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3D PRINTING OF PHARMACEUTICALS – A POTENTIAL TECHNOLOGY IN DEVELOPING PERSONALIZED MEDICINE

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ABSTRACT

The 3D PRINTING technology has caught the attention of medical devices industry and pharmaceutical industry due to its applications on various platform in health care industry. Even though this technology exists for a long time it is of public interest highly now due to the approval of 3-D printed tablet and other medical devices and also with the advent of USFDA's guidance on technical considerations specific to devices using additive manufacturing which encompasses 3-dimensional (3D) printing has triggered many thoughts about this technology which needs to be considered for successful delivery of intended product. This paper presents regulatory agencies expectations, limitations, problems in establishing such setups for production of drug products, advantages, disadvantages, applications, methods and associated risks involved in manufacturing. It also provides the comprehensive review of the current status of research and development on this platform.

Key words: *Three dimensional printing, personalized medicine, novel drug delivery*

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INTRODUCTION

Drug delivery is the technology and formulation developed to efficiently transport a pharmacologically active compound in the body to achieve therapeutic efficiency in a safe manner. The efficiency and safety of a pharmaceutical product can be improved by controlling the release profile which in turn modulates the pharmacokinetics of a drug. The inter-species variability is an obstacle frequently faced in the clinical scenario. Customized medicine and dosing receives increasing attention because of the high chances of undesirable side effects. The probability of adverse reactions is higher in the pediatric and geriatric populations when the bulk manufacturing of pharmaceuticals concentrates on the average population (1, 2).

3D printing can play a significant role in multiple active ingredient dosage forms, where the formulation can be as a single blend or multi layer printed tablets with sustained release properties. This reduces the frequency and number of dosage form units consumed by the patient on a daily routine. 3D printing technology has high potential in individualized dosage form concept called the polypill concept. This brings about the possibility of all the drugs required for the therapy into a single dosage form unit.

Three dimensional printing technology is a novel rapid prototyping technique in which solid objects are constructed by depositing several layers in sequence. The rapid prototyping involves the construction of physical models using computer-aided design in three dimension. It is also known as additive manufacturing and solid free form fabrication (3). 3D printing technology has enabled unprecedented flexibility in the design and manufacturing of complex objects, which can be utilized in personalized and programmable medicine.

It is an effective strategy to overcome some challenges of conventional pharmaceutical unit operations (1, 4).

History

3D Printing posed as a possible platform for personalized medicine in the 1990s. There are major achievements in 3D printed medical device, FDA's Center for Device and Radiological Health (CDRH) has reviewed and cleared 3DP medical devices. [5]

The first 3D printing technique used in pharmaceutics was achieved by inkjet printing a binder solution onto a powder bed, binding therefore the particles together. The process was repeated until the final desired structure was obtained. This first happened in the early 90's at the Massachuset Institute Technology invented and patented by Sachs et al (6).

In 1989, Scott Crump, filed a patent on another 3D printing technology: fused deposition modeling, where extruded polymer filaments heated into a semi-liquid state were extruded through a heated nozzle and deposited onto a build platform layer by layer to harden (7, 8).

Inkjet printing was the method used to manufacture Spritam (levetiracetam) tablets for oral use, the first 3D printed drug approved by the Food and Drug Administration (FDA) in 2016 by Aprecia Pharmaceuticals (7).

3D printing is more advanced in the fields of automobile, aerospace, biomedical and tissue engineering than in the pharmaceutical industry where it is in its initial phase. FDA encourages the development of advanced manufacturing technologies, including 3D-printing, using risk-based approaches.

Regulatory Expectations (9)

US FDA, 2017 issued guidance on Technical Considerations for Additive Manufactured Medical Devices, this guidance outlines various requirements, like Design and Manufacturing Process Considerations, Device Testing Considerations and labeling. It also suggests the validation of the processes involved to provide high degree of assurance according to the established procedures. In addition documentation must be done to conform to the existing guidelines in the Quality System regulation for device validation. Process validation must be performed to ensure and maintain quality for all devices and components built in a single build cycle, between build cycles, and between machines, where the results of a process (i.e., output specifications) cannot be fully verified by subsequent inspection and test. Software also must be validated for its intended use according to an established protocol (9, 10).

