3D Printing: Opportunities and Challenges

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Abstract:

There are wide range of drugs and different dosage forms available in the pharma market. Drug delivery is the technology which helps to transport active drug efficiently within the body to achieve therapeutic and pharmacological effect. Recently 3DP has caught attention of different pharma, food, biotechnology and medical industry. 3DP has enabled us to design and manufacture complex material which will be helpful for delivering personalized and programmable medicine to patient. This technology will be helpful for fulfilling the growing demands for medicine by its precise manufacturing and low cost in comparison to other techniques. The first FDA approved 3D printed medicine SPRITAM (levetiracetam)in 2016 by Aprecia Pharmaceuticals was formulated by ZIP DOSE technology enables the high drug load up to 1000 mg in single dose. This report highlights the different 3DP technologies, unlimited benefits, and limitations of additive manufacturing technology with the perspective of potential challenges that may affect broad based applications in the field of pharmaceutical drug delivery.

Keywords: 3DP Printing, personalized medicine, thermal inkjet Printing, Fused deposition modelling.

Introduction:

Three-dimensional printing technology includes computer aided design which are based on digitally controlled depositing of material (layer by layer) to create freeform geometrics. when we compare this to other conventional manufacturing technologies it has high production rate due to its operating system. It has ability to achieve high drug loading with much desired precision and accuracy especially for poorly water-soluble peptides and proteins, also the drugs having narrow therapeutic window. 3DP plays important role in formulation of multiple active dosage form, where we can formulate single blend or multilayer printed tablet having controlled release properties. This tablet will reduce frequency of number of dosage form consumption by the patient in their daily routine. [2]This technology will be highly beneficial for improving HealthCare network as well as patient compliance. This idea of 3DP uses sensor technology which will enable sensor to be placed on patients. This sensor will generate clinical data that will be stored in healthcare network. The healthcare professionals from the respective field will manufacture the dose according to patient's physiology. Hence this system offers the advantage of time shortening and improve patient compliance.[2]

Discussion:

History of 3D Printing:

The most important achievements in 3D printing in pharmaceutical and biomedical applications.[1]

1984	(SLA) Stereolithography (SLS) Selective laser sintering patent
1990	(FDM) Fused deposition modeling 3D Printing (color jet Printing, DOS) First 3DP Placebo Tablets (DOS Method)
2000	RepRap Concept Open Source In vivo Evaluation 3DP implant (DOS)

2010	FDM Printed tablets Bilayer Tablet and multi drug Delivery Device Printed by paste extrusion (bioprinting of artificial liver)
2015	SPRITAM first 3DP drug

Among the 40 years of history many different techniques were developed by scientist and evolved with the technological progress.[1]

This technique is based on:

- Powder solidification
- Liquid solidification
- Extrusion based system

Powder solidification	Drop on solid deposition
Liquid solidification	Drop on drop deposition Stereolithography
Extrusion based system	Solid -fused deposition modelling FDM Semisolid – pressure assisted syringe

Summary of 3- dimensional printing technologies applied in the development of pharmaceutical drug delivery systems.:

Printer type / Printing technique	**Dosage Form/ system**	**Model Drug used**	**Reference**
Fused filament 3D printing	Tablet	Fluorescein	[4]
3D printer	Tablet	Paracetamol	[4]
3D printer	Tablet implant	Isoniazid	[4,5]
Fused deposition 3D Printer	Immediate Release Tablets	5- Amino salicylic acid Captopril	[4,5]
Fused deposition 3D Printing	extended release Tablet	Prednisolone	[4,5,6]
Fused deposition 3D	Modified release drug loaded Tablet	Printer 5-Amino salicylic acid	[3,4]
3D Printer	complex matrix tablet with ethyl Acetaminophen	Cellulose Gradient	[3,4,5]
3D Printer	Fast Disintegrating Tablet	Acetaminophen	[4,5]
Extrusion based printer	Multi active Tablet (polypill)	Captopril, nifedipine and glipizide	[5]

