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A COMPREHENSIVE REVIEW OF 3D PRINTING TECHNOLOGY – IN DOSAGE FORMS

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ABSTRACT:

The development of 3D printing since the 1990s is discussed in this article along with how it is used to create pharmaceutical dosage forms. In addition to having many advantages, 3D printing for drug administration is among the simplest techniques available, has a wide range of applications in the pharmaceutical business, and is helpful for both the types of pharmaceuticals used and a variety of drug delivery systems. There are numerous technologies used in three-dimensional printing that can be used to create different drug dosage forms.

KEYWORDS: 3D printing, Additive Manufacturing, drug delivery, Technologies, Printed Medicines.

INTRODUCTION:

A significant advancement has been made in medication design, with better knowledge of material qualities, manufacturing technologies, and processes that aid in the creation of high-quality dosage forms. Through each step of the product development process, the nature of the physicochemical and biopharmaceutical characteristics of active pharmaceutical ingredients should be taken into consideration and studied. 3D printing is one of the new technologies that have emerged to manufacture dosage forms as needs and development capabilities have grown.[1]

The three-dimensional technique is a manufacturing process that creates products by layer-by-layer deposition of materials to create a three-dimensional object. Another name for this 3D printing is an additive manufacturing (AM). Another novel idea in the pharmaceutical industry is the incorporation of solid freeform 3D printing technology or prototyping.[2]The designs for 3D printed products are computer-aided and can be of any shape or geometry. They have a distinct medication release pattern that is useful for individualized pharmacological therapy. These days, a variety of sectors and industries are using 3D printing more and more. Different techniques and types of 3D printers are available. The applications and benefits of 3D printing are numerous. The development of numerous new dosage forms by 3D printing is tremendously beneficial to the pharmaceutical industry.[3]

HISTORY:

At MIT, a significant shift toward the development of 3D printing technology in the pharmaceutical business was started in the early 1990s (Massachuset Institute Technology, Cambridge, MA, USA). 3D printing first became apparent in 1884. A significant advancement in the 3D system occurred in 1992 when SLA and SLS 3D printers were created by 3D systems. The wax printer for Model Mark was introduced in 1994. In 1997, Aeroment created the first laser 3D printer. development of modified organs using 3D printing in 1999. Z-Corporation created the first multicolor 3D printer in 2000. Solidimesion produced the first 3D printer in 2001. A person with a 3D-printed prosthetic leg walks in 2008. The "Reprap Project Launched" in 2005 was the biggest advancement in 3D printing technology to date. In the year 2008, the first self-replicating printer was developed that can produce most of its components. Organovo created the first 3D-printed blood vessel in 2009. 2011 saw the creation of the first robotic airplane, 3D-printed automobile, and even 3D-printed silver and gold jewelry. Doctors and engineers from the Netherlands created a customized prosthetic lower jaw for the first time in 2012. The world's first 3D pistol was created in 2013. The first 3D-printed medication produced by Aprecia Pharmaceuticals, called SPITRAM in 2015. [4]

ADVANTAGES AND DISADVANTAGES OF 3D PRINTING IN PHARMACEUTICAL INDUSTRY:

ADVANTAGES	DISADVANTAGES
1. A parameter particular to dosage 2. Microdosing devoid of oxidation 3. Enhanced soluble 4. Quicker trails 5. Customized dosage forms 6. Non-contact processing 7. Reliably accurate[5] 8. It is eco-friendly 9. Increased output 10. Enhanced cost-effectiveness[6] 11. Increased preciseness 12. Individualization 13.Decrease wastage[7]	1. The procedure is slow 2. Inadequate strength of the component 3. Raw material costs 4. The price of 3D printers has not decreased. 5.Technology abuse 6. Material limitations and more 7. The production of risky goods 8. Limitation on size

THE MEDICAL APPLICATIONS OF 3D PRINTING PROCEDURE:

Researchers from The International Journal of Pharmaceutics tried a partial coating with a semi-solids 3D printer in April 2020. Without changing the makeup of the medications themselves, they aimed to fine-tune the release of two components. They were successful in part because 3D technology can mix several dissolving profiles. The Fickian diffusion-a feature of the polymer relaxation process can be used in 3D tablet coating.[8]This is hardly the only use of tablet coating that 3D technology has made possible. Additionally, enteric polymers with accurate medication loading amounts and infill percentages can be made using fused deposition modeling (FDM). Oral solid dosage formulations are not the best for gastrointestinal absorption. For decades, researchers have worked to enhance colon medicine delivery, which 3D printers are now making achievable. [9]