The following examples were suggested in the guidance with respect to powder bed fusion technologies,

- In-process monitoring of parameters such as: temperature at the beam focus, melt pool data,
- Build-space environmental conditions (e.g., temperature, pressure, humidity),
- Power of the energy delivery system (e.g., laser, electron beam, extruder), and
- Status of mechanical elements of the printing system (e.g., recoater, gantry)
- Manual or automated visual inspection with defined acceptance criteria,
- Non-destructive evaluation, and
- Test coupon evaluation

Changes to the device, manufacturing process, or process deviations should be identified and analyzed for the potential risks they introduce. Based on this assessment, the change or deviation may trigger the need for revalidation of the process (9). Manufacturers should rely on existing FDA Guidance for their regulatory pathway when considering a change to a previously cleared or approved device that uses additive manufacturing. Some examples of triggers for revalidation specific to additive manufacturing are: (11-14)

- Software changes (e.g., change or update of build preparation software),
- Changes in material (e.g., supplier, incoming material specification, reused powder, new formulation) or material handling,
- Change in the spacing or orientation of devices or components in the build volume,
- Changes to the software workflow,
- Physically moving the machine to a new location, and
- Changes to post-processing steps or parameters

The distinction between compounded and manufactured medicine is a central question about the regulations of 3D printed medicine. Tragic incidents such as the New England Compounding Centre (NECC) in 2012 (15) and dozens of other dangerous safety problems at compounding pharmacies, have put the safety of pharmaceuticals under the spotlight (16-17). Like manufacturing of dosage forms, a 3D printed drug product have to be manufactured by following the established regulations for manufacturing of drug products meeting the current chemistry, manufacturing and control (CMC) standards provided in the 21 CFR 200 & 300 and other applicable guidance (18-19).

Important issues concerning 3D printed medicines like tort liability and intellectual rights need to be addressed to protect manufacturers and end users.

Meeting current regulatory requirements of the FDA may pose a significant hurdle that can impede their introduction to the market (20). FDA may need to issue short term guidance documents and look into modifying its traditional regulations to follow up with this rapidly-evolving technology (21). Two laboratories within the FDA's Office of Science and Engineering Laboratories (OSEL), the Laboratory for Solid Mechanics and FDA's Functional Performance and Device Use Laboratory are being utilized for the purpose of studying the potential effects of 3D printing (22-23).

In spite of all regulatory hurdles associated with 3D printing medicine, the FDA approved the first 3D printed pill, Spritam® (levetiracetam) in August 2015. In this case the product is considered as approving new mass production for equivalent product (24).

STEPS INVOLVED IN A 3D PRINTED DOSAGE FORM

Pharmaceutical product is designed in three dimension with computer aided design

Design is converted to a machine readable format which describes the external surface of the 3D dosage form.

The computer program then slices this surface into several distinct printable layers and transfers that layer-by-layer to the machine (1, 3).

Advantages of A 3d Printed Drug Delivery

- High drug loading ability when compared to conventional dosage forms
- Accurate and precise dosing of potent drugs which are administered at small doses
- Reduces cost of production due to lesser material wastage
- Suitable drug delivery for difficult to formulate active ingredients like poor water solubility, drugs with
- narrow therapeutic window
- Medication can be tailored to a patient in particular based on genetic variations, ethnic differences, age, gender and environment.
- In case of multi drug therapy with multiple dosing regimen, treatment can be customized to improve patient adherence.
- As immediate and controlled release layers can be incorporated due to the flexible design and manufacture of this dosage form, it helps in choosing the best therapeutic regime for an individual
- Avoids batch-to-batch variations seen in bulk manufacturing of conventional dosage forms (25).
- 3D printers occupy minimal space and are affordable.
- Manufacture of small batch is feasible and the process can be completed in a single run.

Integration of Personalized Medicine with Healthcare Network

As 3D printers perform as computerized fabricators that manufacture 3D objects based on command generated by computer software, it has an immense possibility of integrating the 3D printers with the healthcare network.

