A REVIEW ARTICLE ON 3D PRINTING TECHNOLOGY IN PHARMACEUTICALS

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***Abstract*: The aim of this present article is to present the information regarding the 3D printing techniques suitable for pharmaceutical manufacturing and also their applications to the development of drug dosage forms, indicating the feasibility of this technology in regular commercial production.**
Three-dimensional printing (3DP) technology allows fabrication of 3D objects with various geometrics in a layer-by-layer process. Some advantages of 3DP methods over the conventional manufacturing processes includes customization of medicines with individually adjusted doses, the ability to fabricate the sophisticated and complex solid dosage forms, on-demand manufacturing, and cost-effectiveness. The present review focused on briefing various techniques, applications of 3D printing in pharmaceutical technology. Furthermore, recent years have seen an increasing interest in applying 3DP technology to the pharmaceutical manufacturing of the drug products and development of various drug delivery systems. However 3DP technology exhibits many potential medical and economic benefits, there are also some technical and regulatory challenges restricting the wide applications of 3DP technology to pharmaceutical products. Accordingly, the continuous innovation and refinement in 3DP methods are needed to overcome the current limitations and facilitate patient-specific health care with on-demand tailored medications in the future.

***Keywords*: 3Dprinting techniques, Personalized medicine, Polypill, Applications, Challenges.**

INTRODUCTION

Three-dimensional (3D) printing is a manufacturing method in which objects are made by fusion or depositing materials – such as plastic, metal, creamics, powders, liquids, or even living cells in layers to produce a 3D object. This process is also referred Additive Manufacturing (AM), Rapid Prototyping (RP), or Solid free-form technology (SFF). Some 3D printers are similar to traditional inkjet printers; however, end product differs in that a 3D object is produced[1].

Charles Hull invented 3D printing, which he called as Stereolithography, in the early 1980s. Later he founded the company 3D systems, which developed the first 3D printer, called as Stereolithography apparatus.

The U.S. Food and Drug Administration (FDA) approved Aprecia Pharmaceuticals Company's 3D printed "SPRITAM" levetiracetam for oral use in treating epileptic seizures recently which furthers the prospect of tailor- made drugs that are customized to individual patient needs[2]. The vision behind AM is that medication will be customized to individuals in way that make it safer and more effective. Normal et al. delineates there are three unique attributes where 3D printing distinguishes itself from traditional manufacturing processes:Product complexity, Personalization, and on –demand manufacturing [3].

Nowadays, 3DP could be extended throughout the drug development process, ranging from preclinical development and clinical trials, to frontline medical care. When compared to the manufacturing process of conventional pharmaceutical product, it has a lot of advantages like high production rates due to its fast operating systems; ability to achieve high drug-loading with much desired precision and accuracy especially for potent drugs that are applied in small doses; reduction of material wastage which can save in the cost of production and amenability to broad types of pharmaceutical active ingredients including poorly water-soluble, peptides and proteins, as well as drug with narrow therapeutic windows[4]. Different types of drug delivery systems such as oral controlled release systems, micro pills, microchip, drug implants, fast dissolving tablets and multiphase release dosage forms have been developed using three-dimensional (3D) printing technology. Hence, it is expected that three-dimensional (3D) printing technology could offer new approaches for developing novel pharmaceutical dosage forms [5].

PERSONILIZED MEDICINE

The purpose of drug development should be to increase efficacy and decrease the risk of adverse reactions, a goal that can potentially be achieved through the application of 3D printing to produce personalized medications. Oral tablets are the most popular drug dosage form because of ease of manufacture, pain avoidance, accurate creating personalized medicines and restrict the ability to create customized dosage forms which are highly complex geometries, novel drug-release profiles, and prolonged stability.

Personalized 3D-printed drugs may particularly benefit for patients who are known to have a pharmacogenetic polymorphism or who use medications with narrow therapeutic indices. Pharmacists may analyze a patient's pharmacogenetic profile, as well as other characteristics such as age, race, or gender, to determine an optimal medication dose. A Pharmacist then print and dispense the personalized medication via an automated 3D printing system. If necessary, the dose could be adjusted further based on the clinical

response. 3D printing also has the ability to produce personalized medicines in entirely new formulations, such as pills that include multiple active ingredients, either as a single blend or as complex multilayer or multi reservoir printed tablets. Patients who have multiple chronic diseases could have their medications printed in one multidose form that is fabricated at the point of health care. Providing patients with an accurate, personalized dose of multiple medications in a single tablet could potentially improve the patient compliance [6].

