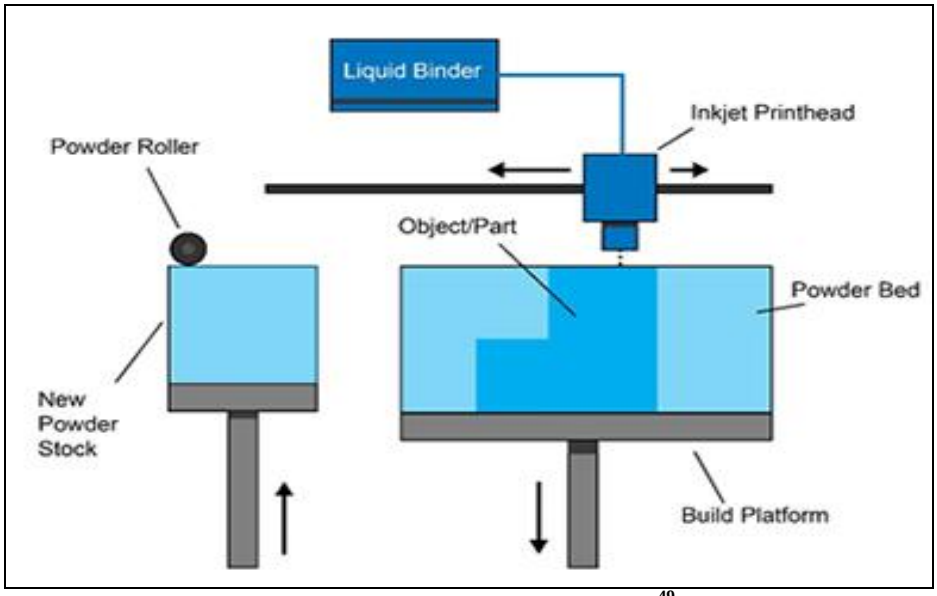

FIG. 5: BINDER JET PRINTING [49]

The second coating of powder is applied on top of the first. Where the powder is linked to the liquid, the object is produced. The unbound powder remains in the area around the object. The technique is repeated until the object is complete [49].

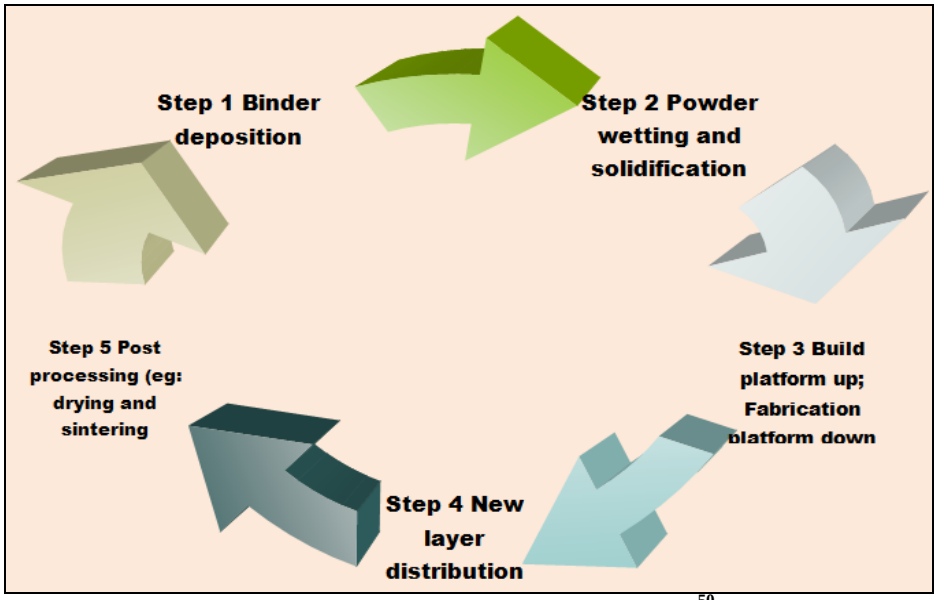

FIG. 6: STEPS FOR BINDER JETTING [50]

