REVIEW ON 3 D PRINTING FOR PHARMACEUTICAL DOSAGE FORMS

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Abstract

Additive manufacturing which is commonly referred as 3 D printing is getting popular due to its marvellous concept of creating physical objects from geometrical representation by, layer by layer fabrication of additive material and turn blueprints on computer into physical objects by the help of CAD (Computer aided design) model. This innovation has widely used in the field of healthcare, agriculture, automotive, food and aerospace industries. This revolutionary printing technology has already entered in pharmaceutical research world, and holds the power to print drugs, tissues, organs and bones. This technology is offering customized medicines, by production of a variety of dosage forms in different shapes and size, use of many active pharmaceutical ingredients and controlled release profiles.

This paper provides an overview of the creation of pharmaceutical dosage forms using 3D printing technology, as well as its performance and application.

Keywords: API, Customized medicines, layer fabrication, dosage form, Additive manufacturing

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INTRODUCTION:

3D printing is a rapid prototyping and manufacturing method in which physical objects are created by adding material successively layer by layer, starting at the bottom.[1] It builds up the printed layers of object layer over layer to complete the production of a 3D product based on a previously generated 3D digital model. According to Weller (2015) et al. Since the 1980s, 3 D printing technology has been in use, however its earlier application was just limited for the creation of prototypes. [2] It is believed that in 1986 Charles Hull invented 3D printing by developing first robotic 3 D printer. Since now 3D printing has touched the field of healthcare, agriculture, automotive, aerospace industries and even food decoration and home use work. After passing many experimental phases since 1986, currently 3D printing technology is becoming stable and useful in many fields.[3] Though 3D printing is proved very useful in other industries but now its application in pharmaceutical manufacturing industry is found very useful too. One of the major objective of formulation development of dosage form is to tailor the need of individual patient. There is a chance that personalised medicines will one day be developed due to 3D printing's capacity to make medicines with exact specifications tailored to the need of patients. The technology made it possible to precisely print dosage forms with desired physical properties such as appearance, shapes, textures, sizes, porosity etc which is challenging to create by use of conventional methods.[1] This unique feature of 3D printing make it research worthy for future generation, so that medicines can be customized as per patient's need.

Pharmaceutical dosage forms consist of active (API) and excipients for formulation. Nowadays new technologies and methods are used to change the composition and structure of dosage form for controlled drug delivery, improved stability and patient compliance.[4] 3D printing has been gradually adopted in pharmaceutical manufacturing due to its marvellous concept of creating physical objects from geometrical representation. The concept of new drug delivery system is also benefited by the utilization of 3 D printing technology.

Production of personalized medicine is a unique characteristic of 3D printing technology. Consider an example of formulation of an oral drug delivery of variable dose size is not possible and manual breaking of dosage form leads dose variation. So ingenious solutions such as 3D printing technology are required for personalization of medicines according to patient's requirement.[5]

In August 2015 world's first 3D printed medicine was approved by Food and Drug Administration and named as SPRITAM® .

The drug is a commonly prescribed anticonvulsant levetiracetam, manufactured by Aprecia Pharmaceutical. Levetiracetam is used orally for treatment of seizures and is designed to dissolve in mouth with little water. [4,6] The formulation was developed by jet 3D printing technology. Printing ink made up of liquid binder and active drug was loaded into the printing head and in precise dose jetted layer-by-layer over a powder bed to produce the desired product. Spritam® has highly porous structure and have large drug loading capacity in comparison to its conventional tablets. The increased surface area of Spritam® allow the tablet to dissolve quickly in water.[7]

Major components for 3D printing:

There are three major components of 3D printing: First hardware i.e 3D printer for object deposition or formation. Second is software and third are the materials required for printing of objects. For development of 3D printed structures, there is need of connecting hardware with right prototyping software which can provide 3D designed files for printing.[9]

TECHNOLOGIES USED IN 3D PRINTING FOR FORMULATION OF PHARMACEUTICALS

For printing, 3D printers work on the basis of three principles:

extrusion-based printing system, inkjet-based printing system, and laser-based printing system. [15]