POLYPILL CONCEPT:

The concept of "polypill" refers to a single tablet that includes the combination of various drugs. This concept is highly beneficial for geriatric population, as patients of this age category are prone to multiple disorders and hence multiple therapy.
The technology has been realized through the research of Khalid et al, where five different active pharmaceutical ingredients with different release profiles have been formulated in a single 3D dosage form. Three drugs (pravastatin, atenolol, and ramipril) were printed in the extended release compartment. The drugs were physically separated by a permeable membrane of hydrophobic cellulose acetate. An immediate release compartment containing aspirin and hydrochlorothiazide was deposited on top of the extended release compartment [7].
Three-dimensional(3D)extrusion-based printing was used to manufacture the 'polypill' to demonstrate that complex medication regimes can be combined in a single tablet and that it is viable to formulate and 'dial up' this single tablet for the particular needs of an individual tablet. The tablets used to provide this concept incorporate an osmotic pump with the drug captopril and sustained release compartments with the drugs nifedipine and glipizide. This combination of medicines could potentially be used to treat diabetics suffering from hypertension. The room temperature extrusion process used to print the formulations used excipients commonly employed in the Pharmaceutical industry [8].

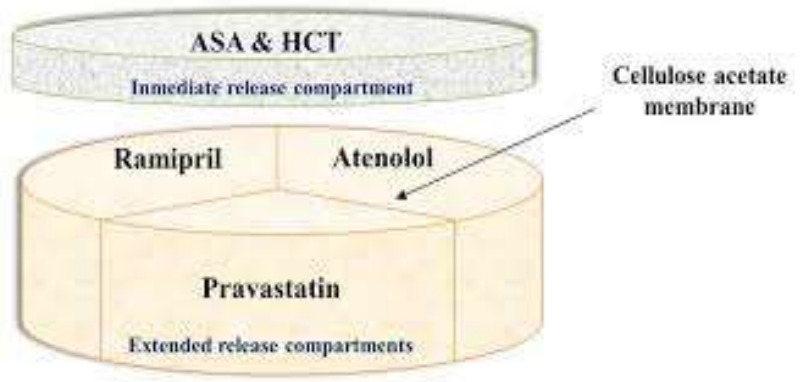

Fig 1: Polypill

TECHNIQUES IN 3D PRINTING

3D printing includes a wide variety of manufacturing techniques, which are based on digitally-controlled depositing of materials (layer-by-layer) to create free form geometries.

THERMAL INKJET PRINTING

In thermal inkjet printing, the aqueous ink fluid is converted to vapour form through heat and expands to push the ink drop out of a nozzle. It is used in the preparation of drug-loaded biodegradable microspheres, drug-loaded liposomes, patterning microelectrode arrays coating and loading drug eluting stents. It is also an efficient and practical method for producing films of biologics without compromising protein activity [9].

In this technique, the Ink is deposited onto a substrate either in the form of Continuous Inkjet printing (CIJ) or Drop on Demand (DoD) printing, hence it provides a high resolution printing capability. Inkjet printing is also called as 'mask-less' or 'tool-less' approach because the formation of desired structure mainly depends upon the movement of inkjet nozzle or movement of the substrate for an accurate and reproducible formation. It has a low processing cost, rapid processing rates, generation of minimal waste, it gives CAD information in a 'direct write' manner and it process material over large areas with minimal contamination [10].

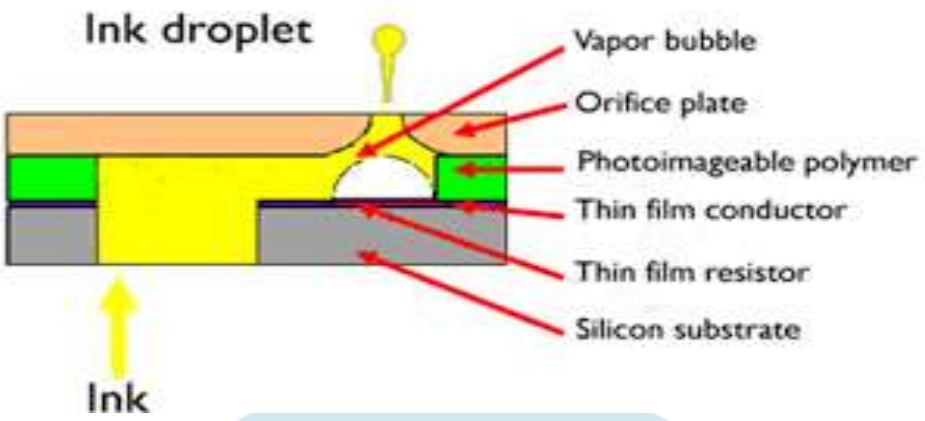

Fig 2: Thermal ink jet printing

FUSED DEPOSITION MODELING (FDM)