LIMITATIONS OF 3D PRINTED MEDICINES:

The lack of material for 3D-printed medications has hampered technology expansion despite significant area advancement. Another restriction is the precision and quality control of 3D printed materials. Additionally, some types of 3D printers have flaws that are clinically undesirable Drugs that are 3D printed are more precise and have a higher loading capacity. The limited yield of 3D-printed medicines is another disadvantage. One tablet can be printed in 2 to 2 hours, but a batch of 15 000 tablets can be processed in just a few seconds.[10] Reduced production costs are achieved by avoiding raw material waste. The primary drawback of medicine is that it requires oral administration to be effective. They don't carry out the sickness diagnosis. Nanomedicines that can be used for diagnosis are used for this purpose. Today's diagnostic and therapeutic technologies are unreliable, cumbersome, and inefficient. Today, the goal is early disease diagnosis so that treatment can begin with thousands of cells instead of millions, for example., melanoma cells.[11]

THE TECHNIQUES OF 3D PRINTING:

The following 3D technologies are used based on the applications.

SELECTIVE LASER SINTERING (SLS): It is a quick prototyping method that transforms 3D CAD data into tangible components in a matter of hours. It is an AM technology that makes use of PEEK, nylon 11, and nylon 12 powders. The components made have excellent heat resistance, great durability, and chemical resistance. The inexpensive production parts are created without the need for pricy tools. First, tiny cross-sections of layers are created using the 3D CAD data. The data is divided and then sent to the SLS AM apparatus. The machine produces the initial layer of powdered material, which is subsequently spread throughout the cross-section by a leveling roller utilizing a laser beam. The powder bed is lowered once the first layer is finished to prepare it for the second layer. The deposition is done layer by layer till the desired component is achieved.[12]

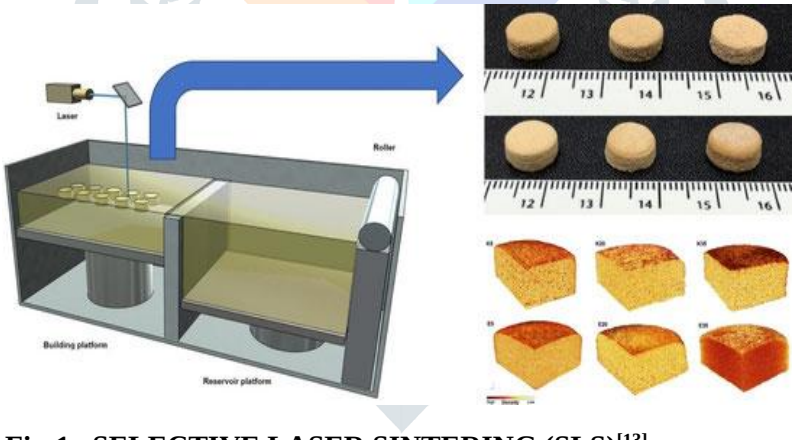

Fig:1 SELECTIVE LASER SINTERING (SLS)[13]

THERMAL INKJET (TI) PRINTING: It is a non-contact process that deposits minute ink droplets onto substrates by digital instructions using electromagnetic, thermal, or piezoelectric technologies. Resistors in this printer generate heat, which causes the ink to evaporate and form a bubble. The ink is forced out of a nozzle and onto the substrate as the bubble swells.

