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3D Printing in Pharmaceutical Technology as a Promising Tool for the Design and Manufacture of Pharmaceutical Oral Formulation: A Review

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ABSTRACT:
By applying material to a substrate, three-dimensional printing is a cutting-edge process that creates three-dimensional things using computer-aided design software and programming. A three-dimensional structure is created by depositing or solidifying successive layers of material in a process known as additive layer manufacturing, or 3D printing. Using a computer-aided design module, medicinal chemicals are designed in three dimensions and converted into a machine-readable form that indicates the outer emergence of the three-dimensional dosage form. This surface is then divided into several printable coats, which are subsequently sent to the machine. Various 3D printing methods have been developed over time to create innovative solid dosage forms, which are some of the most well-known and distinct items available today. The pharmaceutical industry wants to support 3D printing technology and explore the amazing things that can be accomplished with it. Using 3D printing opens up a world of new possibilities for improved medical care.
Now that the FDA has approved Spritam, the first 3D-printed tablet, there is precedent for using 3D printing to prepare medication delivery systems. The ability to precisely manage the spatial distribution, precisely dispense small quantities, and assemble layers upon layers facilitates the creation of intricate compositions and geometries. The creation of dosage forms including several active medicinal components with complex and customized release profiles is made possible by the high degree of flexibility and control that comes with 3D printing. A special chance for this technology to prepare customized doses to meet the demands of each particular patient.

KEYWORDS: 3D printing, Structure, Print, Laser, Pharmaceuticals, Drugs.

INTRODUCTION:

Personalized medicines are becoming increasingly popular as they empower patient genetics and aid in improved treatment formulation with fewer negative effects. Various dosages can be mixed into a single dose that meets the needs of the patient. 3D printing is a novel method for producing medicine based on patient needs. It employs controlled devices to layer-wise prepare active pharmaceutical ingredients (API) to generate a suitably customized drug transport structure. It includes a variety of technologies, such as inkjet printing and fused deposition modeling. Scientists employed a variety of polymers for this purpose, including polyvinyl alcohol, polylactic acid, and polycaprolactone. These materials have been

used to design and develop shapes for fine-tuning medication release. The 3D printing process can be used to create a variety of dose forms, including tablets (immediate and pulsatile release) and transdermic dosages. Furthermore, 3D printing can be utilized to create personalized medicines to treat life-threatening disorders. In the instance of individuals who require many medications, a 3D printer can be utilized to design and manufacture only one dosage including multiple medications. The current medical treatment scenario is based on the "one size fits all" concept, in which most patients receive the same drugs at the same doses and frequencies as others. It was discovered that the "one size fits all" notion does not apply to all therapies. Different individuals' responses to the same active component at the same dose have differed. The response could be excessive and associated with adverse drug reactions (ADRs), or it could be too mild, resulting in insufficient or no pharmacological effects. Both of these scenarios can be followed by additional patient issues. As a result, personalized medicines are being developed, in which pharmaceuticals are tailored to patients or designed specifically for them as part of a group of genetically, physiologically, or pathologically similar people. With the tagline "one size does not fit all," its purpose is to dispense the best drug at the best dose, for the patient's particular indication, at the correct time. More accurate treatments are what personalized medicine promises. These are safer and more effective, improve patient compliance, and are less expensive. Three-dimensional printing, commonly known as 3D printing or additive manufacturing, is the process of depositing material layer upon layer to progressively build a solid model. It uses computer-aided design (CAD) software to send the necessary signals to a 3D printer, which turns the computerized digital model into two-dimensional (2D) sections and generates solid layers to construct the required things. It has been widely used in a variety of industries, ranging from car and aerospace to biomedical and pharmaceutical. It is also utilized in building construction, entertainment, the fashion industry, art, and jewelry. It has been used in the pharmaceutical industry to make a variety of pharmaceutical products such as controlled-release tablets, polypills, orodispersible films, gastro floating tablets, self-emulsifying drug delivery systems, microneedles, and transdermal patches. Inkjet printing, binder jet printing, fused deposition, selective laser sintering, stereolithography, and pressure-assisted microsyringe are some of the printing processes available. Pharmaceuticals have the potential to significantly alter the design, use, and manufacture of several pharmaceutical items via 3D printing. When it comes to large-scale production, traditional manufacturing procedures, while cost-effective, may require strenuous work and be time-consuming. Doses in current production techniques cannot be easily modified to meet the demands of the patient. 3D printing has the potential to alter healthcare by enabling personalized medicine, which improves patient compliance by personalizing medication to the patient. To provide the finest medical care, on-demand manufacturing in clinical settings might be used. A substantial quantity of literature has been reviewed on 3D printing and its application in drug delivery. However, there are just a few publications that explain the many technologies involved in 3D printing, as well as their applications in pharmaceuticals, personalized medicine, and their ability to care for various populations. (1-8)

HISTORY:

Charles Hull is regarded as the 3D printing pioneer since, in the mid-1980s, he created, patented, and commercialized the first apparatus for 3D printing of things, as well as the STL file format that interfaced with existing CAD software. Hull's approach, stereolithography (SL), consists of a laser moving across the surface of a liquid resin, curing the resin before submerging the stage to cure another layer; this process is repeated layer by layer until the required geometry is printed. Parallel work was

being done at the University of Texas at Austin (UT Austin), the Massachusetts Institute of Technology (MIT), Stratasys, Ltd., and other companies to develop additional additive manufacturing techniques at the same time. A researcher and his advisor from the University of Texas at Austin were granted a patent for selective laser sintering, a process in which a laser beam is scanned over a powder bed to sinter or fuse the powder; the powder bed is then lowered, fresh powder is spread, and the process is repeated to produce a solid object, the same year Hull was granted a patent for his stereolithography apparatus. Professors at MIT are credited with coining the term "3D printer" with their invention of a layering technique that uses a standard inkjet print head to deposit "ink" or a binder solution onto a powder bed to bind powder, then repeating this process layer by layer to produce a desired geometry. The un-bonded or loose powder that serves as a support during the procedure is subsequently removed. To strengthen the bonding, the structure can be further treated, for example, using heat. This is usually known as 3D printing. This technique will be referred to as 3D powder bed or powder bed inkjet printing in this review. Scott Crump, co-founder of Stratasys, Ltd., filed a fused deposition modeling (FDM) patent in 1989. This method of object fabrication involves applying layers of hardening material until the desired shape is produced. Self-hardening waxes, thermoplastic resins, and molten metals can all be used in this method. In 1996, Helisys, now Cubic Technologies, invented a laminated object manufacturing technology that entailed shaping (typically with lasers) and stacking sheets of predetermined materials, with adjacent layers connected by adhesives or welding. (9-15)

THE IMPORTANCE OF PERSONALIZED MEDICINE:

The pharmaceutical industry has recently witnessed a tremendous revolution and development in patient care that produces effective and safe pharmaceuticals. Personalized medicine (PM) has grown in popularity. It can provide maximal protection boundaries, reducing side effects and ensuring increased patient safety. PM aims to provide a one-of-a-kind opportunity to change patient biology through drug choices, dosages, and treatments. Its objectives are to improve healthcare facilities, streamline research, and uncover diagnostics and treatments. Herceptin, a drug used to treat breast cancer, was rejected in Phase-III patient trials in 1997 because it was deemed ineffective for all residents. Despite this, women who tested positive for HER2 had a considerably improved response. The Food and Medicine Administration of the United States approved the medicine in 1998 after receiving medical trial evidence from HER2-positive patients. Controllers in Europe rejected the Vectibix medicine because it could not be used for a variety of patients. This medication was intended to treat Amgen's colon cancer. The company did an overall data review and discovered that Vectibix can work well in patients with tumors that lack the KRAS gene mutation, and the medicine was only approved for such patients. As a result, a physician can examine a patient's gene variant profile, select a prescription, and recommend a treatment that reduces side effects, giving beneficial results. Individual susceptibility to various diseases could be recognized before they manifest. As a result, PM can be used to prevent infections in vulnerable people. With PM help, doctors can use a one-size-fits-all approach to prescribing medications for particular patients. Gene reactions to specific medications may range from person to person due to patient genetic differences. As a result, PM has spread a distinct science known as "pharmacogenomics," which determines an appropriate gene affecting medicine. Scientists are investigating many ways to develop tailored medicine, one of which is 3D printing. This article examines 3D printing in drug delivery in depth. (16-23)