Thermal Ink-Jet Printing: The aqueous ink fluid is changed to a vapour state by heat, which expands to force the ink drop out of a nozzle in thermal inkjet printing. It's utilized to make drug-loaded biodegradable microspheres, drug-loaded liposomes, patterning microelectrode arrays, and

loading drug-eluting stents, among other things. It's also a tried-and-true way of creating biologics films without compromising protein activity [50].

Inkjet Printing: It is often known as 'mask-less' or 'tool-less' printing, relies heavily on inkjet nozzle movement or substrate movement for accurate and repeatable structure development. In this process, the ink is put onto a substrate using either Continuous Inkjet printing or Drop on Demand printing. As a result, it allows for high-resolution printing. It has a low cost, a high rate of printing processing and produces a low amount of waste.

It provides CAD data in a 'direct write' format and processes material over wide regions with little contamination [50, 51].

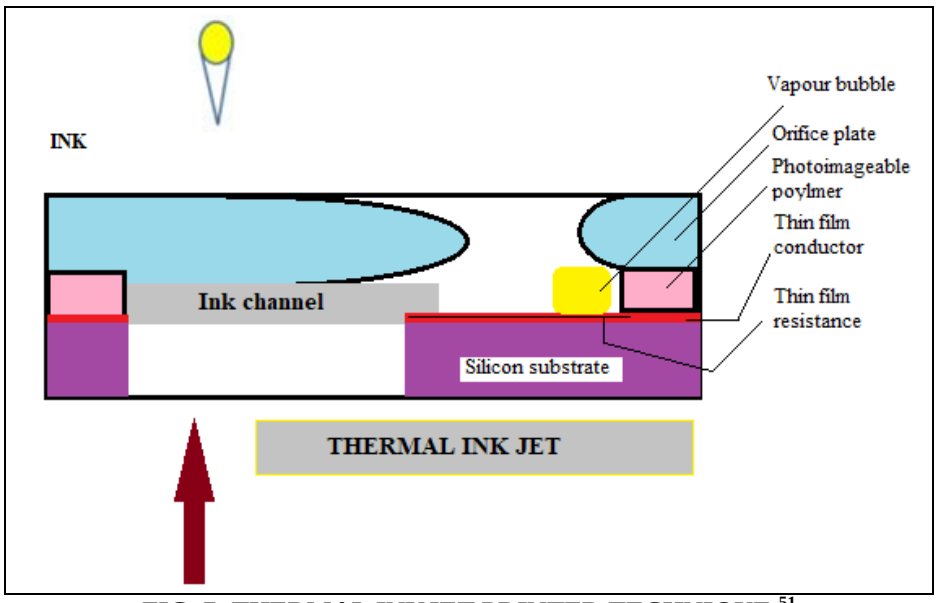

FIG. 7: THERMAL INKJET PRINTER TECHNIQUE [51]

The injection printing method's key advantage in the pharmaceutical industry is its great accuracy in generating 3D medication items. One of the downsides of TIJ is that the high temperature used may cause heat-labile active components and excipients to degrade, limiting its usage in pharmaceuticals [51, 52].