3D extrusion Printer	Multi active Solid Dosage form	Aspirin, Hydrochlorothiazide, Pravastatin and Atenolol	5
Micro -drop Inkjet 3DP	Nanosuspension	Folic Acid	4,5
Thermal Inkjet Printer	Dosing drug solutions in to oral Films.	Salbutamol Sulphate	4,5
Commercial Inkjet printer	Nanocomposite structure	Rifampicin and Calcium Phosphate	4,5
Laboratory scale 3-DP™	Capsules with immediate release core	Pseudoephedrine hydrochloride Machine and release rate regulating shell	4,5
Inkjet printer	Implant with Lactic acid Polymer	Levofloxacin Matrix	3,5
Thermal Inkjet Printer	Oral Solid Dosage Form	Prednisolone	4,5
Stereolithography printer	Anti -acne patch	Salicylic acid	4,5
Electrodynamic atomization Technique	Patterned micron scaled structures	Tetracycline hydrochloride	4,5

Advantages and Limitations of 3DP in Pharmaceutical drug delivery:

In comparison to conventional pharmaceutical product manufacturing process 3DP has lots of advantages

1. It has ability to customized product
2. Accurate and precise dosing of potent drugs
3. Low cost of production
4. It has ability to achieve high drug loading with much – desired precision and accuracy especially for potent drug that are applied in small doses.
5. This technology is more suitable formulation of active ingredient having poor water solubility.
6. It helps to avoid batch to batch variations that are found during the bulk manufacturing of the conventional dosage forms.
7. In comparison to conventional manufacturing equipment 3D Printers occupy less space.
8. Batch manufacturing is easier and process can be completed in single run.
9. It improves the accessibility, safety and efficacy of the medicine.
10. It reduces the cost of production because of lesser material wastage in comparison to conventional dosage form preparation methods.

Biomedical applications of 3D printing:

- Wound dressing - Anbacterial , dressing, vascular grafts , dressing
- Implant ,prostheses - Limbs ,Craniofacial implant , casts, stent
- Surgical model- organs , Vasculature , Tumor models, Disease Models

Advantages	Material
High resolution	Silicon
Good Stability	Titanium
More effective treatment	Hydroxyapatite
Multipurpose material	Nylon
Good fidelity of patient anatomy	PCL
Design to precise shapes	PEG
Aesthetic and functional outcome	
Increase surgeon's skill	
Reduced risk of intraoperative complications	

Bio- Inspired, Bio Based 3D Printing:

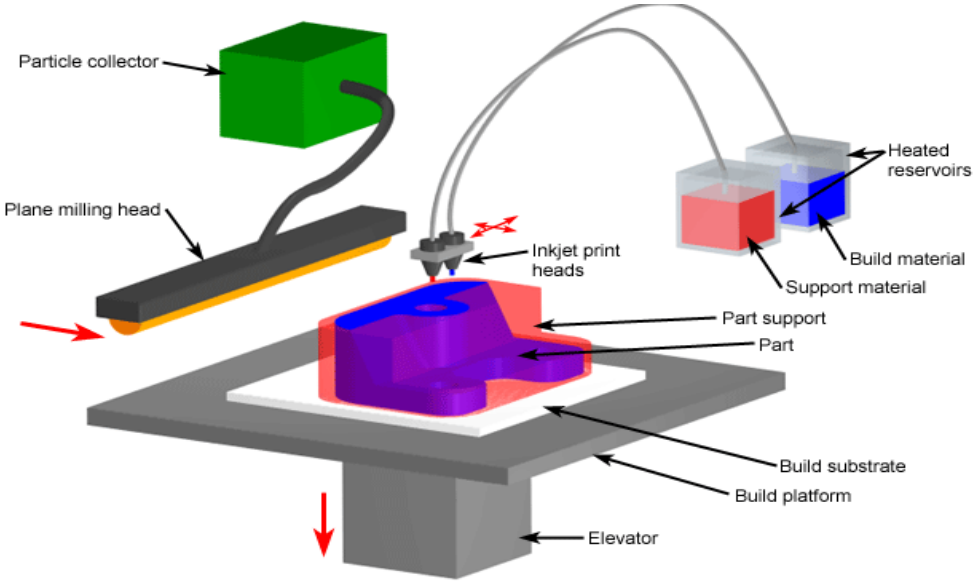
- Bioprinting - cartilage, organs- on- chip
- 4D printing - stimuli-response
- Bio robotics - Heart pump, actuator