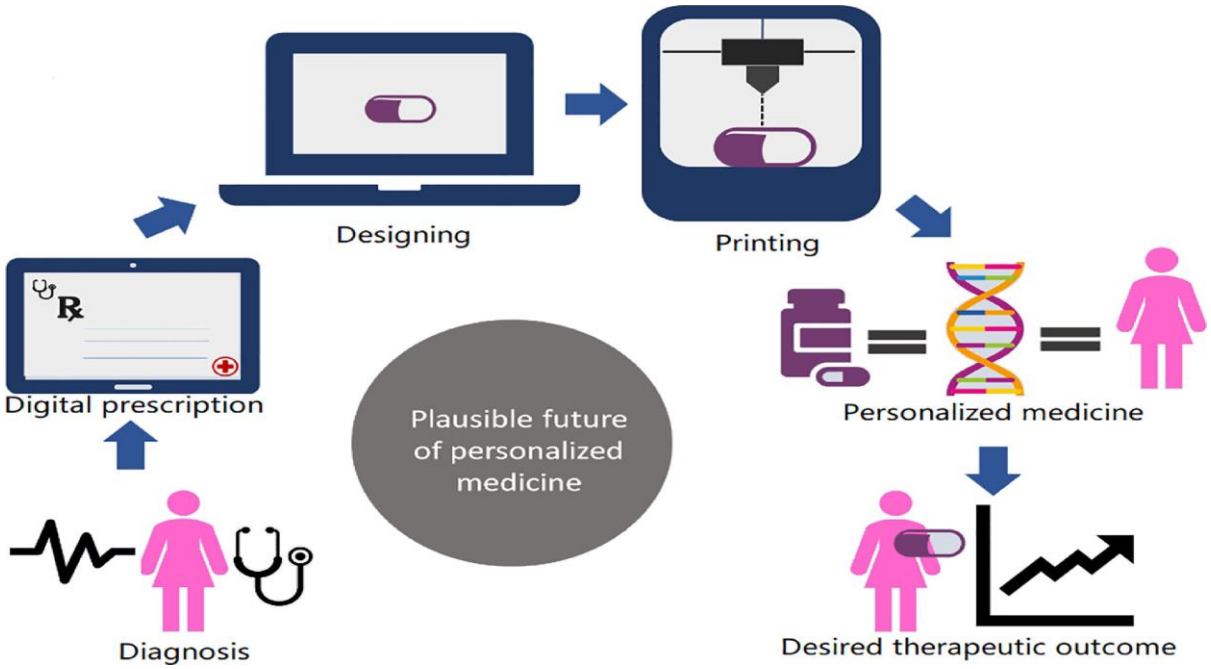

Fig 1: Personalized medicine using 3D printing.

REGULATORY PREDICTIONS: In 2017, the FDA (US) announced Technical Considerations for Additive Manufactured Medical Devices. This document contains the requirements for Design and Manufacturing Process Considerations, Device Testing Considerations, and Labeling. It also suggests validating the processes involved to provide a high level of confidence as per standard procedures. Furthermore, paperwork must conform to the Quality System Regulation criteria for device validation. To establish and sustain quality, process validation must be performed. For all devices and their components constructed in a single build cycle, between build cycles, and between machines where the results of a process (i.e., output specifications) cannot be fully confirmed by subsequent inspection and testing. Software must also be certified for its intended purpose using an established procedure. (24-25)

ADVANTAGES OF 3D PRINTED DRUG DELIVERY:

- High medication loading capabilities when compared to traditional dose formulations.
- Accurate and precise dosing of powerful medications supplied in small quantities for action.
- Reduced production costs owing to less material waste.
- Suitable drug delivery for active substances that are difficult to synthesize, such as those with low water solubility and narrow therapeutic windows.
- Medication can be personalized to a specific patient depending on age, gender, genetic variations, ethnic characteristics, and environment.
- In the event of multi-drug therapy with multiple-dose regimens, treatment can be tailored to increase patient adherence.
- Because of the variable designs and manufacturing methods of dosage form, immediate and controlled release layers can be integrated, which aids in the selection of the appropriate treatment regimen for an individual.
- Avoids batch-to-batch variability encountered in conventional dosage form bulk manufacturing.
- Small batch production is achievable, and the process can be finished in a single run.

- 3D printers use up little space and are inexpensive. (26)

DISADVANTAGES:

- Nozzle issues pose a significant obstacle, as they cause the print head to halt, affecting the end product's structure.
- Another difficulty is powder printing blockage.
- The ability to change the final structure in response to mechanical stress, storage conditions, and ink formulation effects.
- Printer settings and their impact on printing quality and printer cost. (27)

APPLICATIONS OF 3D PRINTING:

- Potential applications include process improvement and performance enhancement in industrial design, aircraft, medical engineering, tissue engineering, architecture, and pharmaceuticals.
- It primarily focuses on two prospective sites for expanding pharmaceutical product development into previously unknown areas: manufacturing advanced structures for distribution and personalized medication.
- Dental implants are made in the healthcare industry.
- On the development of an organized release multi-drug implant for bone TB treatment.
- Aids in the production of organs, biological materials, and cell-laden materials. (28)

THE SIX MAIN 3D PRINTING TECHNOLOGIES IN PHARMACEUTICALS:

1. BINDER JET PRINTING PROCESS (BJ3DP):

BJ3DP is a powder-based 3D printing technology that involves jetting a binder solution onto a powder bed and binding it together to form a 3D-printed structure. A BJ3DP system typically consists of a binder solution reservoir, a powder reservoir, and a build platform for the printing process. Powder discharges from the powder reservoir on the build platform during the printing process. Following this, a thin layer of discharged powder is distributed with a roller on the build platform before jetting a binder solution based on the image design file of the desired object geometry. The same powder spreads after the first layer is generated, and the jetting process is repeated layer by layer until the desired object is printed. Emanuel Sachs invented BJ3DP at the Massachusetts Institute of Technology and patented it. Later, the Z firm commercialized technology that added color capability and termed it "3D printing." BJ3DP is widely utilized in rapid prototyping applications like electrochemistry, plastic surgery, bone scaffolds, and the cosmetic sector. The use of BJ3DP in the pharmaceutical business was first recognized in 2015 when the FDA approved the first 3D-printed tablet made with BJ3DP. Several experiments have been conducted since then to generate various sorts of solid dosage forms employing this printing technology, such as orally dissolving, traditionally durable tablets, complicated release dosage forms, and so on. (29-40)