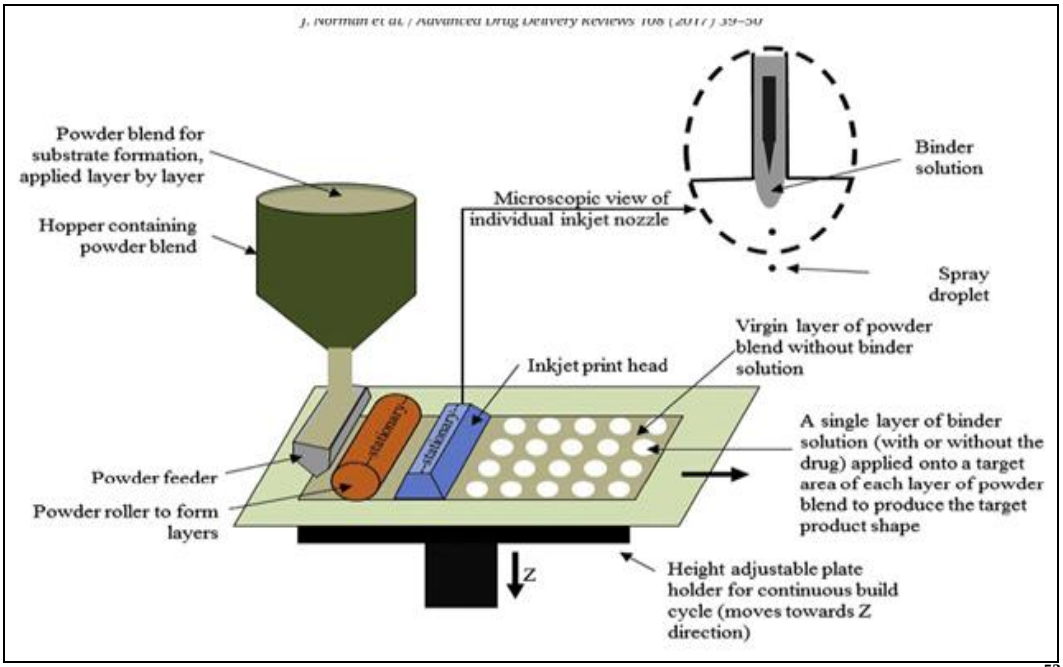

FIG. 8: THERMAL INKJET PRINTING THIS IMAGE IS TAKEN FROM REFERENCE [53]

Fused Deposition Modeling (FDM): S. Scott Crump invented extrusion-based printing in 1988, which is also known as fused deposition modeling (FDM) or fused filament fabrication (FFF). Extrusion of thermoplastic or composite materials are drawn via a heated extrusion head (with one or many extrusion nozzles) is the basis of FDM. Layers of fused materials were deposited using a numerically controlled machine tool to regulate the horizontal and vertical movement of nozzles. Metal printing, polymer printing, and bioprinting all use extrusion-based printing.

