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Methods and Prospects of 3d Printing in Pharmaceuticals

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ABSTRACT

The FDA gave its initial permission to 3D printing in the year 2016. There are numerous approaches to 3D printing, the most common of which are the powder-based method, the binder deposition method, stereolithography, and the inkjet printing method. 3DP has evolved into one of the most comprehensive and potent tools available to serve as a technology for the fabrication of developed dosage forms. Include in this article the regulatory agencies that are in charge of putting in place such systems for the production of drug items. Three-dimensional printing (3DP) makes it possible to generate multiple geometries for pharmaceutical drug delivery drugs through the use of computer-aided designs employing a variety of processes and materials. It provided a concise summary of the recent accomplishments of the manufacturing sector in the field of biomedical and pharmaceutical research.

INTRODUCTION

Three-dimensional printing, also known as 3D printing or 3DP, is a relatively new method of fast prototyping that involves the construction of a solid item by the sequential deposition of many layers. The field of 3D printing is one of the areas of technology, art, and science that is developing at the quickest rate. The International Organisation for Standardisation (ISO) gave the following definition of the word "three-dimensional printing": the manufacture of an item by the deposition of a substance utilising a print head, nozzle, or some other type of printer technology. The additive manufacturing process known as 3D printing creates three-dimensional objects by depositing successive layers of material to build up the object in question. On demand, 3DP can manufacture objects of virtually any size and shape imaginable. The 3D models that are produced by computer-aided design software are used to make the structures. Recently, technology has been applied to the pharmaceutical industry in order to make medical devices, and the term 'printlets' refers to solid oral dose forms that have been manufactured using 3D printing. As a result, a wide variety of formulations have been developed, some of which comprise numerous active medicines with distinct geometrics and release properties. These technologies have found applications in a wide variety of fields, including as the consumer products business, research in the aerospace sector, the creation of regenerative medicines and medical devices, the automobile industry, and more. In spite of this, it is currently being considered a scalable manufacturing technique. Over the past 30 years, the usage of 3D printing and other additive manufacturing processes in engineering and biomedical applications has been gradually rising. Apercia Pharmaceuticals" spritam' was the first 3D-printed tablet to be given the go-ahead by the United States Food and Drug Administration (USFDA) for the treatment of epilepsy in the year 2016. ‘Spritam’ Antiepileptic medication levetiracetam an orodisperssible tablet The most potent and innovative new development in the pharmaceuticals and biomedical markets is three-dimensional printing, which has been launched as part of a number of discoveries in these fields. It can be used as a tool for the development of novel dosage forms, the engineering of tissues and organs, and the modelling of diseases. It has recently been described how its application can be used in the creation of drug delivery systems to make fast-disintegrating tablets, time regulated release tablets, multi-layer caplets, multi-active solid dosage form, microneedles, implants, and topical drug delivery devices.

History

Charles hull field was awarded the first stereolithographic patent in 1986, the same year that he also founded the firm 3D system and developed the STL file format.

1990 Scott Crumps and Scott Field filed for a patent on an additional 3DP technology. Fused deposition modelling is a process in which extruded polymer filament is heated into a semi-liquid condition and then extruded through a heated nozzle before being deposited layer by layer onto a build platform so that it can harden.

In 1993, Emanual Sachs and Michael Cima received a patent for the first equipment that could print plastic, metal, and ceramic components and called it a 3D printer. Scientists from MIT, together with their colleagues, have successfully printed a "Three-dimensional printing technique" that is based on combining a specific section of powder with binding material.

The inkjet printing of a binder solution onto a powder bed was the first 3D printing technique to be utilised in the pharmaceutical industry. This technique proved successful in bringing together the powder particles. The first one was in the early 1990s at the Massachusetts Institute of Technology, where Sachs and his colleagues were involved in the technology and patented it.

The tablet form of Spritam (levetiracetam) that is intended for oral administration was produced using inkjet printing. Aprecia Pharmaceuticals submitted and received approval from the FDA for the first 3D-printed medication in 2016.

Regulatory Assumptions:

2017 was the year that the US Food and Drug Administration issued recommendations on Technical Considerations for Additive Manufactured Medical Devices. This guidance provides the definitions for a variety of needs, such as labelling and device testing considerations. In addition to this, it proposes that the validation of the processes involved should provide a high degree of assurance in accordance with the procedure that has been developed.

It is important to recognise any alterations to a device, manufacturing process, or process deviation and conduct an investigation into the hazards that may be posed by these alterations.

