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3D printing represents a promising new direction for printlets.

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ABSTRACT: The industry of 3D printing is uncharted territory that has yet to be completely explored. Due to the 2015 FDA approval of Levetiracetam(SPRITAM®), the pharmaceutical industry has gained momentum. As the solid dosage form is printed layer by layer, it is particularly useful for personalized and multi-layer tablets because of its precision. Emerging novel methods for modified release profiles, dimensions, and sizes have also contributed to the development of the 3DP field. Much remains to be discovered and investigated in this area of thirst, as well as much to be considered.The obstacles produced are also crucial and a stumbling block for the development of large-scale production.The purpose of this article is to provide an overview of the various 3DP techniques and their advantages and disadvantages.

Keywords:3DP, FDM, SLS, STI, IJP, and HME.

I. INTRODUCTION

3D printing, also known as Additive Manufacturing (AM), is a process in which material is deposited layer by layer onto a substrate using Computer Aided Design (CAD). Also known as Rapid Prototyping (RP) and Solid Freeform Technology (SFF), this method is also known by these terms.
The World Health Organization defines 3D printing as "the fabrication of objects by deposition of a material using a print head, nozzle, or other printer technology."
In 2015, the first medication utilizing this technology, Levetiracetam (SPRITAM®), was approved by the Food and medication Administration. Charles Hull invented stereolithography for the first time in 1884, however. After that, numerous techniques were developed, including fused deposition modeling (FDM), inkjet printing, zip dose, extrusion 3D printing, and selective laser sintering (SLS).

This technology has gained traction in the pharmaceutical industry due to its adaptability, time-saving capabilities, and preference over conventional dosage forms, where factors such as milling, compression, etc. can negatively impact the quality of the drug, which 3D printing prevents. When compared to the manufacturing process of conventional pharmaceutical products, it has many advantages, such as high production rates due to its fast operating systems; the ability to achieve high drug- loading with much desired precision and accuracy, particularly for potent drugs that are administered in small doses; the reduction of material wastage, which can reduce the cost of production; and its adaptability to a wide range of pharmaceutical active ingredients, including those that are poorly water-soluble.1
Since rapid prototyping (RP) can be completed in a matter of minutes, it offers a variety of benefits, including increased cost-effectiveness and production speed. To ensure that 3D-printed medications have the same efficacy, safety, and stability as conventional pharmaceuticals manufactured by the Pharmaceutical Industry, a significant barrier remains.2
The area of greatest interest is patient-specific tailored drugs or personalized medications, as the one-size-fits-all mechanism is ineffective due to the fact that each patient has unique needs and reactions to certain drugs. Another important application is release-targeted drugs3, it can also provide medications of various geometries, compositions, and release kinetic profiles.

Advantagesof3D Printing

• The 3D printing industry has not yet acquired traction in the pharmaceutical sector; however, it is superior in certain areas to conventional dosage forms, particularly for potent medications that are administered in small dosages. This provides high accuracy and precision, and it has a high production rate.

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As almost everything is completed using CAD, the operating system is excellent.

• It includes precise control of particle size and dose, high reproducibility, and the ability to manufacture dosage forms with complex drug-release profiles (Lee H. & Cho D.-W.; 2016 b).

• As milling, compression, and other processes are minimized, this method is also more cost-effective than conventional methods, and it generates less waste.

• In this method, the substance is formed layer by layer so that it is porous and disintegrates rapidly.

• It offers versatility in terms of dose, dosage form, shape, and drug release.

• This method is particularly useful for "personalized" medicine that can be specifically tailored to a patient's needs; it aids in patient compliance, as patients with serious illnesses are typically administered multiple drugs; instead, a multi-layer drug can be made specifically for the patient using this method.

• It is appropriate for orphan medications, which are intended for the diagnosis, prevention, or treatment of rare diseases that are life-threatening or extremely severe. Then, research on these possibilities can enhance the quality of life and attract the attention of the healthcare industry5.

Disadvantagesof3DPrinting

• This technology is primarily founded on nozzles and computers. If the nozzle does not stop between processes or does not stop at all, the product may be altered. CAD errors can also affect the final product. Until now, it has not been possible to manufacture on a significant scale using this method, which is more expensive than traditional methods.
• Additional issues with this technology include printer parameters such as cost and printing quality, which will impact the overall product quality.
• Several essential parameters, such as printing rate, printing passes, line velocity of the print head, interval time between two printing layers, distance between nozzles and powder layer, etc., must be optimized for 3D product quality. 6,7

II. DIFFERENT3DPRINTINGTECHNIQUES

STEREOLITHOGRAPHY

In 1986, Charles Hull, co-founder of 3D Systems, Inc., patented this method. This technique employs a stereolithography apparatus (SLA) machine that employs liquid plastic that is then cured or solidified to create a solid object. In this process, a layer of photopolymer is exposed to a UV laser8,9,10, which "paints" the pattern onto the object. It is of two kinds, top-down and bottom-up, based on its position.
In the bottom-up type, the light source is positioned beneath the resin tank and the component is constructed facing up down, whereas in the top-down type, the light source is above the tank, the part is constructed facing up, and the second layer is affixed to the first.
The prepared item is then cleansed with rubbing alcohol to remove superfluous resin before being cured in a UV furnace to strengthen the print.9,11,12

Advantages

Its greatest advantage over other 3D techniques is its high resolution and absence of thermal processes, allowing the use of thermolabile medications. Stereolithography is preferable to all other solid free-form fabrication (FFF) techniques in terms of accuracy and resolution, with an accuracy of up to 20 m13.