This concept uses sensor technology which will enable sensors to be placed on patients. These sensors generate clinical data feed that eventually gets stored in healthcare network. The healthcare professional can manufacture the next dose according to the patient's physiological changes reflected in the clinical data transmitted. Hence, such a dispensing system offers a clear advantage of shortening the time of a clinical response to patient's needs and improving patient's compliance (4).

To incorporate the practical application of 3D printed dosage form into the dispensing scenario existing today, further research and development in the clinical scenario is essential. First of all, the software technology used can be further optimized and improved. Secondly, excipients need to be developed for optimum application in 3D formulations. Thirdly, manufacturing process has to be developed and optimized for a wide range of drug products. Fourthly efficacy, safety and stability of new 3D-based formulations have to be studied further because the built in flexibility should not become a liability on safety (25).

The principle employed in 3D printing drug delivery systems is the construction and stacking of layers of 3D printed objects. The name of the technology is usually related to the technique involved in layer formation. 3D printing is repeated and co-ordinated two-dimensional printing (4).

Spritam® - Fda Approved First 3d Printed Pill

SPRITAM utilizes Aprecia's proprietary ZipDose® Technology platform, a groundbreaking advance that uses three-dimensional printing to produce a porous formulation that rapidly disintegrates with a sip of liquid

ZipDose Technology enables the delivery of a high drug load, up to 1,000 mg in a single dose. SPRITAM enhances the patient experience - administration of even the largest strengths of levetiracetam with just a sip of liquid. Aprecia developed its ZipDose Technology platform using the 3DP technology that originated at Massachusetts Institute of Technology (24).

The ZipDose technique is based on layer-by-layer powder bed fusion system. The first layer consists of the active pharmaceutical ingredient and excipients required for the matrix tablet. Subsequently, a binder liquid is deposited for perfect integration and aggregation between all of the successive and identical layers (26-27).

Polypill concept

The concept of "polypill" refers to a single tablet that includes the combination of several drugs.This concept is highly beneficial for geriatric population, as patients of this age category are prone to multiple disorders and hence multiple therapy (2).

The technology has been realized through the research of Khalid et al (28), 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 (29).

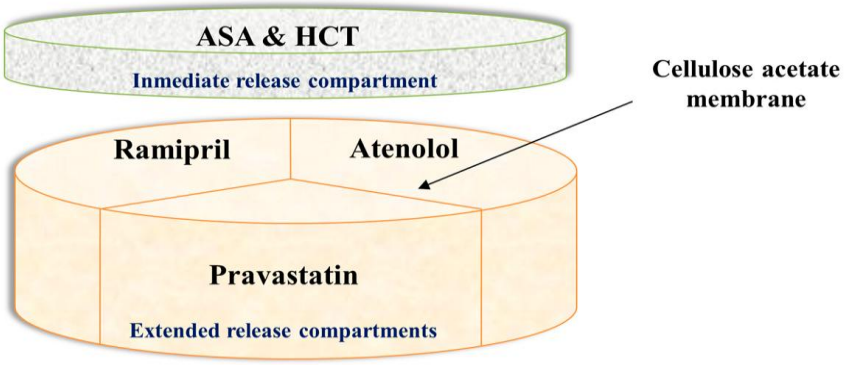

Fig. 1: 3D printed polypill (3)

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. The tablets used to illustrate 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 (29).

Inkjet Printing

This approach to personalized medicine originates from the same technique of computer-operated inkjet printing. It was adapted for pharmaceutical application by the replacement of the ink with pharmaceutical solutions containing drugs and normal paper with edible sheets known as substrates (30).

Dose alterations are done by altering the number of layers printed in a given area or changing the area to be printed. The drug and excipients are design in a ratio such that it has a potential to print as microdots onto an edible substrate. The two main printing types employed under inkjet printing are thermal inkjet printers and piezoelectric inkjet printers (31).

Printing-based inkjet systems encompass two types of techniques: continuous inkjet printing (CIJ) and drop-on-demand (DOD) printing. In continuous inkjet printing, the liquid ink is directed through an orifice of 50-80 µm diameter creating a continuous ink flow. The liquid is caused to flow and break into drops at a specified speed and size at regular intervals using a piezoelectric crystal. These parameters are controlled by creating an electrostatic field. Thus, the droplets are charged and separated by "droplets of guard" to minimize the electrostatic repulsion between them. The electrostatic field created directs the charged droplets to the substrate (4).