Material	Advantage
Nanocellulose	High resolution
Alginate	Good stability
PCL	Low costs
Silicon	Possibility of manufacturing Programmable device with tunable functionality
PNIPAM	Reduce risk of transplant rejection

Discussion on some of the 3D printing technologies:

Inkjet Printing:

In this technology replacement of ink with the pharmaceutical solutions containing drug and normal paper with edible sheet known as substrate. Alterations are done by altering the number of layers in given area. The two main printing types are used under inkjet printing are thermal inkjet printers and piezoelectric inkjet printers. Inkjet printing technology used for drugs which have very low therapeutic dose. Because if we formulate this dosage form in to higher doses this leads to longer drying time for multiple layer printing on a particular area. Increasing surface area to sort this problem would also increases the size of dosage form.



Thermal inkjet printing fig.1

- **Inkjet printing system consist of two types of techniques:**

1. **Continuous inkjet printing (CIJ)**
2. **Drop on demand printing (DOD)**

Continuous inkjet printing (CIJ)

In this technique liquid ink is directed through an orifice of 50-80 um diameter creating a continuous ink flow. The liquid is allowed to flow and break into small drops at a specified speed and size at regular intervals using a piezoelectric crystal. All the parameters are within control with the help of electrostatic field. Thus, all the droplets are charged and they are separated by "droplets of guard" to minimize the electrostatic repulsion within them. Thus, electrostatic field direct the charged droplet to the substrate.

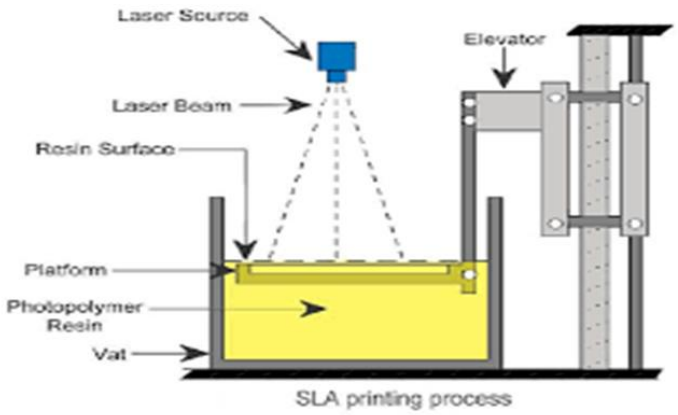
Drop on demand printing (DOD)

Drop on demand technique contain multiple heads (100-1000) and can use two types of translators, thermal head or a piezoelectric crystal. the thermal head is restricted only for volatile liquid, while the piezoelectric crystal covers most of the liquids. thermal head reaches temperature up to 300 degree Celsius, which indicates that use of solvent of high vapor pressure may cause the degradation of the bioactive compounds. This factor limits the heads for pharma applications (andrea). The piezoelectric crystal changes fast, but this can generate a sudden variation of volume. both of the heads can produce droplets of between 10 and 50 µm, having volume of between 1 to 70 mL They have ability to operate at room temperature by using less volatile and more biocompatible liquids, makes piezoelectric printing technology more suitable for the development of drug delivery devices.

Stereolithographic 3D Printing:

Stereolithography is a method which uses vat of UV curable photopolymer resin and ultraviolet laser beam to build parts layer by layer but one layer at a time. For building each layer, the laser beam traces a cross-section of the part pattern on the surface of the liquid resin. When Ultraviolet laser light is exposed this light cure and solidifies the pattern traced on the resin and joins it to the bottom layer. After the pattern has been traced, the SLA's elevator platform goes down by a distance equal to the thickness of a single layer, which is 0.05 mm to 0.15 mm (0.002" to 0.006"). after that the resin- filled blade sweeps across the cross section of the