Disadvantages

The greatest limitation of this method is the resin/polymer, which must be approved for use as an excipient and have a low molecular weight.

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Expensive and cytotoxic14.

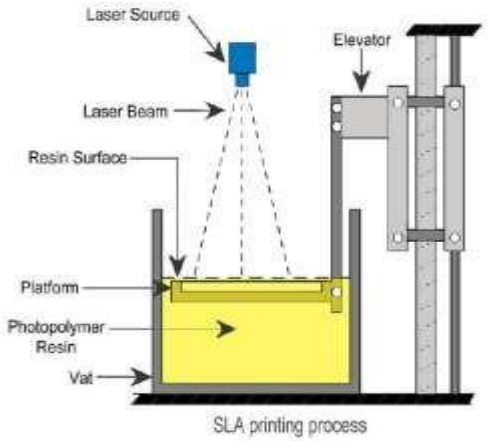

Figure1-Stereolithographyin3Dprinting.[15]

S.no.	Drug name	Formulation	Use	Reference No.
1	Paracetamol	Oral modified release tablet	Anti-pyretic	16
2	Salicylic acid	Anti-acne patch	Psoriasis	17

Table 1- Examples of drugs made usingstereolithography

1. SELECTIVELASERSINTERING(SLS)

A laser beam is used in the SLS procedure to create the pattern in the powder bed. In this method, after the first layer is drawn on the powder bed, a second powder bed is created on top of it, and the pattern is again drawn on it. The product pattern is then printed layer by layer, and the product is obtained from underneath the bed.

Fine et al. used SLS in the preparation of paracetamol tablets coated with Kollicoat®IR or Eudragit®L100-55.Moreover, Candurin®gold luster was added because it was discovered to absorb laser light during the sintering process18.The SLS can be used to produce porous, rapidly disintegrating, and modified dosage forms devoid of a binding agent.

Advantages

SLS is advantageous for printing with a high resolution and printing medication without the need for a solvent.
Simple removal of granules

Disadvantages

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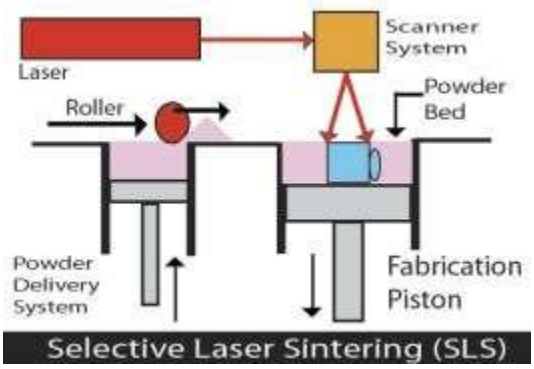

Figure2-Selective LaserSintering(SLS).[19]

2. FUSED DEPOSITION MODELLING(FDM)

In FDM, the material is softened or dissolved via heat extrusion, and the melted material is deposited on the platform in a manner that creates the design specified by the software. The molten substance is deposited in successive layers, which then fuse together.

The molten material is deposited using a nozzle with a tip size between 50 and 100 m.As the process continues, the nozzle in FDM technology moves horizontally, while the build platform moves vertically downward. After each layer, the construct platform descends and the subsequent layer is deposited on top of the previous layer (Fig. 3). FDM has a high XY resolution, but a poor Z resolution; consequently, the thickness is not homogenous. Therefore, additional refining processes may be necessary if a flat surface is desired20.

Genina et al. presented an alternative method for formulating the combination of anti-tuberculosis medications rifampicin and isoniazid by physically separating the APIs in a novel dual compartment dosage unit designed with CAD and fabricated with FDM21-based 3D printing.

Advantages

This method is useful for the production of personalized dose medications and delayed release prints without outer enteric coating. Disadvantages

Due to a paucity of polymers that are thermally stable and nonvolatile, this method proves to be challenging.

As the drug is frequently entrapped in the polymer, there appears to be a problem with delayed and inadequate drug release.