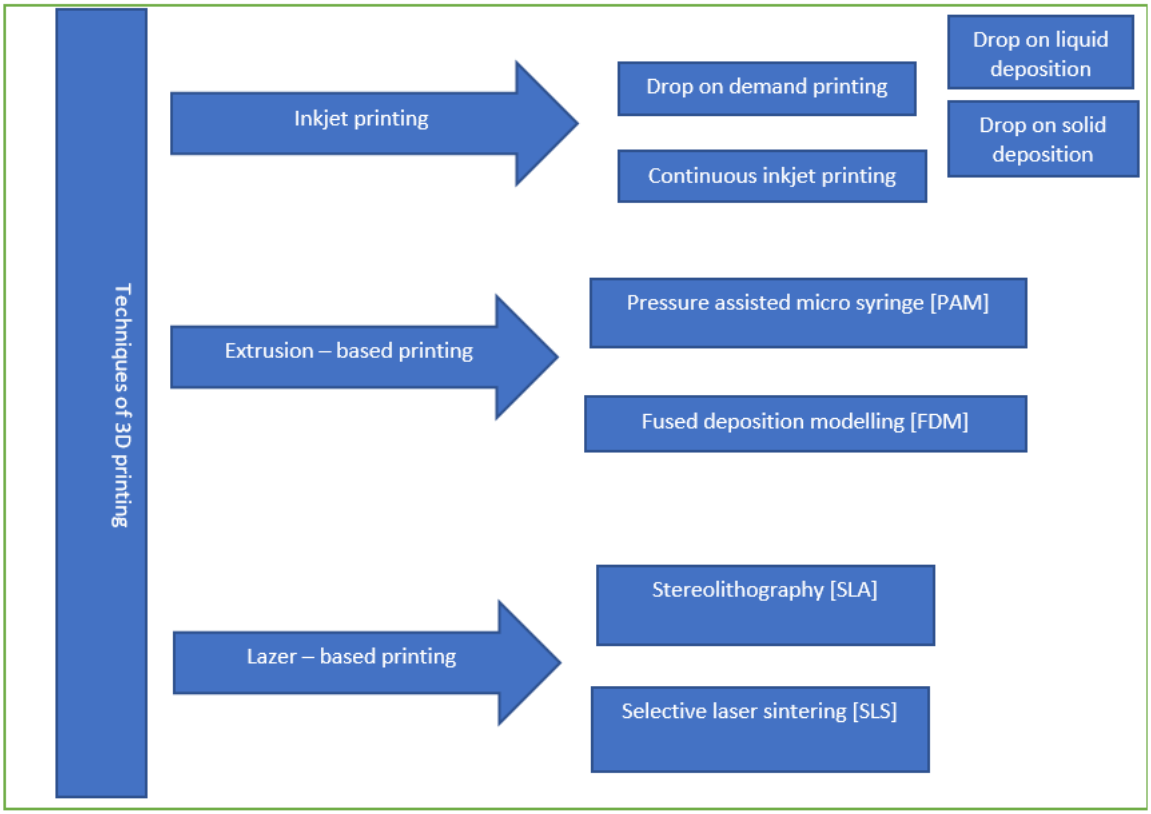

Figure 1: Techniques of 3D printing

The DOD inkjet printing can be classified into two categories: *Drop on Liquid printing* (also known as drop on drop deposition technique) and *Drop on Solid printing (Also called* drop on powder deposition).
In Drop on Liquid the liquid droplets are deposited on above of one another while being heated by a thermal stream, resulting a layer by layer structure formation as the solvent evaporates. This technique enables the creation of microstructures with a high drug loading capacity and suitability for individualised drug administration.[13]

In Drop on Solid printing, liquid droplet deposit on a powder bed surface, where the powder fuses to produce a solid structure. The liquid droplets act as a binder for the powder particles, or they may do it on their own by drying and completely evaporating the solvent to form a solid bed.[15] This drop-on-solid technique may be used for formulation of controlled and targeted drug delivery systems of many pharmaceutical compositions, by using polymers with controlled release rate as binder ink.[14]

Extrusion based system:
Extrusion based printing techniques may classified as Pressure Assisted Micro-syringe (PAM) and Fused Deposition Modelling (FDM) technique

Pressure Assisted Micro-syringe (PAM): In PAM, semi-solid material is fed into a syringe-based head called a pressure assisted micro-syringe, where it is continuously extruded in layers to produce 3D printed product. A pneumatic, mechanical, or solenoid piston may serve as the foundation for the extrusion. A suitable blend of polymer, solvent, and extra required excipients with printing-friendly qualities make up the semi-solid mixture. Due to the employment of solvents during the printing process, drying afterward becomes essential to prevent deformation or shrinking of the finished product. Moreover, if the deposited layer is not sturdy enough to withstand the weight of the next layers, the printed object may collapse. The lack of high temperatures during this method is its key benefit.[8]

