



3D printing in pharmacy: A burgeoning field in development of drug delivery system

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ABSTRACT

Three-dimensional printing (3DP) is an emerging field that can be found in medicine, electronic, aviation and other fields. 3DP technology are constantly implemented to novel fields, laying foundation for a new commercial revolution. Basically, 3DP is a fabrication method in which routinely layer-by-layer substance are being deposited to create various layout of choice. It is beneficial for remedy with slim therapeutics indices. 3DP can fabricate stable dosage shape with variable densities and diffusivities, complicated inner geometries, a couple of tablets and excipients. 3DP technology inclusive of stereolithography, deposition modeling, inject- primarily based totally printing and selective laser sintering were developed. The need of computer aided design (CAD) in 3DP technology permits the producing of drug method among the preferred launch free and pattern. Recently, the FDA has authorized 3DP tablet known as Spritam, which distinctly increase with inside the coaching of fabricated drug shipping device and customized medicine. 3DP technology can be used for targeted drug release. In addition, this article illustrates the methods, convenience, deprivation, application and challenges of 3DP technology within side the subject of pharmaceutical method development.

KEYWORDS Three-dimensional printing, layer-by-layer, drug delivery, computer aided design, customized medicine.

1. INTRODUCTION

Three-dimensional printing (3DP) has won momentum in lots of industries as a branded-new modern production tool. This additive gadget is unexpectedly converting the manner that items are layout and produced; via way of means of the use of a 3-D computer model, bespoke items may be created in a layer-via way of means of-layer manner under automation.^[1] 3DP aims to provide tailor made tablets as per patient necessity. It takes into deliberation the pharmacogenomics with the wisdom about their diet, life-style, and ecosystem.^[2] 3DP is particular technology that turned into first describe via way of means of Charles Hull in 1986. Computer based drug layout beside with 3DP technology hurries up production of customized pharmaceutical drug products. 3DP technology has a fantastic embryonic in a person dosage shape concept especially polypill concept. In 2015, the U.S. Food and Drug Administration (FDA) branch vouchsafe the approval of Spritam (Levetiracetam), the primary 3DP tablets for the treatments of epileptic seizure.^[3-5] The different 3DP technology utilized in pharmaceutical fabricating encompasses Fused deposition modeling (FDM), Stereolithography (SLA), Direct energy deposition (DED), Selective laser sintering (SLA), Thermal inject printing, Power bed inject.^[6-7] 3DP is appropriating growing interest in pharmaceutical preparation improvement as a powerful method to affected a few challenges of conventional pharmaceutical unit operations. When it comes to drug burdening, the usual manufacturing unit operations of milling, coupling, granulation, and compression might provide different final product attributes. Pharmacological dosage form stability, medication delivery and drug stability.^[8-9] The first wave of 3DP pharmaceutical was formulate using endure inject printing. In 1996, Wu et al. created the first medication delivery device using 3DP.^[10] This paper covers 3DP's impact on the pharmaceutical and medical device industries as well as its capacity expansion, quality control issues, and regulatory issues. Medical application for 3DP, both actual and potential, are categorised into a number of broad categories, including: tissue and organ fabrication, development of custom medical devices, implants, and anatomical models; and pharmaceutical research pertaining to drug discovery, delivery, and indefinite quantity forms. Increased productivity, democratised design and production, improve cooperation, and the capacity to customise and personalise medical items, drugs, and equipment's are just a few advantages of the usage of 3DP in the medical industry.^[11] In the final 15 years a distinctive multiplicity of 3DP technology have interpolate in the pharmaceutical industry. Auxiliary asset of 3DP encompass authentic control of droplet surface as well as dose, complex drug-release profile, and additionally capability to make dosage form with

complicated drug-release profile. ^[12-13] Additionally finished production strategies also can be made less complicated and simpler via way of means of the use of this technology. ^[14]

1.1 IDENTICAL

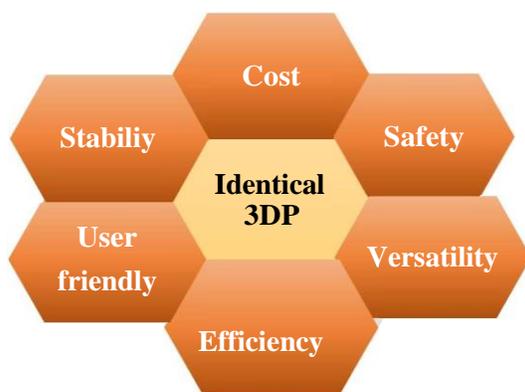


Figure 1. Identical 3DP

Identical 3DP	
Cost	Equipment, Labour, Time
Safety	Excipients, GMP
Versatility	Dosage form, Raw material
Efficiency	Equipment size, Continues processing
User friendly	Equipment, Portability, Software
Stability	Excipients, Drug