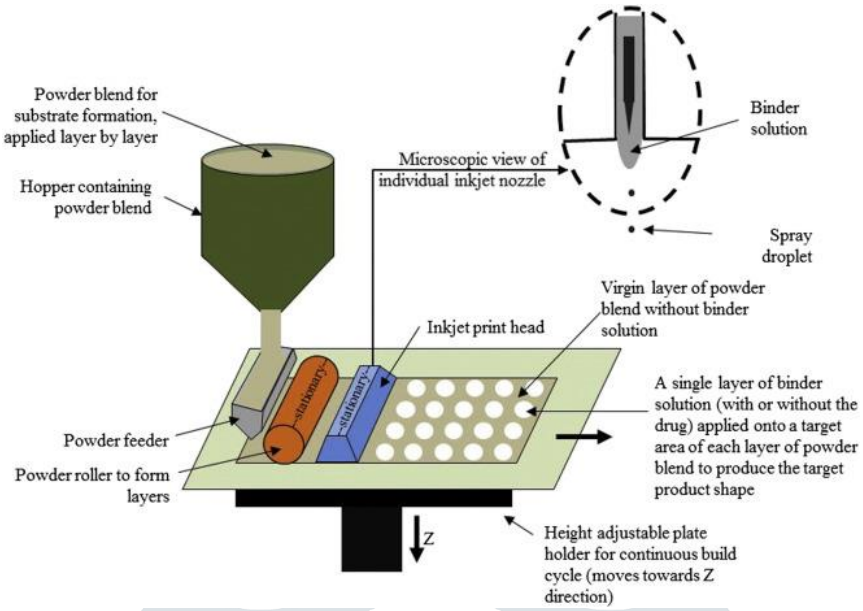

Fig:2 THERMAL INKJET (TIJ)PRINTER[14]

SEMI-SOLID EXTRUSION (SSE): It needs a low temperature, unlike FDM. Using a semi-solid mixture as the starting material and an extruder with a syringe-based tool head nozzle, a 3D object is produced using this method. Processing temperature, material flow rate, and printing speed should all be taken into account for the best mechanical properties. This method requires post-processing processes of drying or cooling. [15]

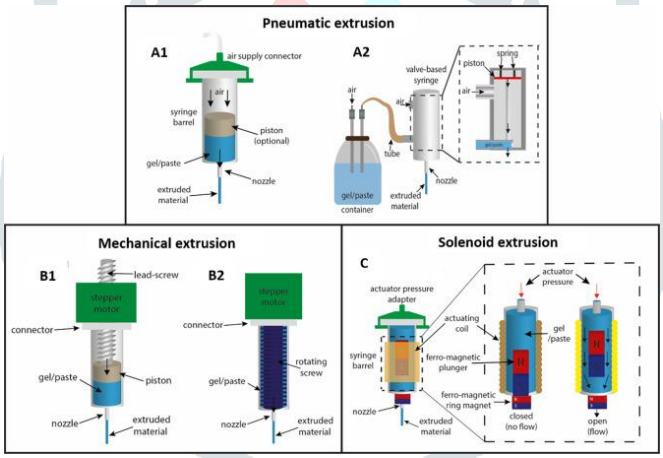

Fig:3 SEMI SOLID EXTRUSION(SSE) PRINTING[16]

STEREOLITHOGRAPHY (SLA): Because it is the most traditional rapid prototyping technology, it is utilized to make idea models or as a model for molding processes. CAD data is initially divided into layers or cross-sections, and then it is sent to an SLA AM system that has a vat of UV-curable photopolymer. The layer is produced by the UV laser using X and Y scanning mirrors. The liquid material immediately becomes solidified when the laser makes contact with the resin's cross-section. The build platform is indexed down once each layer is finished so that the following layer can be deposited. Using a bottom-up method, the layers are constructed one by one on top of one another.