Fused deposition modeling (FDM) is the second most important commercial layered manufacturing technique. This process is used to fabricate final products directly without the use of any tooling, die, or molds, which are some of the major constraints of the traditional manufacturing process. This technique has gained popularity due to its short cycle time, high-dimensional accuracy, ease of use, and easy integration with different computer-aided design (CAD) software. FDM is an additive manufacturing technology and commonly used for modeling, prototyping, and batch production applications[11].

Fused deposition modeling (FDM) is commonly used technique in 3D printing, in which the materials are soften or melt by heat to create objects during printing, Hence there are several dosage forms. FDM 3D printing helps in manufacturing delayed release printlets without an outer enteric coating, and also provides a personalized dose medicines. FDM 3D printing however, indicates several limitations of the system such as lack of suitable polymers, slow and often incomplete drug release because the drug remain trapped in the polymers and the miscibility of the drug and additives with the polymers used was not evaluated [12].

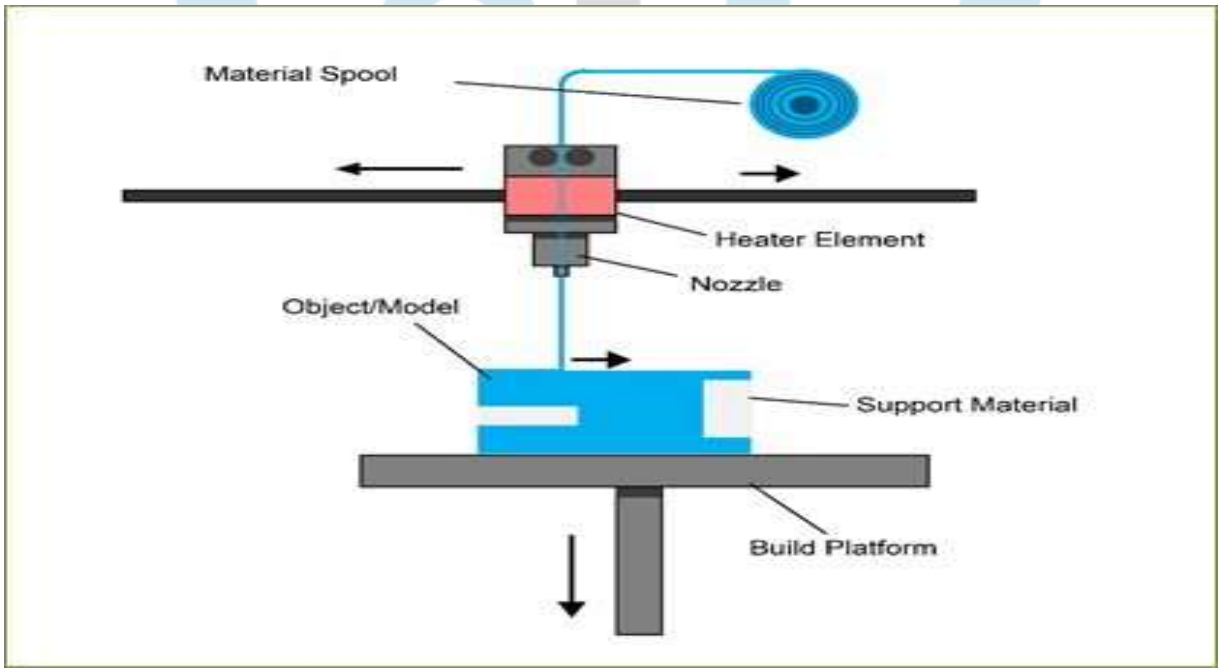

Fig 3: Fused deposition modeling

ZIP DOSE

Zip dose is the world's first and only FDA-validated, commercial-scale 3DP in new therapeutic areas for drug manufacturers. It has a unique digitally coded layering and zero-compression processes, which is used for formulating a tablet with high dose and rapid disintegration. Hence it helps in overcoming a difficulty in swallowing.