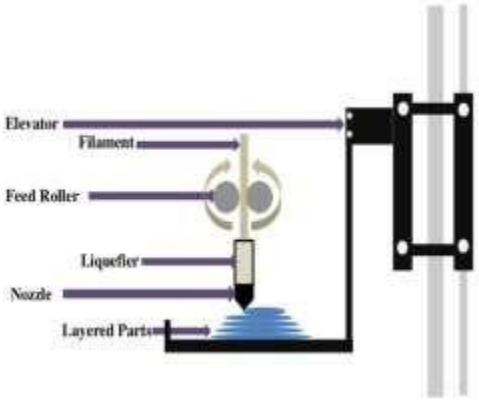

Figure3-FusedDepositionmodeling[22]

3. INKJETPRINTING(IJP)

In inkjet printing, the printing material is extruded layer by layer through a small orifice. The deposited layer is cured, and the curing process is dependent on the material used to print the product. Continuous inkjet printing (CIJ) and drop-on-demand inkjet printing (DoD) are two classifications for inkjet printing. Additional DoD printing methods include Piezoelectric and thermal inkjet printing. Based on the sort of print head, it can be categorized as

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drop-on-drop or drop-on-solid.With the aid of a roller, a powder bed is formed uniformly, and the print head deposits particles onto this bed, which then merge with the powder layer by layer. The mechanism of ejection distinguishes between piezoelectric, thermal, and continuous ejection. After the first layer has been created, a second layer is applied to the powder base to create a stratified product.

Advantages

As only the print head nozzle is utilized, it is a tool-free process that is cost-effective, requires minimal maintenance, and generates little waste. The CAD message is transmitted as a "direct wire" message. Easily accessible and reasonably priced28.

4. HOTMELTEXTRUSION(HME)

It is a continuous process in which heat and pressure are used to dissolve the materials through an orifice in order to produce a product with a uniform density and shape. When a substance is forced through an orifice or die in a hot melt extruder3, the extrusion process can alter its physical properties.[8].

III. MATERIALSUSEDIN3DPRINTING[47]

Someofthepolymersused inthisare

1. AcrylnitrileButadieneStyrene

It is one of the most commonly used 3D printing polymers due to its high temperature resistance, flexibility, and ease of extrusion, as it requires less force than polylactic acid. Its glass transition temperature is approximately 105 degrees Celsius, and temperatures between 210 and 250 degrees Celsius are typically used for printing with acrylonitrile butadiene styrene materials.

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2. PolylacticAcid

In addition to being biocompatible with the human body, this biodegradable thermoplastic derived from maize is environmentally benign compared to other plastic materials. Poly lactic acid has a stiffer structure than Acrylonitrile Butadiene Styrene and has a lower melting point, between 180 and 220 degrees Celsius. The glass transition temperature of polylactic acid is between 60 and 65 degrees Celsius, so polylactic acid and acrylonitrile butadiene styrene could be utilized in a variety of applications.

3.HighImpactPolystyrene

High Impact Polystyrene filament is manufactured from a High Impact Polystyrene material. This material is widely used in the food packaging industry. It is also used to generate containers in medicine, this filament has brilliant white colour and it is also biodegradable. Curling and adhesion issues with High Impact Polystyrene filaments can be mitigated by using a heated substrate during printing48..

IV. APPLICATIONS

It is acquiring popularity in the pharmaceutical industry due to its use in the production of implants, as well as its contribution to organ printing for the production of cells, biomaterials, and cell-laden materials.

individually layer by layer and directly forming a 3D structure resembling tissue49.Benefits of 3D printing include precise control of particle size and dose, high reproducibility, and the ability to manufacture dosage forms with complex drug-release profiles (Lee H & Cho D-W; 2016 b).

As the focus of the industry shifts toward precision and personalized medicine, the 3D industry is gaining traction, as medications can be tailored to the individual patient's requirements. Pharmacists could examine a patient's pharmacogenetic profile, along with other characteristics such as age, race, or gender, to determine the optimal medication dose50 and prepare medication accordingly.

As 3D-printed pharmaceuticals are layered, the layers can be separated and can provide a controlled release profile for drugs with complex release profiles. These are also permeable, allowing for rapid disintegration if desired.

With the aid of ZipDose Technology, which Aprecia used to manufacture SPRITAM®, porous, rapidly disintegrating, and high-dose orodispensable medicines (Dominic Basulto 2015; Robert J. Szczebra 2015; 3D Printing; Aprecia Pharmaceuticals) up to 1000mg can be manufactured without compression.

Through the translation of X-ray, MRI, or CT scans into digital 3D print files51,52,53, implants and prostheses can be made in virtually any imaginable geometry. This method has been utilized for the fabrication of dental, spinal, and hip implants53.

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V. FUTUREPERSPECTIVES

(i) The advances in 3DP in the pharmaceutical field have created opportunities for personalized medications that can be exploited further, and we anticipate that 3DP will also be required for conventional solid dosage forms due to their difficulties. It is anticipated that the technology will be beneficial in the development of novel dosage forms and excipients in the near future. Avoiding incompatibilities will also be advantageous for multidrug preparation. (i) optimization and improvement of software performance; (ii) development of new excipients or assessment of old excipients for application in 3D formulations; (iii) development and optimization of manufacturing process for a broad range of drug products; and (iv) clinical studies to evaluate the efficacy, safety, and stability of new 3D-based formulations16.

VI. CONCLUSION

With the development of new technologies, 3D printing has evolved from scaffolds and implants to various dosage forms with altered release profiles and geometries. The field of personalized medicine, which caters to the specific requirements of each patient, has also developed. A printlet can be manufactured in a brief amount of time due to the time- and cost-saving capabilities of the technology. As the technology is still in its developmental stage, safety and regulatory concerns are lacking. And there is also a security risk, as all medications would be computerized and susceptible to hacking and theft.

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