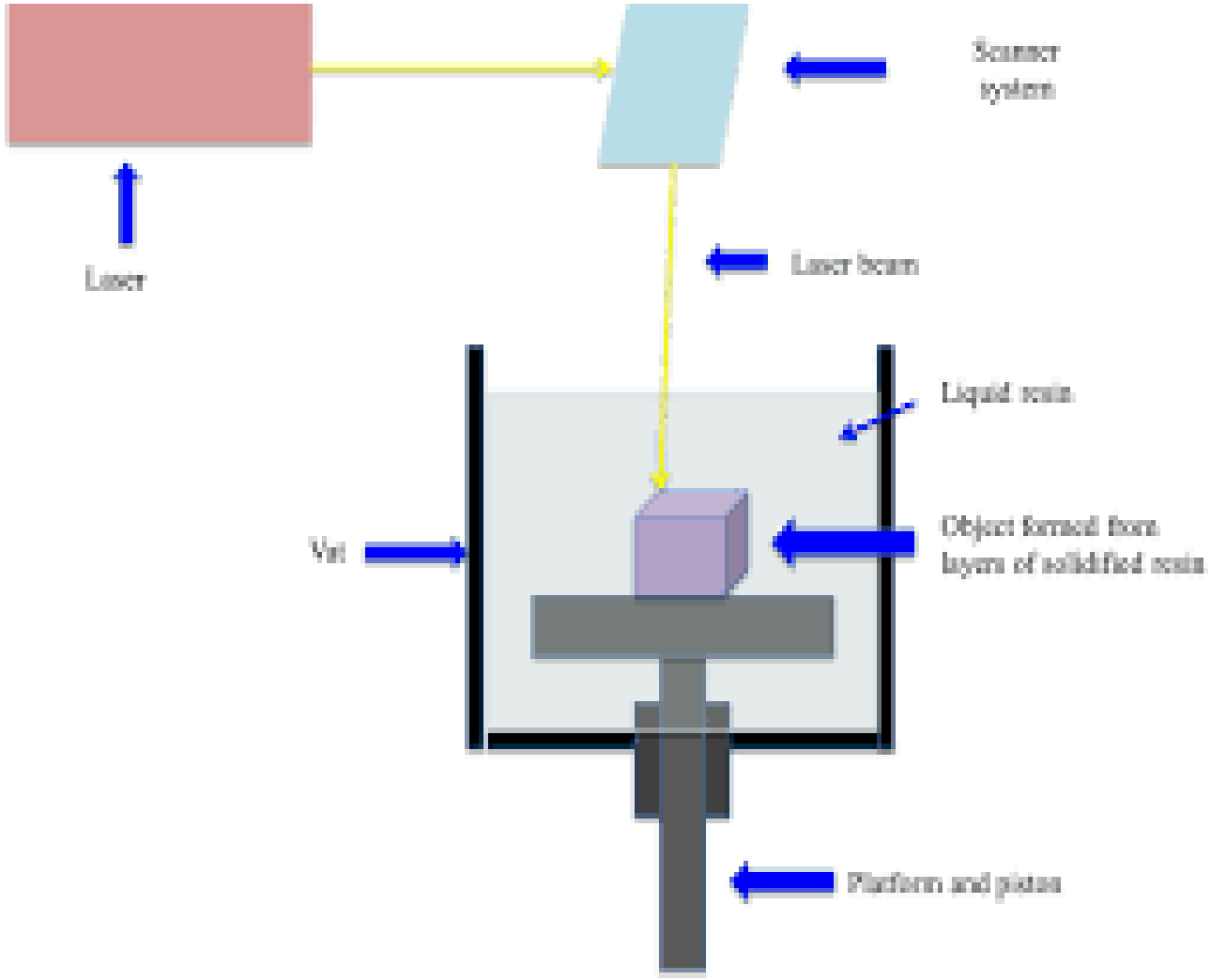

Fig:4 STEROLITHOGRAPHY(SLA) PRINTER[17]

FUSED DEPOSITION MODELING (FDM): Using this technology, commonplace items can be made to last. Using a bottom-up construction method, the 3D printer uses industrial-grade thermoplastic filament that is melted and extruded on a tray to produce an entire part layer by layer. The requirement for a high processing temperature for the development of active thermo-labile compounds is the technique's constraint.