The drop-on-demand technique contains multiple heads (100–1000) and can use two types of translators, a thermal head or a piezoelectric crystal. The thermal head is restricted only to volatile liquids, whereas the piezoelectric covers a wide range of liquids (32). In addition, the thermal head reaches temperatures of up to 300 ºC, which implies that the use of solvents of high vapor pressure could cause the degradation of bioactive compounds. This factor limits the use of thermal print heads for pharmaceutical applications [andrea]. The piezoelectric crystal changes rapidly, but this can generate a sudden variation of volume. Both of the heads are capable of producing droplets of between 10 and 50 µm, corresponding to a volume of between 1 to 70 pL (3, 32). The ability to operate at room temperature, with less volatile and more biocompatible liquids, makes piezoelectric printing technology more suitable for the development of drug delivery devices (3).

The DOD technique has 2 subtypes: drop-on-drop deposition and drop-on-solid deposition (powder bed fusion). Inkjet drug printing offers a significant advantage of accurate control of dose combination and pattern of drug release. Ink jet printing requires the starting materials to possess certain characteristics mainly; particle size needs to be <1 µm to avoid clogging the printer head, viscosity needs to be < 20 cP and surface tension between 30 and 70 mN/m for efficient flow (4, 31).

This makes inkjet printing suitable for drugs with very low therapeutic doses. Formulating higher doses through this technology poses difficulty in the form of longer drying time for multiple layer printing on a particular area. Increasing surface area to sort this problem would in turn increase the size of the dosage form (4).

Laser-Based Writing System

It is based on the principle of photopolymerization, in which free radicals are released after the interaction between the photoinitiator and UV light

Stereolithographic 3D Printing

This technique involves the curing of photosensitive material/s (photo-polymerization) to produces a 3D object. Scanning a focused Ultraviolet (UV) laser over the top of a photopolymerizable liquid in a layer by layer fashion, SLA employs a digital mirroring device to initiate a chemical reaction in the photopolymer which causes the gelation of the exposed area. This process is repeated layer after layer to build the entire parts of the object.

This occurs as unreacted functional groups on the solidified structure in the first layer polymerises with the illuminated resin in the next layer ensuring adhesion and

therefore, layer formation. Post printing processing is usually required to further cure the final product, to improve its mechanical integrity and to polish or remove the attached supports to the fabricated object (33). This technique however possesses a health hazard in the form of potential carcinogenic resins. This is also a very slow process.

SLA printers are composed of an ultraviolet light beam, in the form of a laser, which transfers the energy into a liquid photopolymerizable resin. The ultraviolet light beam is aided by baffles, axes x and y, to traverse the surface of the liquid resin, in order tovaccurately represent the 3D model, previously designed. When a layer solidifies, the lifting platform descends its position to the height of a new layer of liquid resin, again beginning the procedure, until the manufacture of the 3D product is finished in a layer-by-layer way (3).

Here thickness of the cured layers depends upon the energy of the UV light to which resin is exposed. The resin should be FDA approved for human use with the ability to solidify upon exposure to laser beam (7, 32).

Selective Laser Sintering 3D Printing

This technique also involves powder bed being spread as thin layers and utilizes laser radiations to liquefy and fuse the powder layers (34). This is a lesser used method due to the possibility of chemical degradation (4). A laser beam sinters the powder and binds it in layer-by-layer fashion