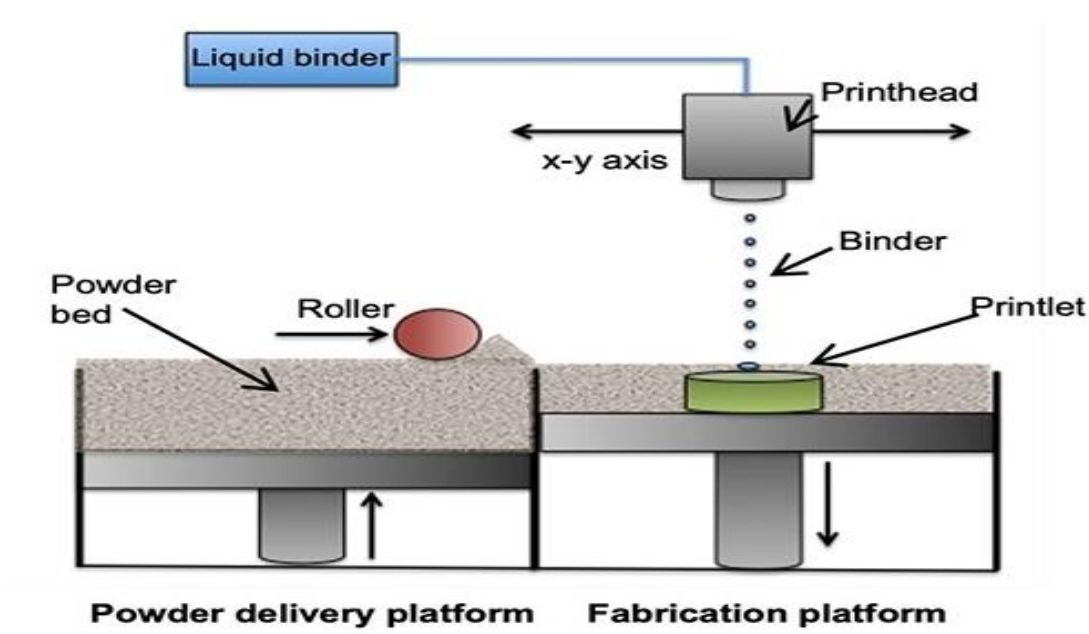

Fig 2: Binder jet printing process (BJ3DP)

2. FUSED DEPOSITION MODELING (FDM):

The most widely used 3D printing technology is fused deposition modeling (FDM), often known as fused filament fabrication. After developing, thermoplastic drug-loaded polymeric filaments are fed into the printer, where they are melted at a specified temperature and extruded via the nozzle. The print head moves within a raster platform, and the extruded filament is unloaded onto the printer platform, resulting in the creation of the object's initial layer. Following that, successive layers are deposited by lowering the platform each time to make way for the next layer. The filaments cool and adhere to the previous coating. This process is repeated to create the final 3D product. Most printers allow you to change the temperature of the print head, allowing you to employ different polymers and polymer blends. The filaments used for FDM are typically made using the hot melt extrusion (HME) process, which incorporates the medication into the polymer along with numerous excipients. This method employs a screw-based extrusion system in a barrel that is powered by a motor and uses heat and pressure to melt the mixture, which is then allowed to cool. This mixture hardens to form the filament that will be utilized as the feed for FDM. The widespread usage of FDM in pharmaceuticals is due to its low cost, high printing precision, guaranteed quality parameters, and incorporation of HME. Direct powder 3D printing (DPP), a one-step FDM approach without HME, was investigated. After putting the powder blends into a stainless steel extrusion cartridge, the tablets with a honeycomb design were successfully printed. (41-44)

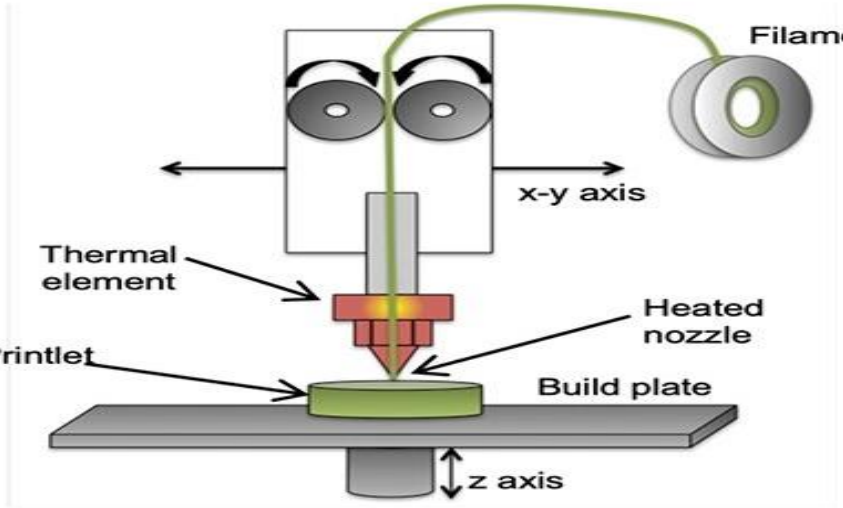

Fig 3: Fused Deposition Modeling (FDM)

3. EXTRUSION BASED BIOPRINTING:

This approach distributes bio-ink via an outlet using a machine- or pneumatically-driven pressure and follows a computer-designed model. This type of printing, like other printing methods, includes printing in layers. Bio-inks are often made of organic ingredients. This approach allows for precise cell printing with minimum cell damage. The printing technique is depicted in the figure below.