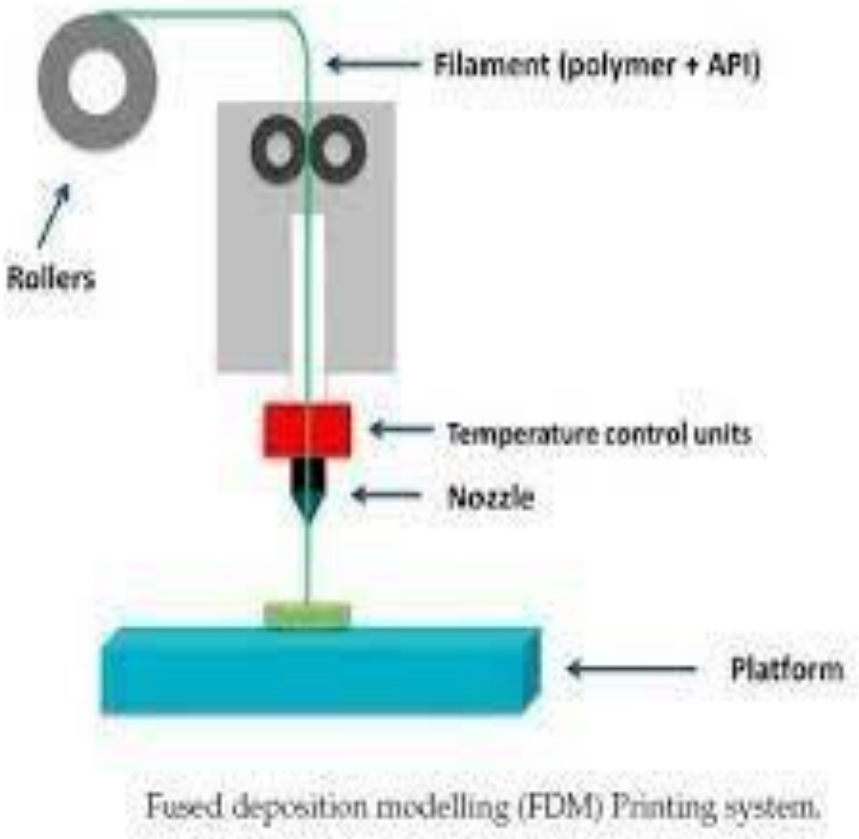

Fig:5 FUSED DEPOSITION MODELING (FDM) PRINTER[18]

BINDER JETTING 3D PRINTING: Various particle materials, like sand, polymers, or freely selected powder materials, are used in this approach. The part's CAD data is the primary need. The loose particle ingredients are first applied to the building platform by a recorder. The printhead then selectively applies the binder to the locations where the future parts must be formed, joining the layers. The layer thickness lowers the building platform once the binder has been applied. Printing is done layer by layer until the required structure is achieved.