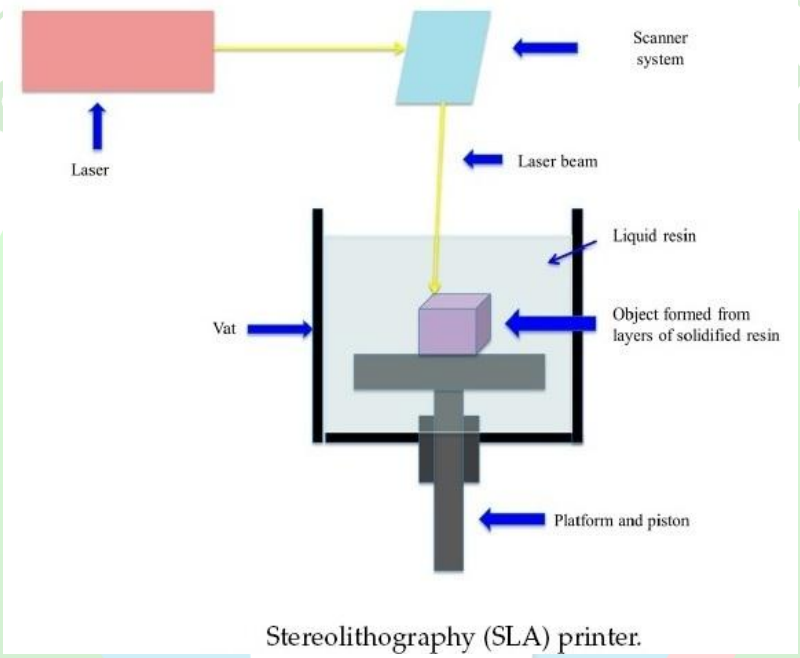

Fig. 2: Stereolithography printer (3)

Continuous Layer Interface Production

This is an advancement in the technique in terms of speed of printing. But the process compromises in the 3D structure manufacture with a non-layer fashion. The speed is increased by an oxygen containing zone which facilitates and guarantees photo-polymerization.

This is similar to Material Jetting where a powder bed is not necessary. A powder bed is not necessary. Inkjets can print free form structures that solidify drop-by-drop. Commonly jetted materials are molten polymers and waxes, UV curable resins and complex multicomponent fluids. The entire formulation needs to be formulated for jetting and rapid solidification (1).

Powder Based 3D Printing

This technique uses powder jetting or powder bed to spread thin layers of powder and simultaneously applying liquid binder drops with the help of inkjet printers (35). The ink (binders and APIs or binder solutions) is sprinkled over a powder bed in two-dimensional fashion to make the final product in a layer by layer fashion. The adaption of this technique into pharmaceutical manufacturing is easier than other techniques as powder and binder solutions are widely used in the pharmaceutical industry. This method has its own disadvantages also. Additional drying is required to remove solvent residues. Excess powder accumulates during printing leading to wastage. Also the mechanical strength of the drug delivery system is poor due to the porous structure of the powder (4, 35).

Nozzle-Based Deposition Systems

Nozzle-based deposition systems consist on the mixing of drugs and polymers and other solid elements prior to 3D printing. The mixture is passed through a nozzle that definitely originates, layer by layer, the three-dimensional product. There are two types of printings according to the type of material used: Fused Deposition Modelling, which uses melted components, and Pressure-Assisted Microsyringes, which does not require the use of melted materials (3).

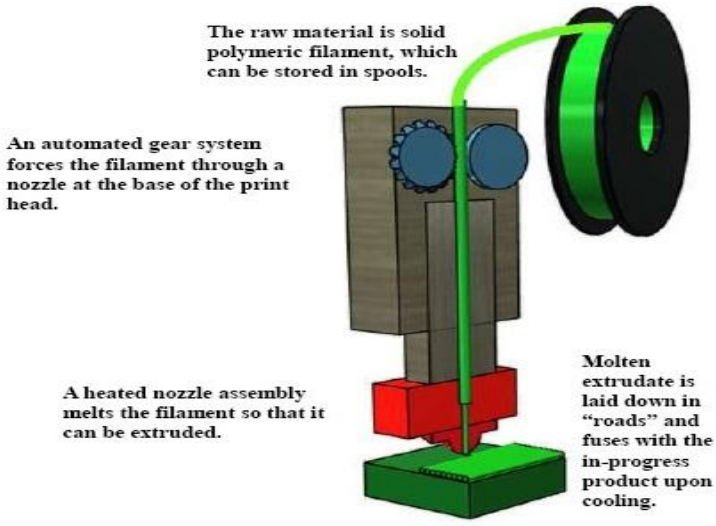

Fig. 3: Nozzle based Extrusion system (1)

Fused Deposition Modelling 3D Printing

This is the extruding a thermoplastic filament through high temperature nozzle into semi-solid fused state filament in layer by layer fashion. The object is formed by layers of melted or softened thermoplastic filament extruded from the printer's head at specific directions as dictated by computer software. The material is heated to just above its softening point which is then extruded through a nozzle, and deposited layer by layer, solidifying in a second. This is why it is also called Fused Filament Fabrication Drug loading in the filament is usually achieved through incubation in organic solvents and poor drug loading may limit its use to low-dosed drugs (36).