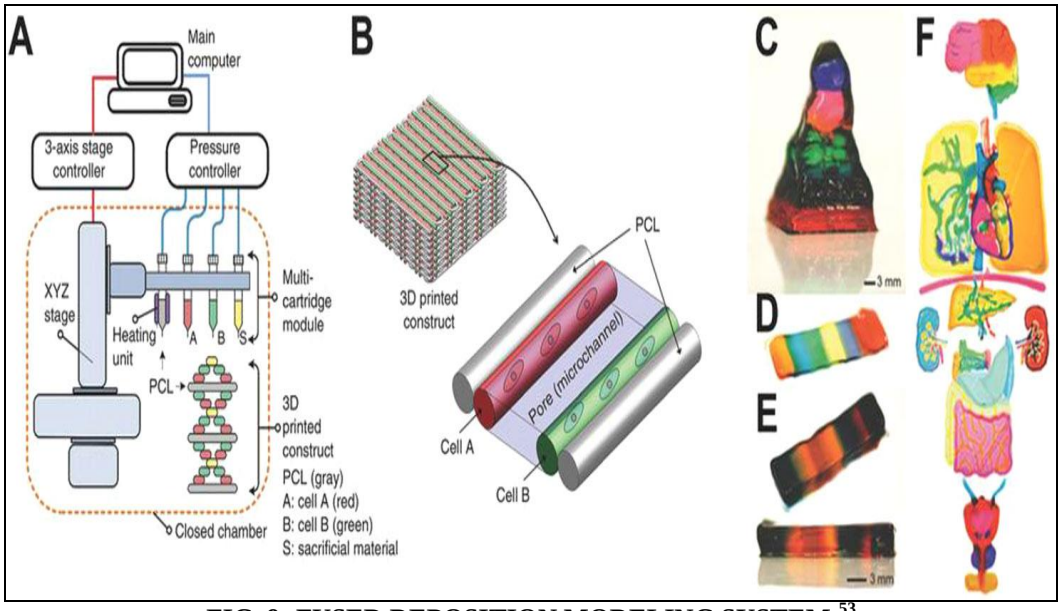

FIG. 9: FUSED DEPOSITION MODELING SYSTEM [53]

Precision extrusion deposition (PED), precise extrusion manufacturing (PEM), and multiple heads deposition extrusion are all printing techniques that have recently been created. Multiple bioprinting applications in vascular, soft-tissue, and bone models have been well-developed in recent years using extrusion-based printing technology [53]. The hydrogels of extrusion-based printing can construct products with high cell density (> 1 106 cells ml1), which is a major benefit of its bioprinting application [54]. Extrusion with a semisolid core (SSE). It requires a low temperature, unlike FDM. A 3D object is generated in this technique using a semisolid mixture as the initial material, which is extruded using a syringe-based tool-head nozzle. Processing temperature, material flow rate, and printing speed should be considered while optimizing mechanical properties. This approach necessitates post-processing processes of drying or cooling. Because of its simplicity and high precise control, this method is preferred. This approach is good for printing materials with high viscosity [5, 55].

Vat Photopolymerization: Light-induced polymerization cures liquid resins in layers for controlled release using light irradiation. Photopolymerization can be categorized based on the curing method **Fig. 10** which includes lasers (SLA), digital projection (DLP), light-emitting diodes (LEDs) and oxygen (continuous digital light processing (CDLP)/continuous liquid interface production (CLIP)). 3D printing with photopolymerization has been utilised to create speedy and practical prototypes, customized goods and serial production [56].

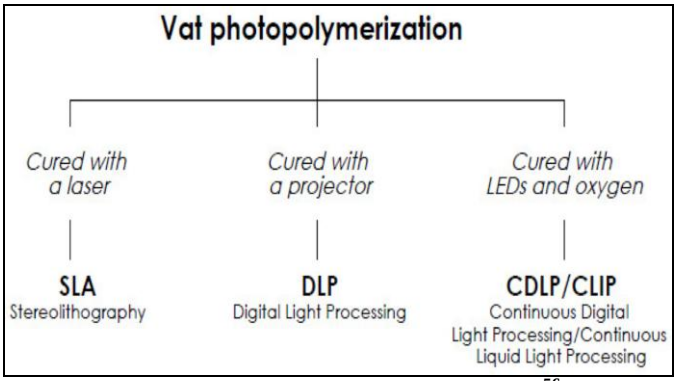

FIG. 10: VAT POLYMERIZATION [56]

- Two-dimensional layers are cured into a hardened three-dimensional structure with the ability to deliver drugs.

- Polypills, excipients, nanosuspensions and hydrogels are examples of 3D technology that have already entered the market. Following are some instances of post-market examples:
- Spritam by Aprecia Pharmaceuticals is an epilepsy medicine that is created in layers until the right dosage is found.
- Guaifenesin is a bi-layered polypill that releases slowly.
- Nifedipine, captopril, and glipizide: A multiactive polypill that relies on extrusion-based printing to incorporate multiple active components.
- To construct a temperature-responsive delivery technique, stereo lithography was used to generate ibuprofen hydrogels.
- A medication delivery device has been created using a selective layer sintering method.
- Binder jet printing is used to make a cubic tabular device with pseudoephedrine [56, 57].