It developed with Aprecia's proprietary 3DP manufacturing process, Zip Dose Technology helps patients who need medicines that are easy to take and caregivers—including physicians and nurse practitioners—who want medicines that are easy to administer. By

enabling the delivery of high-dose medications in a rapidly disintegrating form, Zip Dose overcomes patient adherence and difficulty swallowing challenges[13].

Spritam (Antiepilipsey drug) is an Orodispersible tablet, marketed by Aprecia Pharmaceuticals based on powder bed fusion by layer-by-layer production system. In which it consists of active ingredients, excipients and a binder liquid to produce a matrix tablet [14].

Fig 4: Zip dose 3D printing

Extrusion 3D printing

According to the ASTM International standards organization, extrusion is an official name given to a specific 3D printing process where material is selectively dispensed through a nozzle or orifice. Extrusion more commonly known as Fused Deposition Modeling

Extrusion is the most common and the simplest 3D printing technique. It is used in almost every environment. The main printing material is plastic filament. The filament is heated, and melted in the printing head of the 3D printer.

Extrusion is an "additive" technology commonly used for the modeling, prototyping, and production applications. It creates an object by laying down the material in layers; a plastic filament or metal wire is unwound from a coil and supplies material to produce a part.

In this technique, material is extruded from the automated nozzle on to the substrate and it does not require any higher support material. It is only used to fabricate tablet containing Guaifenesin as expectorant. The materials that can be extruded are molten polymers, suspensions, semisolids, pastes [15].

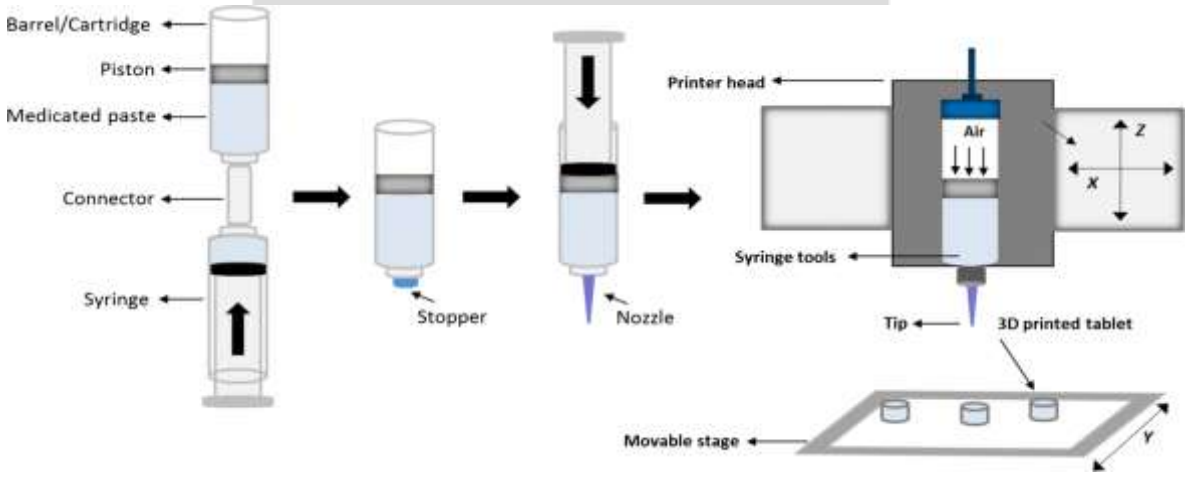

Fig 5: Extrusion 3D printing

3D printer

The 3D printer is a valuable tool which is used to create customized medications with tailored release profiles and the medication is changed as per the patients comfort.

HOT MELT EXTRUSION (HME)

Hot melt extrusion (HME) is the process of melting polymer and drug at high temperature and the pressure is applied in the instrument continuously for blending. It is a continuous manufacturing process that includes several operations such as feeding, heating, mixing and shaping. In recent years, it has proved that HME has the ability to improve the solubility and bioavailability of poorly soluble drugs[16].