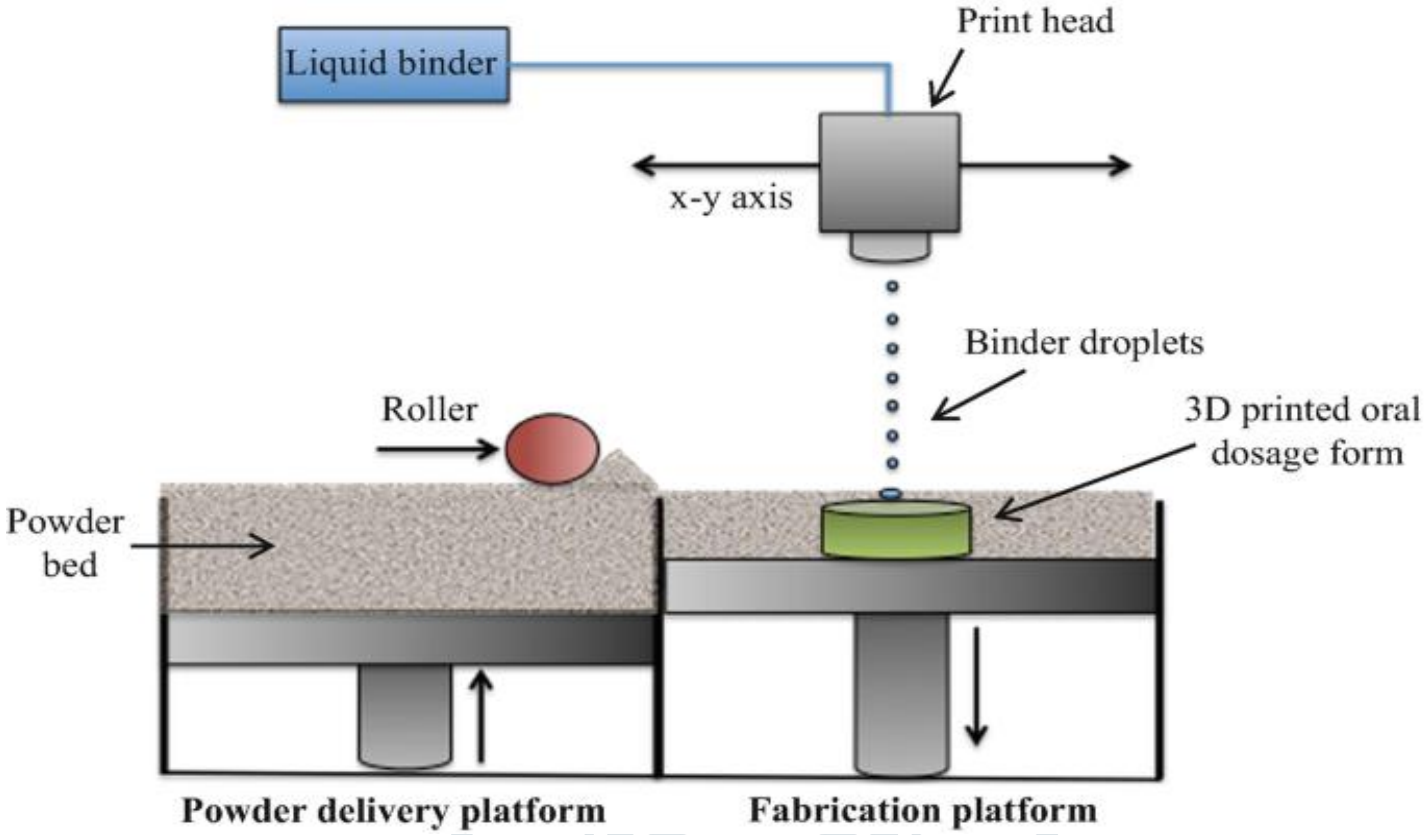

Fig:6 BINDER JETTING 3D PRINTER[19]

COMPLEX DRUG-RELEASE PROFILES:

The creation of medications with complex drug-release patterns is one of the most researched uses of 3D printing. Traditional compressed dosage forms often have a homogenous blend of active and inert ingredients, which results in a simple drug-release profile. However, 3D printers may print binders in layers typically 200 micrometers thick onto a matrix powder bed to assist in controlled medication release. This separates the active components from one another. Additionally, complex geometries with porous interiors that are loaded with a variety of drugs and surrounded by barriers that govern release can be created for 3D-printed dosage forms.[20]

S.NO	API	3DPRINTING TECHNIQUE USED	FORMULATION	REFERENCE
1	IBUPROFEN	SLA	Hydrogels	21
2	SALICYLIC ACID	SLA	Facial masks	22
3	RIFAMPICIN AND ISONAZIDE	3D PRINTING	Multidrug implant	23
4	SALBUTAMOL SULFATE	TIJ	Solution	24
5	CAFFEINE	FDM	Caplets	25
6	ARIPIPRAZOLE	FDM	Oral films	26
7	HYDROCHLOROTHIAZIDE	FDM	Tablets	27
8	PROGESTERONE	SLS	Drug delivery device	28
9	PARACETAMOL	SLS	Tablets	29
10	NIFEDIPINE,GLIPIZIDE AND CAPTROPIL	SSE	Multiactive tablets (polypills)	30
12	GUAIFENESIN	SSE	Bilayered tablets (polypills)	31
13	METHYLENE BLUE AND ALIZARIN YELLOW(dyes)	BINDER JET PRINTING	Tabular devices	32
14	CHLORPHENIRAMINE MALEATE AND FLUORESCEIN	BINDER JET PRINTING	Tablets	33
15	LEVETIRACETAM	BINDER JET PRINTING	Orodispersible tablets	34
16	PSEUDOEPHEDRINE	BINDER JET PRINTING	Cubic tabular devices	35

DRUG WITH COMPLEX GEOMETRIES:

Using 3D printing, it is possible to create tablets for drugs in a variety of odd shapes that are difficult to produce using traditional production methods. Researchers from Fabrex Ltd. and the Pharmacy School at University College London (ULC) have done work on it. Five tablets were made for their study.[36] using auto CAD software, and each one had a unique shape: a cube, pyramid, cylinder, sphere, and torus. By altering the sizes and shapes of each tablet, the scale function of the software was utilized to produce tablets with constant surface area, surface area/volume ratio (1:1), or weight (500mg). However, the ratio of each shape's length, width, and height was always maintained. Finally, using a "MakerBot replicator 2x desktop 3d printer" and drug-infused filament, researchers manufactured each tablet. Researchers performed disintegration tests on the printed tablets to ascertain the medication release characteristics of each tablet. When the surface area of the printed tablets was maintained constant, they discovered that the pyramid-shaped tablet had the fastest drug release rates, followed by the torus, cube, sphere, and then cylinder. This ranking is based on the ratio of the surface area to the volume of the tablet, with the pyramid tablet having the highest value and the cylinder having the lowest. This led the researchers to the conclusion that a tablet's geometric design unquestionably affects the drug release profile.[37] Patients must take the tablet's appearance into serious consideration. Tablet shape and size are very important for patient medication adherence.[38]