Zip Dose: Patients who require easy-to-take medications and caregivers, such as physicians and nurse practitioners, who require easy-to-administer medications benefit from ZipDose Technology. ZipDose solves patient adherence and difficulty swallowing concerns by allowing high-dose drugs to be delivered in a quickly dissolving form [58]. By creating a very porous material, the ZipDose Technology approach gives a tailored dose that contains a high dosage load and maintains quick dissolution with just a sip of water because of its unique digitally coded layering and zero-compression procedures [56].

Direct-Wise: A pattern-generating device is used to build a 3D microstructure. The procedure is guided by a computer-controlled translational stage [58].

Benefits of 3-D Printing:

- Increased solubility
- Repeatable accuracy
- Dosage specific parameters
- Non-contact processing
- Unique dosage form and demand
- Micro-dosing without oxidation
- Faster trials [57]

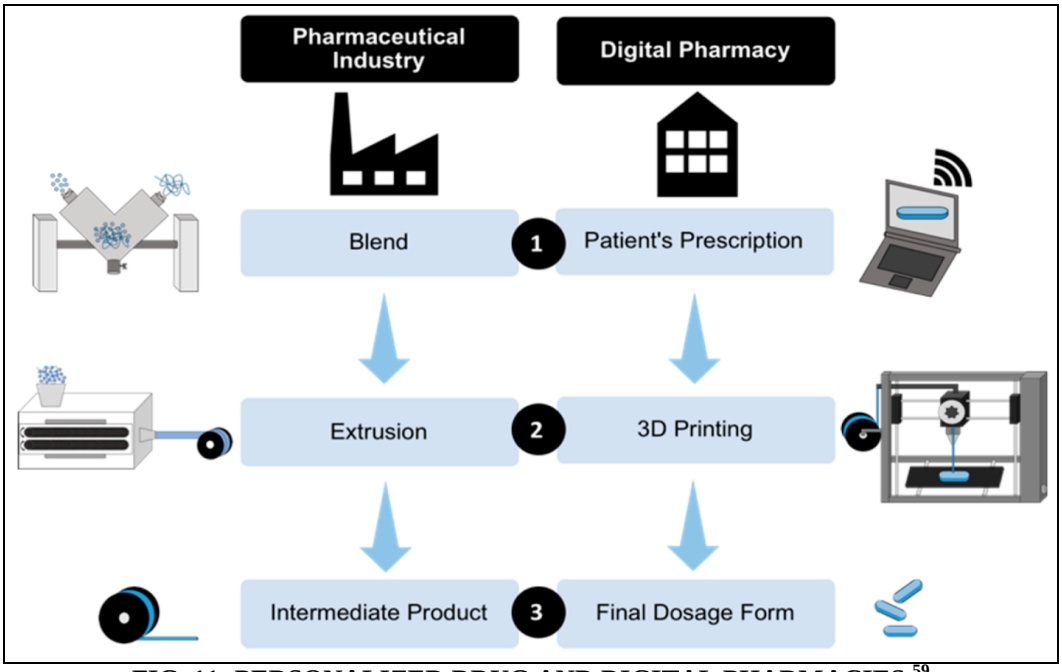

FIG. 11: PERSONALIZED DRUG AND DIGITAL PHARMACIES [59]

Medical Application of 3D Printing:

Bio-printing of Tissue and Organ: The failure of organs and tissues due to accidents, congenital flaws, aging, and other factors is a serious medical problem, and the current remedy is organ transplantation from deceased or living donors [60].

Organ transplant operations are so costly that they are out of reach for most people. Another concern with transplant surgery is the difficulty in finding tissue match donors [61].

"Surgeons can practice on patient-specific organ prototypes created using 3D printing before undertaking more challenging operations" [62].

Stem cells are separated, mixed with growth factor, and then multiplied in the laboratory in the traditional tissue engineering approach from a tiny tissue sample. The cells are then sewn onto scaffolds, which guide cell proliferation and differentiation into a working tissue [63].