Fused Deposition Modeling (FDM): FDM is most extensively applied technique for 3D printing and it is also known as Fused filament fabrication. The polymeric thermoplastic filaments are created and fed into the printer where at certain temperature they are melted and extruded through the nozzle. The initial layer of the object is created as the printhead rotates on a platform and the extruded filament is discharged onto the printer platform. Then, after periodically lowering the platform to make way for the new layer, successive layers are deposited. After cooling, the filaments affix to the

layer below. To create the finished 3D piece, this process is repeated.
The filaments used in FDM technique are made using the Hot Melt Extrusion (HME) method, in which the active and other excipients are integrated into the polymer. This method uses a motor-driven screw-based extrusion system in a barrel, the mixture is melt under pressure and heat, then allowed to cool. Later the solidified mixture is used to create the filament that utilised as the FDM feed.[16]

Laser based system
In laser based 3D printing system, material surface is exposed to UV laser beam to create the layers that make up the 3D design.
Stereolithography (SLA) and Selective Laser Sintering (SLS) are two types of laser-based 3D printing techniques based on the solidification of liquid and powder.[15]

Stereolithography (SLA): The concept of stereolithography is the photo-polymerization of ultraviolet light to harden liquid resin. There are two possible configurations for the printer: Top down, in which the UV source is at top and the platform lies below (down), or Bottom up, where the UV source lies down and the platform at top. The initial layer is photo-cured and adheres to the building platform after the laser has traced it in the x and y axes under the direction of scanning mirrors. After then, the platform moves across the z-axis to a degree that is determined by the breadth of each layer. (elevated in top down approach and moved down in bottom-up approach). The process is then continued to form the 3D item by redistributing the liquid resin over the previously hardened layer to complete its hardening.[8]

Selective laser sintering (SLS): In SLS laser beam is used to heat and fuse the powder particles which is hardened to create 3D objects. Laser system, powder bed and spreading platform are the major components of Selective Laser Sintering. Firstly the powder is equally distributed on the platform by spreading system and the surface is made uniform by the help of roller blade. The 2-dimensional laser system's scanning pattern is set on the basis of characteristics of the final product. The laser radiation is utilized for melting the material by heating it to a temperature below its melting point to cause fusion and the height of the bed is adjusted to focus the laser on the newly created surface. The powder bed is moved down each time by a height of one layer and then the subsequent layer is deposited and fused repeatedly to create the final printed product. The final 3D printed object gets cool in the printer and collected. This method is preferrable due to fast production method which does not require any solvent and create high resolution objects because of the laser precision. [17]

PHARMACEUTICAL DOSAGE FORMS BY 3D PRINTING TECHNOLOGY

Tablets

The most common 3D printing technique used for formulation dosage forms is Fused deposition modelling.[32] First 3D printed dosage form was a tablet SPRITAM®. After that many oral formulations have been prepared and are still about to prepare by 3D printing. 3D printed dosage form does not only provide the personalise tailored medication but it also improved few characteristics of dosage form which affect the kinetics of active drug.
Sadia, M., et al,. formulated Thiazide diuretic methacrylate tablets by using feed ink of Eudragit E based filament (FDM 3D printing). The 3D designed tablet has more effective surface area and has shown better media perforation. [18]
Martinez, P. R. et al, printed Ibuprofen-filled hydrogels made of cross-linked polyethylene glycol diacrylate by using SLA printing. The printed hydrogels consist of 10 percent w/w Ibuprofen and 30 percent w/w water, the release of drug depends on amount of water due to which drug releases at faster rate. [19]
Skowyra, J., et al., used Fused Deposition Modelling based 3D printer to create regular ellipse-shaped prednisolone loaded extended release tablet by using poly(vinyl alcohol) (PVA) filament. This 3D printed tablet has shown an extended *In vitro* drug release up to 24 h.[20]

Genina, N.,etal formulate Oral Dual Compartmental Dosage Unit (DCDU) with the intention of modulation in drug release profile and physical isolation of Rifampicin- isoniazid drug combination (Anti tuberculosis drug combination). The DCDUs fabricated in two steps by Computer aided design. First step includes 3D printing of outer corona and second step hot melt extrusion of drug carrying filaments. The 3D printed compartmentalized shells were loaded with filaments of active drug and sealed selectively for modulating drug dissolution. This work support the development of DCDU system for combination drug therapies of oral dosage forms.[21]