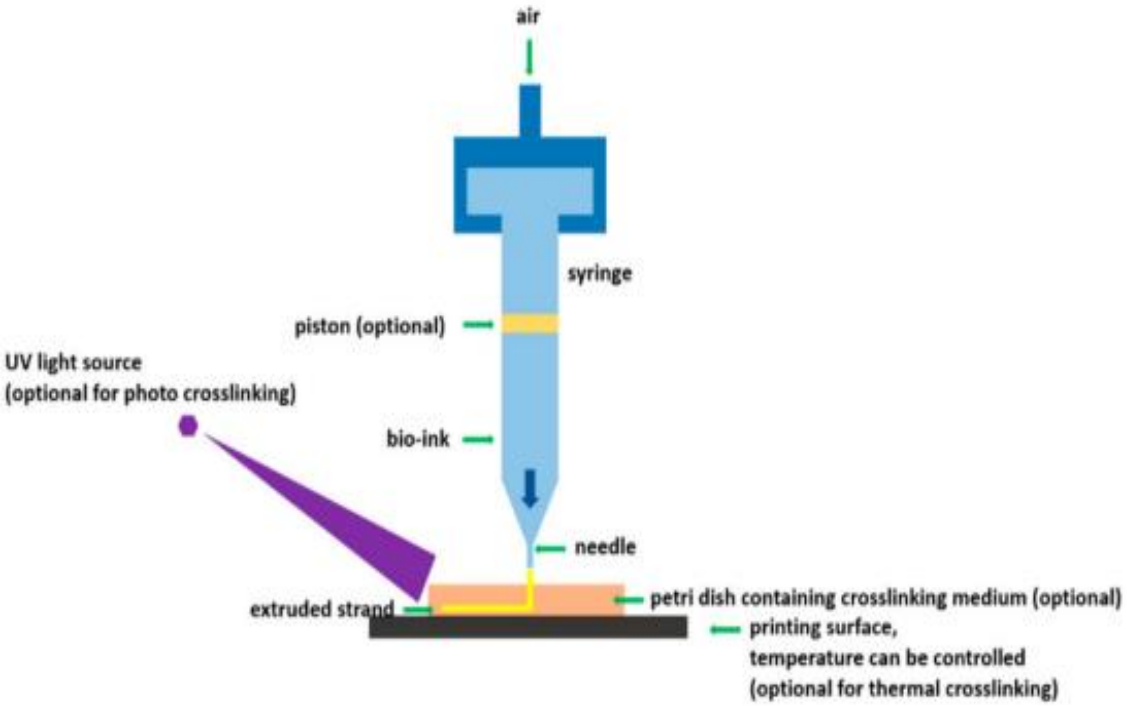

Fig 4: Extrusion Based Bioprinting

Pneumatically controlled setups are associated with distribution delays because they require compressed air. On the other hand, they are extremely effective for high-viscosity materials. However, piston-controlled printing often provides a simple instruction on the nozzle's hydrogel stream. Screw-based setups, on the other hand, provide enhanced three-dimensional dominance and are recommended for hydrogels with high viscosity. Using this technology, the cells can be printed and dispersed more precisely, speeding up the printing process. This is why organic scaffolds are created in this manner. On the other side, the printing pace is relatively fast, and desirable models are possible. This method has so far been used in bone healing, heart valves, tissues, muscles, and neurology. big decision and hardness remain a big issue in this procedure. The researchers are addressing these concerns by incorporating sacrificial elements into the bioprinting process. (45-55)

4. POWDER-BASED BINDING METHOD:

Rapid prototyping with a powder-based approach is particularly appealing to the pharmaceutical industry since it shares many similarities with current manufacturing processes and may provide a more efficient long-term printing solution. Multilayer 3D printing items are created by spraying a binder or medication solution containing extra excipients in small droplets from an X-Y print head (in two dimensions) over a powder bed on a built platform. Then, based on the height of the layers, it is lowered along the Z-axis until the next layer is built. The layers could be bonded in a liquid solution or suspension via adhesion or welding. Finally, the leftover solvent and unbound powder are removed under appropriate circumstances, allowing the 3D product to develop properly (post-printing step). The powder bed 3D printing process is quick and suitable for printing a wide range of pharmaceutical ingredients. Furthermore, the quality of produced 3D items is high, which adds to a significant reduction in production costs. The technology offers considerable potential for producing large-dose formulations of drug material, controlled and quick-release drug formulations, and multilayer tablets containing diverse and exact active components. These benefits have resulted in the widespread use of this technology in pharmaceutical applications. Choosing the right binder and concentration can result in the proper integrity of 3D medicinal formulations. Furthermore, the particle size of the powder is a significant component that influences the quality of the final 3D goods. (56-60)