Xuyu Chai et al (37) used fusion deposition modeling 3D printing to prepare intragastric floating sustained release tablets of domperidone. The drug was loaded into hydroxypropyl cellulose filament using hot melt extrusion. The filaments were then printed into hollow structured tablets through changing the shell numbers and the infill percentages.

Skowyra et al. (38) demonstrated the capability of Fused Deposition Modelling in printing PVA filaments exhibiting an extended drug release of prednisolone for up to 24 h following oral administration. The potential of Fused Deposition Modelling in achieving extended release was also shown for 5-aminosalicylic acid (5-ASA) or 4-aminosalicylic acid (4-ASA) (39). Nevertheless, a major limitation for the use of Fused Deposition Modelling is the elevated temperature required for its operation (~220°C), which may degrade a significant number of pharmaceutical excipients and active drugs (39).

Pietrzak et al. (40) bridged Fused Deposition Modelling 3D printing with hot melt extrusion in an attempt to increase the range of polymers that can be adapted with Fused Deposition Modelling and achieve higher drug loading. They demonstrated the feasibility of printing immediate and extended theophylline caplets based on cellulosic or methacrylic polymeric filaments with 50% drug loading.

To facilitate the processing, materials must have adequate rheological properties. These properties are influenced by the nozzle diameter, the pressure drop, the feed rate, and others factors related to the thermal properties of the feed material, such as thermal conductivity, density, or glass transition temperature (3).

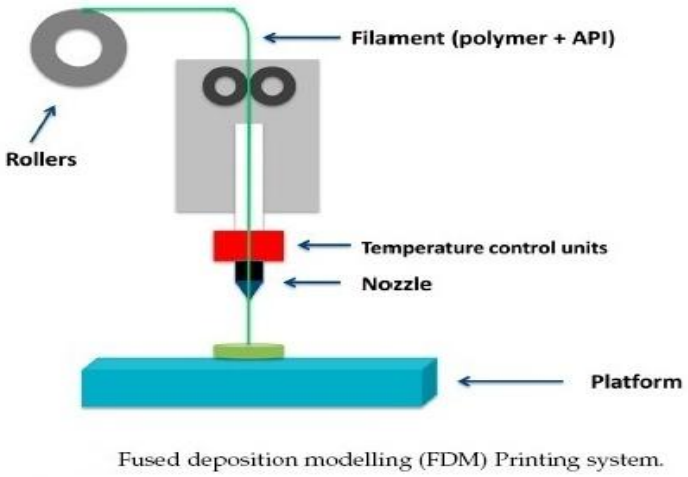

Fig. 4: Fused deposition modeling printing system (3)

Advantages of Fluid Deposition Modelling technique

- Higher resolution over powder-bed printing, which allows a better dosing accuracy
- Good mechanical strength
- Obtain different release profiles of the printed dosage forms by modifying the infill percentage, the 3D model design, or the surface area of the formulation
- Disadvantages of Fluid Deposition Modelling technique
- Limited thermoplastic materials options with good melt viscosity properties for extrusion
- Inability to use some APIs due to the high temperatures of the process

Pressure-Assisted Microsyringe technology

This technology uses syringe extruder which deposits a viscous material using pressurized air piston. It deposits in layer-by-layer fashion in the predetermined geometry. The important parameters that decide the robustness of the technology are viscosity, viscoelasticity, and the apparent elastic limit.

Advantage: flows continuously and works at room temperature

Disadvantage: use of solvents could pose as health hazard and can degrade the active pharmaceutical ingredient as well

Use: tissue printing substitutes or scaffolds of soft tissues (3).