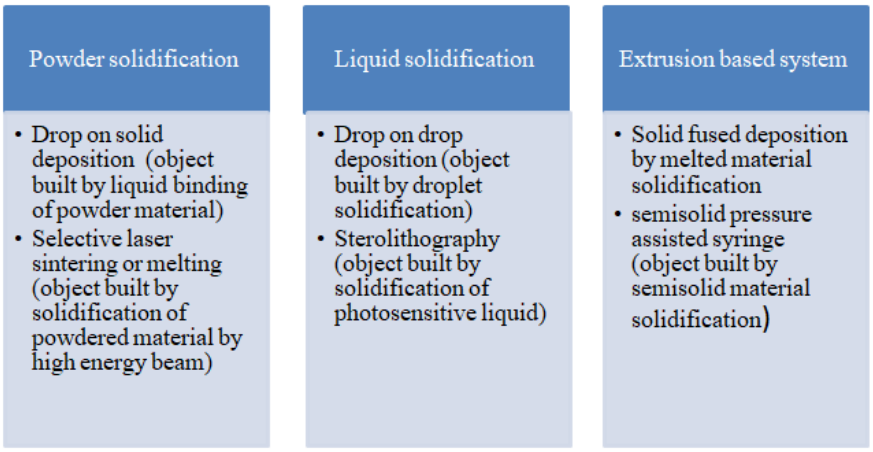
In light of this evaluation for the purpose of revalidating the method. The manufacturer should base their regulatory strategy off of the already available instructions from the FDA. When thinking about making a change to a device that has already been cleared or approved, consider using additive manufacturing.

Some examples for revalidation specific to additive manufacturing are:-

1. Software changes (eg- change or uptake of build preparation software).
2. Changes in material (eg- supplier incoming material specification, reused powder, new formulation) or material handling.
3. Changes in spacing or orientation of devices components in the build volume.
4. Changes to the software workflow.
5. Physically moving the machine to a new location.
6. Change to post-processing steps or parameters.

The difference between compounded and manufacturing medicine is a central question about the regulation of 3D printed medicine.

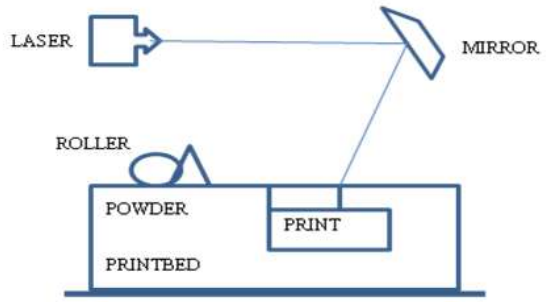
The New England Compounding Centre (NECC) in 2012 & other dangerous safety problems at compounding pharmacies have put the safety of pharmaceuticals. A 3d printed drug product have to be manufactured by following the established regulations for manufacturing of drug product meet the current chemistry, manufacturing and control (CMC) standard in 21 CFR 200 & 300 & other guidance.



3DP methods applied for the drug formulation

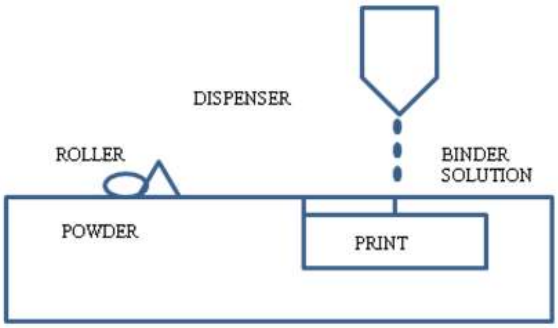
METHODS OF 3D PRINTING

Powder based method



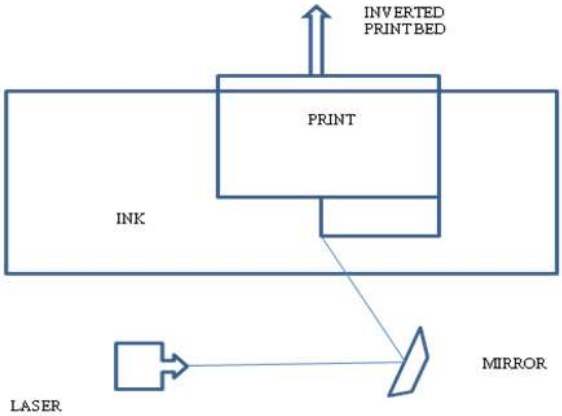
In this method a powder bed is pressed over the surface by the roller & pressed to form a thickness layer. After a powder layer is formed, a laser supplies thermal energy to the powder into the desired form.

Binder deposition method



In this binder deposition method , that build from the bed of the powder layers. As in selective laser sintering a binder solution is spotted onto the powder. Binder solution dissolve the powder then re- crystallize to form the solid form.

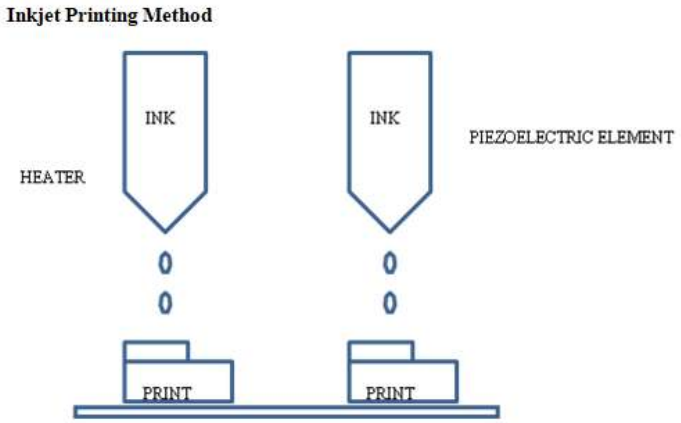
Stereolithography



It utilizes a laser or projector to solidified material, stereolithography is also known as photo-polymerization. Drug is dissolved into a liquid pool of hydro gel or resin material.