HME is used to prepare solid solutions/dispersions for drug delivery systems such as pellets and granules, it can reduce the number of processing steps in dosage form manufacturing and can be automated as a continuous process to give better drug homogeneity, capabilities of sustained, modified, and targeted release. Uniting Hot melt extrusion (HME) with solid freeform fabrication (SFF) such as Fluid deposition method (FDM) offer great chances for designing a wide variety of drug delivery systems by 3D printing technology [17].

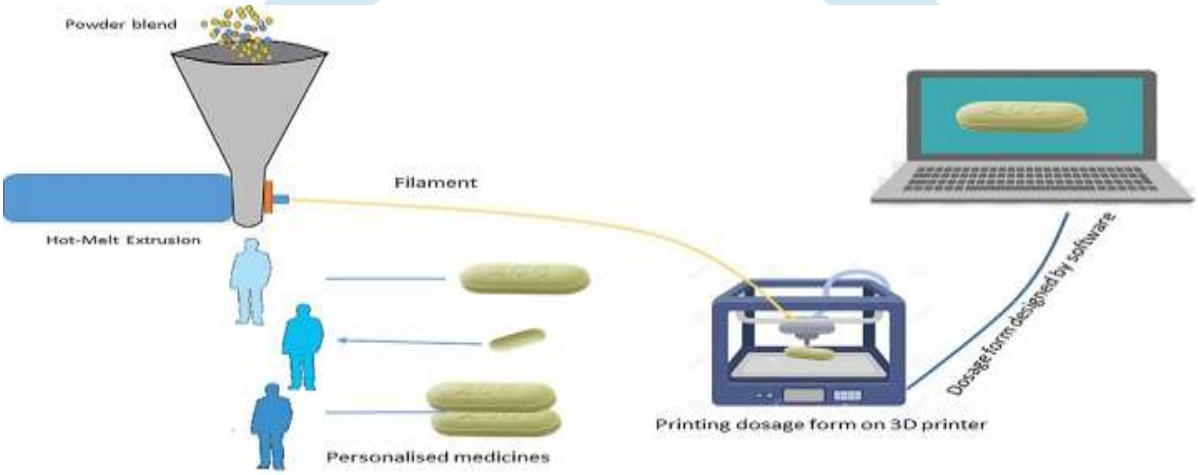

Fig 6: Hot melt extrusion

STEREOLITHOGRAPHY

Stereolithography (also known as Stereolithography apparatus, Optical fabrication, Photo-solidification, (or) Resin printing) is a form of 3D printing technology used for creating models, prototypes, patterns, and production parts in a layer by layer fashion using the photochemical processes by which light causes chemical monomers to link together to form polymers. Those polymers are then make up the body of a three-dimensional solid[18].

Stereolithography is the technique in which a computer controlled laser beam is used to solidify the liquid polymer or resin, thereby creating a 3D structure. SLA has some advantages over other types of 3DP, mainly it's remarkable resolution and the avoidance of thermal processes can be detrimental for certain drug molecules [19].