Tablets printed in three dimensions using different geometries to perform a certain function:

Goyanes et al. investigated the viability of fabricating tablets in a variety of sizes and forms using a fused filament technique. Acetaminophen-loaded PVA filaments were created by mixing a small amount of varicut, a plasticizer, with an aqueous solution of paracetamol (2% w/w). Then, using a single-screw filament extruder, the formula was printed in a variety of shapes, including a cube, pyramid, cylinder, sphere, and torus. It was thought that the printed geometries were repeatable, precise, and printable at a scale suitable for mass manufacturing.

They discovered that altering the printed shape of acetaminophen tablets caused varying rates of drug release, enabling a high degree of personalization. The fastest acetaminophen release rate was disclosed by the pyramid-shaped tablet, which had the highest surface area to volume ratio, while the slowest release rate was revealed by the cylinder-shaped tablet, which had the lowest ratio.

Additionally, their research demonstrated that tablet form had a significant impact on transit time in vivo, which may be useful for the development of targeted drug delivery systems to a particular gastro-intestinal region.[39]

Proprietary medicine items made via 3D printing :

DRUG PRODUCT	FABRICATION TECHNIQUE	DOSEAGE FORM CHARACTERISTICS	REFERENCE
Ritonavir 3D tablet	Hot melt extrusion	Solid dispersion of drug in hydrophilic polymer to improve the drug solubility and bioavailability	40
Theophylline immediate and extended release tablet	Hot melt extrusion	A combination of different release mechanisms into a single system with digital control of excipients	41
Colon delivery tablet of aminosalicylate	Hot melt extrusion	Monolithic controlled release tablet as patient-tailored medicinne	42
Acetaminophene controlled release tablet	Hot melt extrusion	Specific 3D structure with different inner core densities and outer shell thickness.	43
Aripiprazoleoro dispersible films	Fused filament method	Printed films with a porous structur and amorphization of the drug substance.	44
Fluorescein 3D printing tablet	Fused filament method	Monolithic tablet for personalized dosemedicine and specific release profile	45
Prednisolone extended release 3D tablet	Fused filament method	Amorphization of prednisolone in formulation /personalized dose medicine	46
3D tablet containing nanocapsule of deflazacort	Fused filament method	Combination of two technologies:3D printing and nano technology to creat innovative formulation	47

CONCLUSION:

Drug delivery systems and medical equipment can be printed in three dimensions as an appealing method of creating specialized goods.

The concept of 3D-printed medicine formulation has been around for a while. Patient-centric medicine swiftly developed and was aimed at enhancing therapy. Studies on oral, oromucosal and topical dose forms advanced extremely quickly after the first 3D-printed medication was approved by the FDA. With the current technological procedures, it is challenging to attain the formulation flexibility that this potential technology offers. When compared to typical pharmaceutical manufacture, additional manufacturing enables the preparation of various dosage forms with high precision of the API-excipients ratio in a completely novel way.

The possibility to build multifunctional drug delivery systems, multidrug devices, and drug formulations for individualized therapy with accelerated release characteristics is another benefit of 3D printing. Therefore, to ensure the desired therapeutic impact, future research should prioritize the development of pediatric and geriatric dosage forms in personalized dosing and dimension-specific drug formulations.

Numerous researches on the development of new medications demonstrate the technology's undeniable advantages, but complete commercial success won't come until intricate new dosage forms are developed.

The use of additive manufacturing in a clinic shortens the duration of medical procedures, lowers their cost, and raises surgical success rates. Additionally, new surgical techniques may be developed as a result, particularly those that are dangerous and infrequently performed. Additionally, 3D printing of very realistic organ models for surgical training can facilitate and speed up procedures and reduce intra-operative complications. The creation of biomaterials for recreating vascularized tissues that can be utilized for implantation, drug screening, disease modeling, and cancer research is made possible by the utilization of living cells. The creation of biorobots expands the potential for the creation of sensors that rely on cellular physiological changes or even a synthetic immune system.

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 things, particularly those made of cells, as well as the complexity of manufactured structures, necessitate a well-thought-out technique.

However, the use of 3D printing brings numerous advantages for patients and the broader healthcare system, which justifies the amount of study needed to establish the procedure.

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