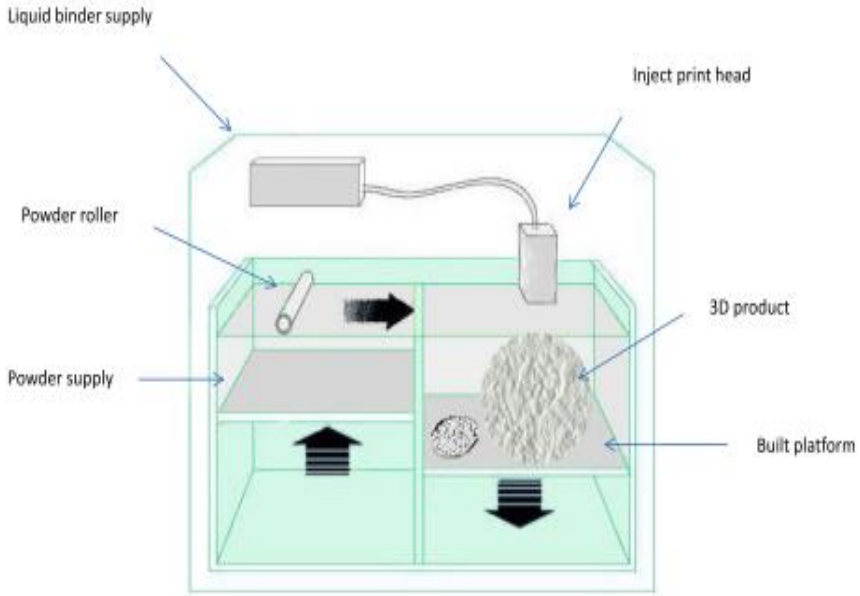

Fig 5: Powder-Based Binding Method

5. STEREOLITHOGRAPHY (SLA):

Stereolithography is based on the photopolymerization of liquid resin with ultraviolet light to solidify it. The printer can be configured bottom-up, with the UV source below the printer and the moving platform above, or top-down, with the UV source above and the platform below. The initial layer is photo-cured and adheres to the building platform after being traced by the laser in the x and y axes driven by scanning mirrors. The platform is then moved across the z-axis to an extent determined by the breadth of each layer (moved down in the case of a bottom-up approach and elevated in the case of a top-down approach). The liquid resin is then redistributed above the previously hardened layer for hardening, and the procedure is repeated to form the 3D item. The piece is then cleaned with alcohol to remove any remaining resin. To make stronger the object, post-curing with a UV oven is probably used. SLA materials must have photo-curable properties to undertake photo-cross-linking. High resolution and reduced heat stress are two advantages of this printing technology. (61-62)

Pharmaceutical Applications of Stereolithography:

Despite its benefits, this printing method has limited application in the pharmaceutical industry. One factor is the scarcity of suitable polymers for pharmaceutical applications, none of which have been designated as generally recognized as safe (GRAS) chemicals. As a result, they are unsuitable for human usage, and their photosensitivity causes stability concerns. Another restriction is that photoinitiator fragments may become trapped in the photopolymerized structures and become cytotoxic when leached out. In addition, one study discovered an unanticipated chemical reaction, namely a Michael addition reaction between the photopolymer and medication. Using polyethylene glycol di-acrylate as the monomer and diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide as the photo-initiator, Wang and colleagues successfully printed paracetamol tablets with changed release profiles. It was also used to create paracetamol pills in a variety of forms to achieve distinct release profiles. This method has also been used to create hydrogels. Martinez and colleagues created ibuprofen-loaded hydrogels made of cross-linked polyethylene glycol diacrylate. Because water may be trapped in the matrices, it was demonstrated that hydrogels that contained and retained water could be printed by adding water to the resin composition. Ascorbic acid-loaded solid dose hydrogels were also created employing the photo-initiating polymer poly(ethylene glycol) di-methacrylate and riboflavin. Various microneedles for transdermal distribution were also created and subsequently drug-coated utilizing inkjet printing. A unique, hybrid manufacturing technique for drug delivery systems with drug depots was devised, in which the matrix of the DDS was formed by SLA, and the drug depots were loaded using inkjet printing. Microreservoirs were created for implantable and transdermal administration. Using FDM and SLA, Goyanes and colleagues created salicylic acid-based anti-acne masks. PEGDA and PEGDA mixes were employed in the SLA-produced masks. SLA was determined to be the superior approach due to its higher resolution, higher drug loading, and lack of drug degradation. (62-71)