Additional advantages of 3D bioprinting over traditional tissue creation include accurate cell placement, digitally controlled speed, drop volume, resolution, cell concentration, and printed cell diameter [62].

Various materials are used to build scaffolds, depending on the porosity, tissue type, and needed strength. Hydrogels are considered the best substance for constructing soft tissues out of all the options [4]. Drill guides for dental implants, physical models for prosthodontics, orthodontics, and surgery, the manufacture of dental, craniomaxillofacial, and orthopaedic implants, and the fabrication of copings and frameworks for an implant and dental restorations are all examples of 3D printing applications [63].

Recent advances in 3D printing have led to the creation of a soft robotic glove that can help move human fingers. This soft robotic 3D-printed glove can help people with arthritis, localized paralysis, and limited hand function. It can also be used as a tool for rehabilitation. These days, 3D printing technology also allows for creating materials that may change shape and are responsive to water, thermal activation, and photosensitivity. These materials may be moulded into any desired shape using heat, light, or water, making them incredibly valuable for soft robotic applications [64]. Soft actuators created with 3D printing technology are a rising application of the technology that has found a home in 3D printing applications. Soft actuators are being developed to cope with soft tissues and organs, particularly in biomedical fields where human-robot interaction is crucial. 3D printed soft actuators are introduced to revolutionise the design and manufacture of soft actuators with bespoke geometrical, functional and control qualities more efficiently and cost-effectively. The layers of the build are made of polymer ink, while the traces and holes that allow electricity to flow are made of silver polymer [65].

During the COVID-19 epidemic, volunteers used their printers to create personal protective equipment items to augment the stressed supply of PPE (i.e., frames for face shields) [66].

Personalized Drug Dosing: The goal of drug development should be to improve medical efficacy while lowering the risk of adverse reactions, which can be achieved by using 3D printing to make personalized medications [60, 67].

Anatomical Models for Surgical Preparations: 3D printed models have proven to be quite useful in this regard, making them a vital tool for surgical procedures. To find out how to construct a donor liver with the least amount of tissue damage, researchers at Japan's Kobe University Hospital used 3D printed models made from a replica of the patient's own organ [68]. The airways of premature babies were recreated using 3D printing technology to test aerosol medication delivery to the lungs. Plaque removal surgery was designed using a 3D printed model of a calcified aorta [69].

CONCLUSION: The rapid growth of 3D printing technologies has the potential to shift pharmaceutical production from mass production to on-demand tailored dosage forms, resulting in safer and more effective medicines for patients. Its ability to change traditional pharmacy practice could be extremely beneficial to the healthcare system. Apart from clinical applications, this technology can be used in manufacturing to create dosage forms with complex geometries and release profiles. This little study has proven that 3D printing may be successfully utilized on a small scale to generate tailored dosages of drug products and has considerable advantages experimentally in manufacturing oral dose forms by evaluating several experimental research. The FDA's approval of Spritam was a watershed moment in the realm of 3D printing, and there has been a flood of promising research since then. Fast manufacturing

speed, cost-effectiveness, and formulation flexibility are the pharmaceutical industry's biggest benefits of 3D printing. Furthermore, the advantages and disadvantages of various platforms must be evaluated in order to build a 3D printer that is suitable for use in a hospital setting. By requiring increased integration of pharmacists' pharmaceutical expertise within interprofessional teams in order to improve medication therapy outcomes, the improvement of pharmaceutical compounding product quality and customization choices will boost pharmacists' opinions of themselves.

Despite its many benefits, additive manufacturing still faces several obstacles in terms of sanitation, device performance, control of design parameters, and biocompatibility of printed materials. Additionally, the delicate nature of printed products, particularly those made of cells, as well as the complexity of constructed structures, necessitate a well-thought-out technique. However, the adoption of 3D printing has brought about all advantages for patients and the broader healthcare system. makes the amount of required research leading to establishing a customized product manufacturing process reasonable [70-72].

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