Khaled SA, etal., manufacture polypill for cardiovascular treatment regime by 3D extrusion printing technique. This polypill contains five compartmentalized drugs with two freely

controlled and well defined release profiles. In this poly pill Aspirin and Hydrochlorothiazide were incorporated as immediate release compartment while sustained release compartments contains Atenolol, Ramipril and Pravastatin. A polypill proves a complex medication regime can be turned into a dingle personalized dosage form. So a patient who is taking many tablets and take one polypill.[24]

Transdermal Patches

Transdermal route is non invasive and painless route of drug administration due to which this is route has attracted more interest from researchers for of drug delivery of various drugs over traditional methods. Apparently 3D printing techniques are capable to manufacture transdermal patches which as evaluated and proved to be safe for use.

Azizoğlu, E.,et al., develop and characterize Montelukast sodium loaded patches by printing the drug filaments directly on packaging material. Polymer blends containing the active montelukast sodium were created and then the drug loaded filaments extruded. By using 3D printing pen all filaments were tested. The flexibility of MS-loaded filaments and patches was comparable to placebo. With this study, printing on disposable packaging material is introduced for the first time.[25]

Maurizii, G.,et al., formulate transdermal patches of two model drugs having different thermal characterstics i.e Ibuprofen and Diclofenac sodium with few different grades of Ethylene vinyl acetate copolymer as feedstock materials by direct powder extrusion technique. This study showed that the direct powder extrusion method and EVA could be useful production processes for transdermal patches. Additionally, it is possible to achieve the ideal medication release and penetration profile, which is a significant benefit in terms of personalised medicine.[28]

Microneedle (MN) systems integrated in a transdermal patch offer a novel way of drug administration that is creative and has promising outcomes.[26] Due to their unique qualities, such as increased patient acceptance and self-administration when compared to conventional parenteral administrations such as iv, im injection, and subcutaneous injection, microneedles have recently dragged considerable attention. The commercialization and clinical applications of these microneedles and patches, particularly for personalised medicine, have been severely hampered by the significant challenges of precisely manufacturing them at the micro scale. Recent studies have shown that the 3D printing process can be used to create sophisticated bio-inspired microneedles as well as artificial cargo delivery systems for transdermal drug delivery. These studies have adopted a variety of printing methodologies and formulation strategies.[27]

Villota, I.,et al., utilize the stereolithography method of 3D printing used to create a transdermal patch with 25 microneedles using Class 1 biocompatible resin. In order to determine the mechanical behaviour of the microneedle, finite element analysis with ANSYS software is used. Additionally, the variables discovered in work are crucial for the eventual construction of a transdermal patches [26].

Lim, S. H., et al., fabricate personalised microneedle patch of Acetyl-hexapeptide 3 using the photopolymer for effective wrinkle management. Acetyl-hexapeptide 3 can be delivered more effectively using custom microneedles (MN) that conform to the skin's surface thanks to 3D printing.[29]

Suppositories

Suppositories are dose forms designed to exert local or systemic effects through the rectal, vaginal, and urethral routes. Suppositories are made using a moulding technique, which involves a number of steps and takes a while to solidify. Suppositories have been manufactured using a revolutionary manufacturing technique called three-dimensional (3D) printing. As a result, multiple suppository sizes might be manufactured in hospital settings using 3D printers to accommodate the comfort of the patient. The discomfort caused during suppository administration was the primary cause of suppositories non-adherence, the capacity to modify suppositories in accordance with the patient's comfort can improve adherence and treatment outcomes as well. Moreover, pharmacists may create a customised suppository for each patient that contained a specific dosage of medication. This is especially helpful for medications with a limited therapeutic index.[31]

Tagami, T et al., formulate hollow type suppositories by using Fused deposition modelling (FDM) type 3D printer and PVA filament as a water soluble substance. Based on the results, it appears that 3D printing technology can be used to create hollow-type suppository formulations and may work with on-site hospital production. [32]