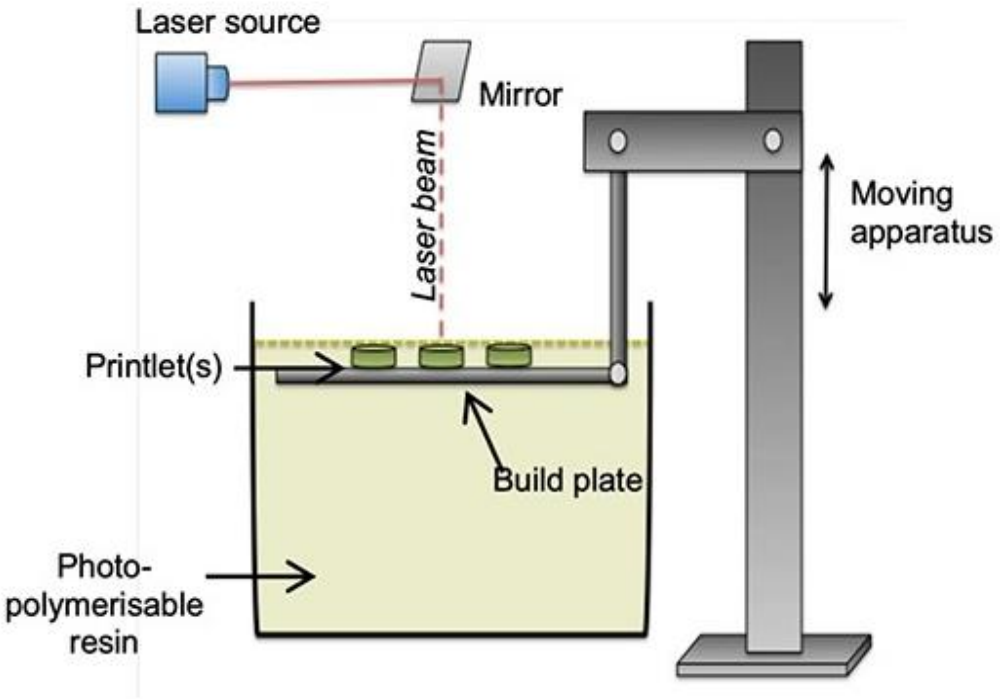

Fig 6: Stereolithography (SLA)

6. SELECTIVE LASER SINTERING (SLS):

Selective laser sintering uses laser energy to heat and fuse powder particles, which solidify to form a three-dimensional object. The spreading platform, powder bed, and laser system are the three primary components of a selective laser sintering (SLS) system. The powder is dispersed consistently over the platform by the spreading system, and the surface is evened using a roller blade. The scanning pattern of the laser system, which moves in a two-dimensional plane, is predetermined depending on the finished product's qualities. To create fusion by melting using a laser, the material is heated to a temperature below its melting point, and the height of the bed is adjusted to center the laser on the newly formed surface. During the procedure, the loose powder on the platform offers stability. The powder bed is shifted down by one layer each time, and the next layer is deposited and fused. This is repeated to create the finished 3D-printed object, which is done manually or with a sieve retrieved from the loose powder after cooling inside the printer. This method is useful since it is a one-step, quick production procedure that does not require the use of any solvent. Because of the laser precision, it also generates things with high resolution. (72-73)

Pharmaceutical Applications of SLS:

Due to the high energy laser, which may damage the pharmaceuticals, SLS is not extensively employed in the manufacturing of drug-loaded formulations. Various drug-loading delivery methods based on SLS have been investigated. SLS has recently been studied in the production of oral drug-loaded formulations. 3D-printed paracetamol tablets (printlets) were created utilizing two polymers, Kollicoat and Eudragit, and there was no evidence of drug degradation. Paracetamol oral disintegrating printlets were created utilizing the polymers HPMC and Kollidon. Printlets of ondansetron were used for complexation after inclusion in cyclodextrin with mannitol and kollidon. A variety of mini-printlets

containing paracetamol and ibuprofen with customizable medication release patterns were also studied. Polymers polyethylene oxide, Eudragit, and ethyl cellulose were also used to create paracetamol-loaded gyroid structures. (73-79)