Semi-solid Extrusion 3D Printing

Extruding semi-solids (e.g. homogeneous paste) over moveable stage in layer by layer fashion into a product. This method uses a syringe like tool head to deposit semi-solid material layer by layer. The semi-solid can be gel or paste is a combination of polymer and solvent in a ratio that makes the consistency of the semi-solid suitable for printing. [Khalid 2014]

Khaled et al. (41) manufactured guaifenesin bilayer tablets using semi-solid extrusion and compared them to commercially available dosage form. Similar release profile of 3D printed tablets and branded tablets demonstrated the versatility of semi-solid extrusion 3D printing in addition to offering an easier approach to drug manufacturing. The technique has also been used in multi-active tablets capable of delivering three drugs via two different release mechanisms; osmotic release and diffusion through the shell and gel layers, respectively (Khalid 2015b). Furthermore, Khaled et al. (42) demonstrated the feasibility of semi-solid extrusion 3D printing in constructing a multicompartment polypill containing five actives and exhibiting a well-defined and independently controlled; immediate or sustained release profiles (28).

Okwuosa et al (43) fabricated immediate release tablets via 3D printing to provide a powerful tool to on-demand individualization of dosage form. They reported an approach to fabricate patient-tailored tablets at relatively lower temperature (110°C) and using pharmaceutically approved and solubility enhancing polymer. This work confirms the possibility of expanding the use of FDM 3D printing to a wider range of temperatures for on-demand fabrication of immediate release products.

As the process involves extrusion, the material used should be in gel or paste form. While drying, this can lead to deformation or shrinking. If the layers of the dosage form are not sufficiently hardened, it may not be able to bear the weight of the subsequent layers leading to collapsing of the delivery system during the printing (4).

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, physicochemical characteristics, thermal conductivity, 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, consistant 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 (44).
- 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 (45).
- Surface imperfections in finished product: due to 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 (46).
- Mechanical resistance: friability is higher in 3D dosage forms especially in powder based technique. Production technology is important for good dosage form strength (4).
- The material choices, colours, and surface finishes currently available for 3D printing are relatively limited when compared to conventional tablet compression processes (4).
- Certain manufacturing process may not be appropriate for thermolabile drugs when printing at high temperatures (36).

RISK ASSESSMENT DURING 3D PRINTING PROCESS

Risk identification is an important step to prevent failure of quality control parameters like appearance, content uniformity, assay etc. Identifying risk involves through analysis of the process and process variables to assure that a quality product is manufactured. Such a critical assessment was done by Norman et al (1)

- When a given printer is unable to print a given design, software controls should be employed

- Variability in layer thickness has to be controlled by real – time layer thickness monitoring
- Improper layering due to environmental conditions should be dealt with controlling the temperature and humidity of the manufacturing area.
- Inaccurate position during printing can be avoided by monitoring print head height and print head speed.
- Uneven layers can be avoided by checking powder water content and powder particle size distribution
- Print head clogging can be prevented by ensuring particle size distribution and monitoring inkjet flow.
- Inconsistent agglomeration or binding can be due to variations in binder viscosity or binder surface tension

CONCLUSION

3D printing has become a useful and potential tool for the pharmaceutical sector, leading to personalized medicine focused on the patients' needs. 3D Printing technology is emerging as a new horizon for advanced drug delivery with built-in flexibility that is well suited for personalized/customized medication. 3D Printing technology will revolutionize the pharmaceutical manufacturing style and formulation techniques.

However, there is still a significant barrier to ensure that 3D printed medicines have the same efficacy, safety, and stability as the pharmaceuticals conventionally manufactured by the Pharmaceutical Industry. Regarding the establishment of guidelines, laws, quality systems and safety of use and consumption of 3D printed medicines, it is a great challenge for the regulatory authorities entailing great obstacles, given the traditional requirements by the pharmaceutical sector.

The FDA guidance entitled "Technical Considerations for Additive Manufactured Devices" provides the FDA's initial thinking on technical considerations associated with the processes, and recommendations for testing and the characterization for devices that include at least one additive manufacturing fabrication step.

In the near future 3D printing approach will be utilized to fabricate and engineer various novel dosage forms. Although commercial production of such novel dosage forms is still challenging; developing personalized medication, optimized drug release from dosage form, compacting or avoiding drug-drug incompatibilities, protection of biomolecules during manufacture, construction of multiple drug dosage form and multiple release dosage forms will be taken to a new era through 3D printing technology

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