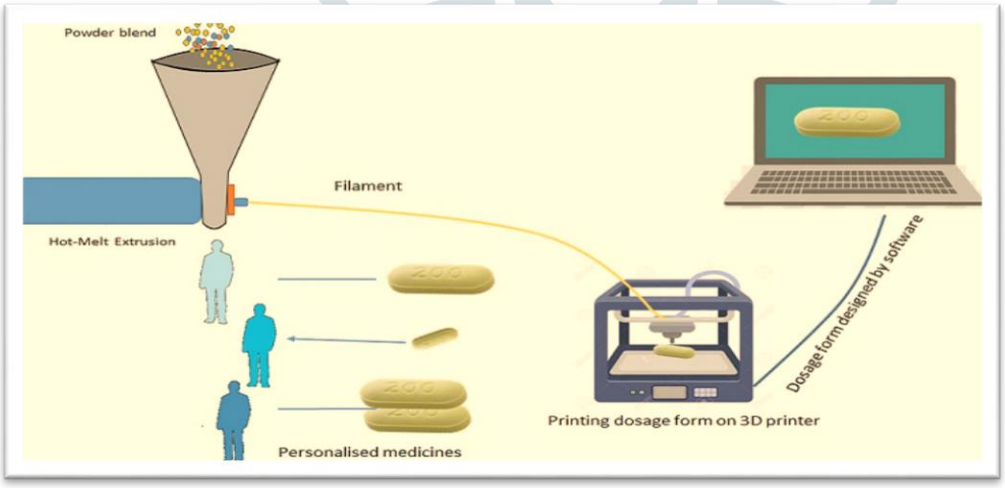
part and perform re-coating it with new material. On this new liquid surface, the next layer pattern is traced, joining the previous layer. A complete new3-D part is formed with the help of this process. After building new parts they are immersed in a chemical bath for cleaning of excess resin and then immediately cured in an ultraviolet oven. Stereolithography uses supporting structures which helps to attach the part to the elevator platform and also helps to prevent deflection due to gravity. It holds the cross sections in place so that they will resist lateral pressure from the re-coater blade. Supports are created during the preparation of 3D CAD models for use on the stereolithography machine, although they may be manipulated manually. Supports are removed from the finished product manually, unlike in other, less costly, rapid prototyping technologies.[14,15]



Stereolithographic 3D Printing Fig.2

Hot melt extrusion (HME):

This process involves melting of polymer and a drug at high temperature. Pressure is applied with the help of instrument for bending. HME is a continuous process which includes number of operations such as feeding, heating, mixing and shaping. In recent studies it is found and proved that HME has ability to improve solubility and bioavailability of the poorly water-soluble drugs.[21]



Hot Melt Extrusion. Fig3

Challenges In 3D Printing Technology:

Although 3D printing technology showed promising result in drug delivery application. The 3DP technology is still under developing stage. Therefore, it has to go through several challenges such as improving performance, process optimization of device for its versatile use, selection of appropriate excipient, post treatments method etc. For achieving a good quality 3D printing product, we will need to optimize many more

parameters such as printing rate, line velocity of the print head, interval time between two printing layers, distance between nozzles and the powder layer etc. 3D printing also holds tremendous promise for orphan drugs, which are designed to treat rare diseases that are sometimes not developed by the pharmaceutical industry due to economic reasons. The number of such rare diseases is estimated to be between 4,000 and 5,000 worldwide.

Conclusion:

In 2015, Aprecia Pharmaceuticals introduce a first tablet manufactured through 3D printing to be approved by the FDA. Two years later, GlaxoSmithKline completed a study where inkjet 3D printing and ultraviolet (UV) curing were used to create tablets that treat Parkinson's disease. 3D printing has applications in controlled release, short-run medicines, and even the potential for on-site printing at pharmacies, 3D-printing technology it has the ability to transform the pharmaceutical industry. Not surprisingly, established players of pharmaceutical industry continue to invest in 3D-printing research, while newer manufacturers are also breaking into the pharmaceutical space. Such experiments can open the doors for personalized medicine and improvements in clinical trials, benefitting patients and manufacturers alike. Researchers 3D printing will be the part of the future pharmacies. If common medicines for chronic diseases are available in a polypill as per the patient requirements. However, there is some resistance to this movement, as it would be more difficult to regulate and ensure safety at local pharmacies than at manufacturing facilities. The practice also opens up concerns about 3D printing and intellectual property, standardizing computer programming, the business model, and the potential for counterfeiting drugs.

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