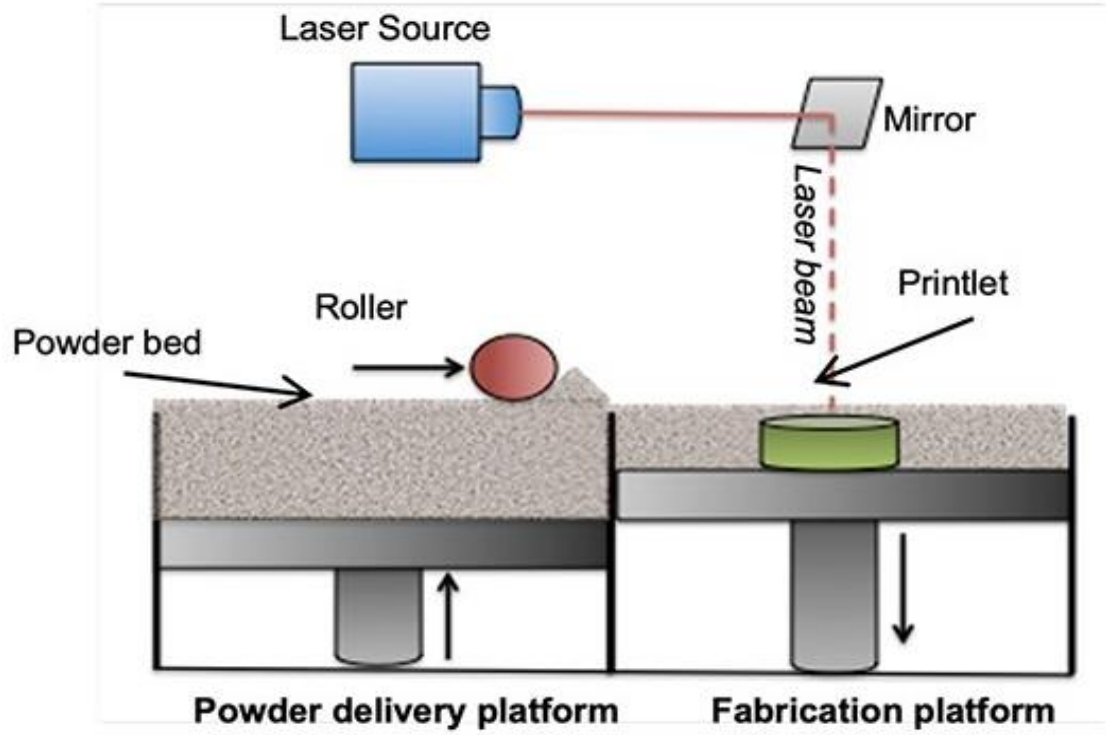

Fig 7: Selective Laser Sintering (SLS)

CONCLUSION:

Complex forms can be made more cost and time effective with 3D printing technology. Its uses in pharmaceutical research and biotechnology may improve. 3D printing has a wide technological range in the pharmaceutical area, including novel drug delivery systems, the development of new excipients, improved medication compatibility, and customized dosage forms. In the future, 3D printing can be regulated and followed by pharmaceutical and other industries that have the necessary level of safety and security concerns. Clinical pharmacy practice could be transformed by 3D printing. It has the potential to shift traditional methods of pharmaceutical mass production toward on-demand production of small batches of highly flexible and personalized dose forms. This technology benefits patients, pharmacists, and the pharmaceutical industry simultaneously by providing unique benefits such as making treatments safer and more effective. Healthcare professionals, such as pharmacists, doctors, and nurses, will be critical in advising academia, the pharmaceutical industry, and biotech businesses on methods to revolutionize the sector utilizing 3D printing.

A variety of causes are driving the rising usage of 3D printing technology in the manufacture of medication delivery systems. The method enables the creation of multifaceted dose forms with precise material deposition, increased spatial control, and geometric flexibility. These characteristics enable the development and production of extremely creative medicines, such as combination medication solutions with multi-mechanism release behaviors, which can significantly improve patient compliance with complex dosage regimens. 3D printing systems are naturally scalable, with the flexibility to be configured as semi-continuous or continuous manufacturing lines, addressing small volume (e.g. orphan

items) to commercial scale (e.g. generics) manufacturing. Accurate, low dose dispensing skills can contribute to improved control, consistency, and safety with low dose and/or powerful substances. 3D printing enables for the fabrication of varied dose strengths in a pharmacy or ambulatory setting, allowing an unprecedented flexibility to individualize dose per patient needs. Furthermore, the capacity to print dosage forms at the point of care may enable patients to have more therapeutic alternatives available to them.

People are depending more on enhanced medication as a result of changed lifestyles rather than focusing on a healthy diet. Depending on the number of disorders, different doses are frequently taken in specific circumstances. As a result, tailored medicine has a lot of promise in terms of medicine design and preparation depending on specific patient demands. The rapid rise of 3D-printed formulations employing various technologies including as inkjet printing, fused deposition modeling, material extrusion, and stereolithography has piqued the interest of the healthcare industry. Because of its high resolution, inkjet printing technology can provide more regulated formulations, whereas fused deposition modeling can achieve dose precision. In recent years, researchers have used 3D printing to provide several doses with minimal material loss. Rapid and safe production of low-cost pharmaceutical devices and poly-pills is possible. Extrusion-based bio-printing can be used to create a wide range of biological tissues with precise shapes that are suitable for human use. Patients suffering from chronic diseases can receive treatment at a reasonable cost. Individualized 3D printing minimizes market rivalry, resulting in higher earnings for pharmaceutical companies. The potential for spatially customized devices and formulations to treat diseases ranging from infection to cancer could pave the way for new directions in medical and pharmacological research. As a result, 3D printing has the potential to play a critical role in the development of customized drugs and medical transport systems, leading to substantial advances in medicine and healthcare.

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