The choice of material must be photosensitive. When the laser light shines onto the surface of the pool of the photosensitive, drug loaded material, the material cures & solidifies.

Inkjet Printing Method



An ink is deposited onto the surface by thermal nozzle or by piezoelectric thermal driven. Thermal element within the print head generates a droplet of ink. The heating element is electrically controlled to produce a spike in thermal energy that is transferred to ink. Increase in thermal energy leads to the formation of small bubble to produce a pressure force to ink out of the nozzle. An alternative method is piezoelectric, in this a piezoelectric printer within the print head is stimulated when voltage is applied, induce a rapid reversible deformation. These deformation distribute acoustic waves supplies the pulse of pressure needed to stop the flow of ink.

Table: Current 3DP technologies and pharmaceutical formulation for drug delivery

Types of 3D techniques	Dosages form	Active ingredient/polymer	Reference
Fused deposition modeling	Tablet	Haloperidol	Solanki et al. (2018)
Fused deposition modeling	Tablet	Hydrochlorothiazide	Sadia et al. (2018)
Fused deposition modeling & Hot melt extrusion	Three compartment hollow cylinder	Polymer polyvinyl alcohol(PVA), mannitol & hydrochlorothiazide, polylactic acid	G Gioumouxouzis et al (2017)
Fused deposition modeling & Hot melt extrusion	T-shaped prototype of intrauterine system (IUS)	Indomethacin poly (caprolactone)	Hollander et al. (2017)
Fused deposition modeling & Hot melt extrusion	Tablet	Domperidone hydroxypropyl cellulose	Chai et al. (2017)
Fused deposition modeling	Nanocapsule	Deflazacort poly (caprolactone)	Back et al. (2017)
Fused deposition modeling & Hot melt extrusion	Compartmentalized shells	Rifampicin & isoniazid	Genina et al. (2017)
UV inkjet 3D printed	Tablet	Ropinirole, cross linked poly (ethylene glycol diacrylate) (PEGDA)	Clark et al. (2017)

Stereolithography	Hydrogel	Ibuprofen, Riboflavin, polyethylene glycol diacrylate (PEGDA)	Martinez et al. (2017)
Fused deposition modeling 3D printing	Tablet	Felodipine, Polyethlene glycol (PEG), tween 80, eudragit EPO	Alhijaj et al. (2016)
Semi solid extrusion 3DP technique in combination with UVLED cross linking	Tablet	Prednisole, polydimethyl siloxan (PDMS)	Hollander et al. (2016)
Fused deposition modeling & Stereolithography	Model of nose adapted to the morphology of individual	FPLA salicylic acid, PCL salicylic acid	Goyames et al. (2016);
3D printed	Biodegradable patch	PLGA, polycaprolactone, 5-fluorouracil	Yi et al. (2016)
Fused deposition modeling & Hot melt extrusion	Subcutaneous rods	Indomethacin, ethylenevinyl acetate (EVA) copolymer	Genina et al. (2016)
Fused deposition modeling	Tablet	Nitrofuran, polylactic acid & hroxypropyl cellulose	Boet et al. (2016)
Thermal inkjet sprinting	Solid dosage form	Rasagiline mesylate	Genina et al. (2013)

Biomedical Application:

Application of 3D printing in medical devices

a) Wound dressing

- Antibacterial dressing
- Vascular grafts dressing

b) Implants, prosthesis

- Limbs
- Craniofacial implants
- Casts
- Stents

c) Surgical models

- Organs
- Vasculature
- Tumour models
- Disease models

Advantages:

a. High resolution
b. Increased surgeon skills
c. Reduction of costs of surgical procedure
d. Reduction of time
e. Design of precise shape
f. Better stability

Materials

a. Silicon
b. Titanium
c. Hydroxyl apatite
d. Nylon
e. PEG

Application of Bio-based 3D printing

a) Bioprinting
- Cartilage
- Organ-on-chip

b) 4D printing
- Stimuli-responses hydrogel
- Actuators for robots

c) Biorobotics
- Heart pump
- Actuator

Advantages

a. High resolution
b. Better stability
c. Low costs
d. Reduced risk of transparent rejection
e. Diagnostic tools
f. Stimuli responsive materials

Materials

a. Nanocellulose
b. Alginate
c. Silicone
d. PDMS

CONCLUSION

3d printing becomes the future and useful tool for the pharmaceutical industry. It provides a perspective on the merits of 3d printing for drug manufacturing. Various rationale for the 3d printing of drugs were also presented, includes control over release of the drug, ability to print precise and unique doses. On the other hand there is still a barrier to confirm that the 3d printed medicines have same safety, efficacy and stability as the manufactured by the pharmaceutical industry. In future the 3d printing approach have been utilize for various novel dosages form. While the commercial production of the novel dosages form is still challenging.

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