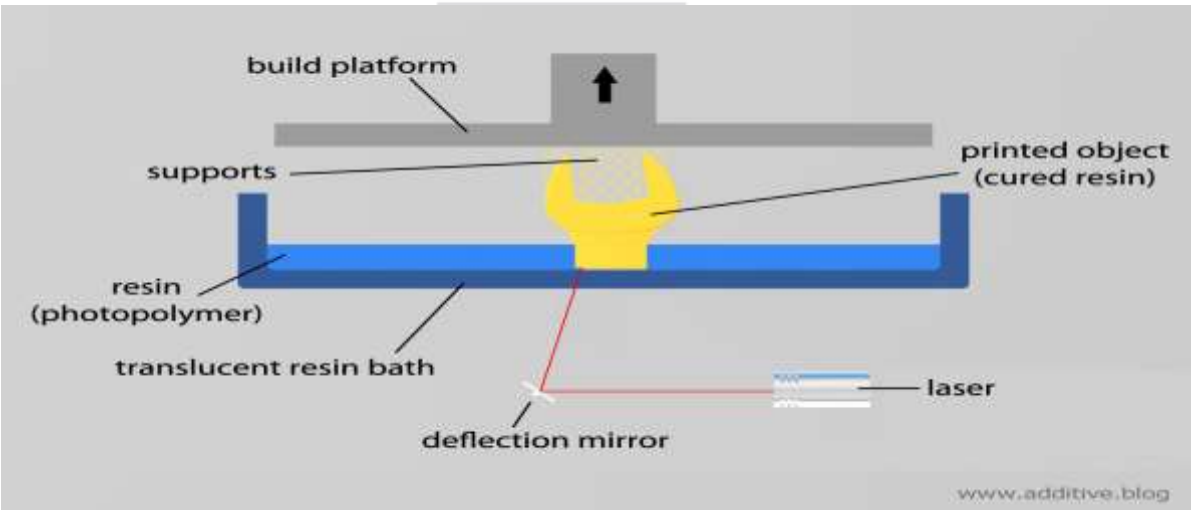

Fig 7: Stereolithography

SELECTIVE LASER SINTERING

Selective laser sintering (SLS) is an additive manufacturing (AM) technique that uses a laser as the power source to sinter powdered material (typically nylon or polyamide), aiming the laser automatically at points in the space defined by a 3D model, binding the material together to create a solid structure.

SLS uses a laser to bind together with the powder particles from a powder bed. During the printing process, the laser is directed to draw a specific pattern onto the surface of the powder bed thereby creating a 3D structure. For example Paracetamol is an Orodispersible tablets which was prepared by this technique. It is currently used for industrial manufacturing of plastic, metallic and ceramic objects [20].

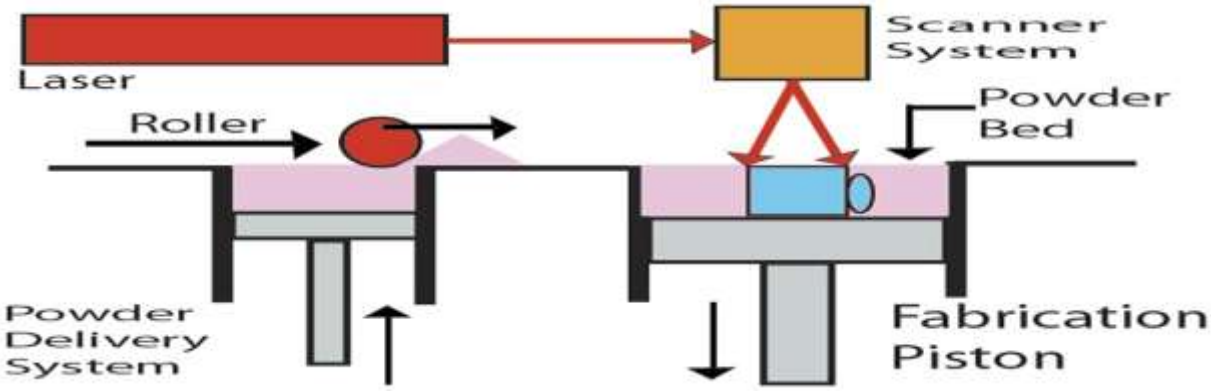

Fig 8: Selective laser sintering

3-Dimensional printing technologies applied in the development of pharmaceutical drug delivery systems.

Printing technology/printer type	Dosage forms/systems	Model drug used
3D printer(21)	Tablets	Paracetamol
3Dprinter(22)	Microflidic pump	Saline solution
Fused deposition 3D printing(23)	Extended release tablet	Prednisolone
Fused deposition 3D printer(24)	Oralpulsatile capsule	Acetaminophen
Ink-jet printer(25)	Solid dispersion	Felodipine
Thermal Inkjet printer (26)	Oral solid dosage forms	Prednisolone
Extrusion–based printer(27)	Multi–active tablets (polypill)	Captopril ,Nifedipine & Glipizide
3Dextrusion printer (28)	Multi-active solid dosage form (polypill)	Aspirin, Hydrochlorothiazide, Pravastatin, Atenolol & Ramipril
Thermal Inkjet printer (29)	Dosing drug solutions onto oral films	Salbutamol sulphate
Thermal Ink jet printer(30)	Oral solid dosage forms	Prednisolone
Stereolithography printer(31)	Anti-acne patch	Salicylic acid

Advantages of 3d printing:

- Personalized drug dosing: - 3D printing could add a whole new dimension of possibilities to the personalized medicine. A doctor or a pharmacist would be able to use each patients individual information –such as age, race and gender –to produce their optimal medication dose, rather than relying on a standard set of dosages.
- Unique dosage forms:- 3D printing may also used to create unique dosage forms in the pharmaceutical production process. In this process, the idea would be to use inkjet based 3D printing technology to create limitless dosage forms.
- More complex drug release profiles:- Drug release profiles explain about how a drug is broken down when taken by the patient. Designing and printing drugs first hand makes it much easier to understand their release profiles.
- 3DP allows precise control of droplet size, dosage strength, complex drug release profile, and multi dosing.
- Creating different release profiles is one of the most researched uses of 3DP.
- The ability to create limitless dosage forms (e.g., orally disintegrating tablets, delayed –release capsules) challenges conventional dosage forms even further.