Seoane-Viao, I. et al. created the first self-supporting Tacrolimus suppositories using 3D printing to treat inflammatory bowel disease patients, by employing a pharmaceutical SSE (Semi-solid extrusion) printer without the use of moulds. Tacrolimus may be administered locally

in precise amounts to lessen the possibility of side effects without sacrificing its immunosuppressive properties. The exceptional flexibility of 3D printing technology may open up new manufacturing possibilities for the on demand production of customised dosage forms. [33]

Awad. A et al ., fabricate the 3D printed suppositories loaded with Tofacitinib citrate and Budesonide (anti-inflammatory agents) by semi-solid extrusion, for the treatment of acute severe ulcerative colitis. The 3 D printed suppositories were able to self-emulsify and has shown improved performance .[34]

Chatzitaki, A. T etal., formulate patient-tailored lidocaine loaded suppositories by the help of the Pressure assisted micro syringes technology. A mixture of an oily compound and surfactants were used for formulation of printable inks and evaluated for the physicochemical properties, as well as for their similarities with the performance of self-nanoemulsifying drug delivery systems (SNEDDS). This work highlighted the capability of 3D printing as an alternative way for formulation of personalized suppositories.[35]

Films:

In the context of films, 3D printing offers precise control over the shape and size of the films, as well as the placement of the drug within the film. This level of customization enables the production of personalized drug delivery systems, tailored to the specific needs of individual patients. [36]

Shing-Yun Chang et,al., utilized the 3D printing technology to create films with a range of release rates for the drug Indomethacin. The researchers found that adjusting the thickness of the film and the location of the drug within the film enabled them to control the drug release rate. This customization potential can have significant implications for personalized medicine, as patients can receive tailored drug delivery systems based on their individual needs. [37]

Dodoo, C. C et,al., utilizes 3D printing technique to formulate films for the treatment of a fungal infection (oral candidiasis) in the mouth. The researchers used a combination of the antifungal drug clotrimazole and the mucoadhesive polymer HPMC to create 3D printed films that showed promising antifungal activity against Candida albicans.[38]

Table1: Summary of research carried out for 3D printing of dosage forms

Sr. No.	Dosage Form	Active drug	3D Printing method	Final outcome
1.	Tablet	Thiazide diuretic methacrylate	Fused deposition modelling	has more effective surface area and has shown better media perforation
2.	Extended-release tablet	prednisolone	Fused deposition modelling	Extended *In vitro* drug release up to 24 hrs.
3.	Oral dual compartmental dosage unit (DCDU)	Rifampicin- isoniazid drug combination	Hot melt extrusion	Development of DCDU system for combination drug therapies of oral dosage forms.
4.	polypill	Aspirin, hydrochlorothiazide, pravastatin, atenolol, and ramipril.	3D extrusion	Complex medication regime into a single personalized dosage form
5.	Patches	Montelukast sodium	3D extrusion	Printing on disposable packaging material introduced
6.	Patches	Ibuprofen and diclofenac sodium	Powder extrusion	Ideal medication release and penetration profile
7.	microneedle patch.	Acetyl-hexapeptide		Delivered more effectively using custom microneedles
8.	suppositories	Tacrolimus	semi-solid extrusion	Reduced the risk of adverse effects
9	suppositories	budesonide and tofacitinib citrate	semi-solid extrusion	suppositories' were able to self-emulsify to improve their performance
10	Suppositories	lidocaine	pressure-assisted microsyringes technology	Alternative pathway to formulate personalized suppositories
11.	Film	Indomethacin	Binder jet printing	Controlled drug release
12.	Film	Clotrimazole	Ink Jet Printing	promising antifungal activity against Candida albicans.

CONCLUSION:

3 D printing is popular opening up the possibility of individualized medicine, it brings manufacturing close to people. This manufacturing method is a revolutionary instrument with greater flexibility in pharmaceutical manufacturing and it took advance drug delivery systems to a new level of innovation. 3D printing provide ground to personalized tailored medicine which is now upgraded and extended to 4D and 5D printing technology. With the use of smart biomaterials, 4D technology adds time as a fourth dimension, and by atering external stimulus, the shape and size of the printed object change over time. While for 5D printing a movable plateau, which enables the printhead to change angles from five dimensions and create curved layers is essential. Though 3 D printing technology is used in various fields but its application in pharmaceutical dosage form is remarkable, hence covered in this review. This rapid prototyping tool is suggesting the possibility of producing unlimited dosage forms that may eventually advance the production of therapeutic administration systems to a new stage.

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