Disadvantages of 3d printing:

- Precise ink viscosity must be achieved for proper flow with inkjet printing.
- Other disadvantage include mechanical properties of the formulations being printed. At least some 3D printing drug products do not have proper hardness and binding of the materials to justify using a printer, as the ink formulation components must be able to self-bind but not bind to other printer elements.
- Binding to other elements may interfere with the timing of the drug release, parameters such as speed and rate of printing must be taken into account and may not be suitable for all drug candidates.
- A need exists for proper post printing process that will not interact or counter interact with the finished printed process [32].

Application of 3d printing

1. 3D printing applications are an enormous challenge, with potential use in a broad range of fields such as industrial design, aerospace, medical, tissue engineering, architecture, pharmaceutical and even food.

2. It mainly focus on two potential directions to bring the pharmaceutical product development to uncharted areas, one is the manufacturing of drug delivery systems with sophisticated structures and the other one is personalized medicine.

3. It has expanded into the healthcare industry, where it's used to create dental implants.

4. Now, there may be an opportunity to use it as personalized healthcare. 5.It also fabricates a newly released multi-drug implant for bone tuberculosis therapy.

5. It also helps in Organ printing to produce cells, biomaterials, and cell-laden materials individually by layer by layer and directly creating 3D tissue like structure [33].

Limitations and Challenges of 3d Printing Dosage Forms:
There are a couple of challenges that 3D printing faces which has to be overcome before it is adopted as a widely used manufacturing technique for personalized dosage forms.

Process Challenges

Raw material selection:-Printability, thermal conductivity, physicochemical characteristics, Print fluid characteristics and viscoelastic property has to be carefully scrutinized along with safety of the raw materials for human use.

- Nozzle mechanism:-During 3D printing, nozzle mechanism is used to form the layers of the dosage form. As the printer head stops and restarts during the sequenced layer formation, consistent flow of the printing material is necessary. The common problems faced at this level are clogging of the nozzles in printer head, scraping, binder migration and bleeding and improper powder feeding.
- Powder based 3D printing:- Confined or Special area is required to perform the printing as powder spillage is critical and can pose as an occupational hazard.
- Surface imperfections in finished product:-Due to the stacking of plastic beads or large-sized powder on top of each other. Since the drying time required for the dosage form made with powder based and extrusion based techniques, there is more possibility of surface imperfections. Rate and method of drying can also affect surface imperfections.
- Mechanical resistance:- Friability is higher in 3D dosage forms especially in powder based technique. Production technology is important for good dosage form strength.
- Certain manufacturing process may not be appropriate for thermolabile drugs when printing at high temperatures [34].

Summary

The 3D printing in pharmaceuticals and medical devices serves as an attractive tool to produce customized product. Since few years ago the concept of 3D-printed drug formulation quickly evolved and was directed to enhance the therapy by patient-centric medicine. The first FDA approval of drug manufactured by the 3D printing technology caused by an exceptionally rapid development of studies on oral, oro-mucosal and topical dosage forms. This promising technology offers a formulation flexibility that is difficult to achieve with the conventional technological processes. Additional manufacturing allows to prepare different kind of dosage forms with the high precision of API-excipients ratio, in totally new manner with comparison to traditional pharmaceutical manufacturing.

Conclusion
3D printing has become a useful and potential tool for the development of Pharmaceutical sector, leading to personalized technology is emerging as a new horizon for medicine focused on the patients' needs. 3DPrinting technology has the ability to revolutionize the Pharmaceutical manufacturing style and formulation techniques. 3DP technology makes it possible to fabricate highly sophisticated and complex dosage forms of drugs and has enhanced the freedom to control the shape as well as microstructures of dosage forms. Furthermore, 3DP is an innovative and highly promising way for the on-demand manufacturing and dosage form

personalization, which may improve the patient compliance and drug effectiveness, reduce the side effects, and resolve the stability issues of drugs with limited shelf-life, and, eventually, lead to the patient-specific health care with on-demand tailored medications.

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