TABLE 1: Identical 3DP

1.2 HISTORY

The history of 3DP is shown in table no. 2 [15]

Table 2. History of major development in 3DP

S. No.	MAJOR DEVELOPMENT
1.	The first patent for (Rapid prototyping) RP technology was submitted in by Dr. Hideo Kodama.
2.	Charles Hull introduced the stereo lithography apparatus (SLA) in 1984.
3.	In 1986 Carl Deckard created a method for selectively sintering components.
4.	Stereo lithography equipment SLA was the subject of a 1989 Carl Deckard patent.
5.	1990 Fabrication of fused filament (FFF)
6.	1992 The first SLA machine made with the 3DP system was created.
7.	E.M. Sachs received a 3DP patent in 1993.
8.	In 1996, biomaterials were applied clinically for tissue regeneration.
9.	In 1999, Luke Massella received the first 3D-printed bladder, which was made of a combination of his own cells and 3DP biomaterials.
10.	SLM technology was introduced by MCP Technologies in 2000.
11.	In 2002 a working miniature kidney was created.
12.	In 2003 the phrase "organ printing"
13.	In 2004 the RepRap idea of an open-source, self-replicating 3DP was created by Dr. Bowyer.
14.	First colour in 2005 was introduced by Z Corp

1.3 ADVANTAGES OF 3DP

1. Exact and accurate dosing of mighty pills which are administered at small doses.
2. Due to lower material cost of blossoming reduces.
3. Eco-friendly production in the process of fabrication formulation with 3DP was no wasted the pollutes the atmosphere.
4. Suitable drug shipping for difficult to formulate active ingredients like poor water

solubility, drug with narrow therapeutics window.

- In suitable of combination with repeated dosing regimen, remedy may be tailor-made to enhance affected person adherence.

2. TYPES OF 3DP

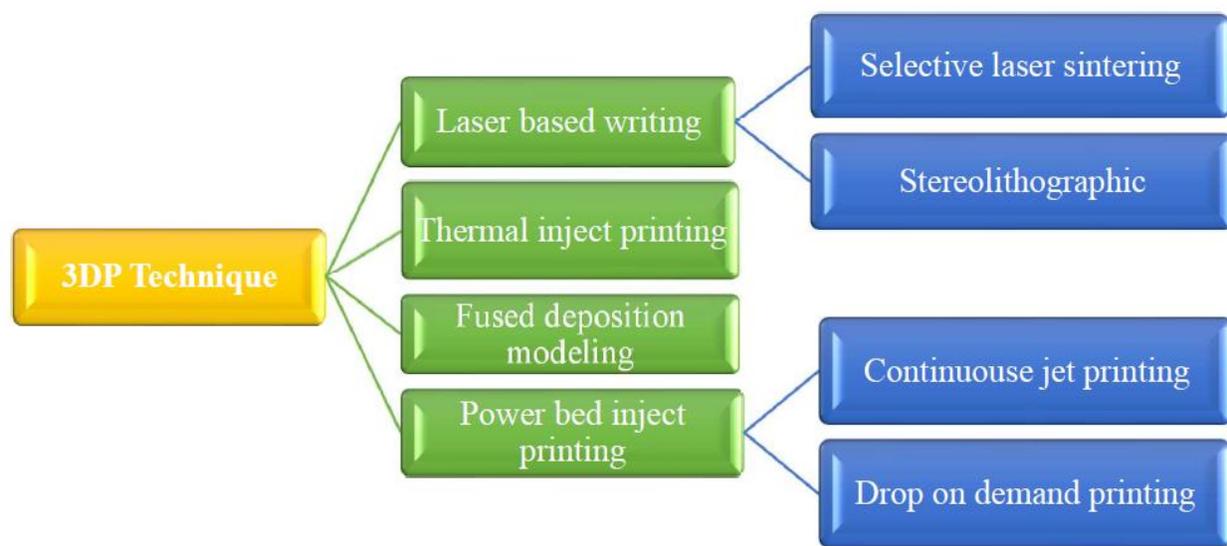


Figure 2. 3DP Technique

2.1 Laser-based writing system Laser-primarily based totally writing machine changed into the primary that commercially offered Solid Freeform Fabrication (SFF) approach and enlargement in 1986. Laser based writing system is primarily based on the totally principle of the standard photopolymerization, in which free atom, molecules or ions are liberated after the interaction among photo initiator and ultraviolet light. ^[16-17] Laser based writing system is divided into two types- Selective laser sintering and Stereolithographic. Selective laser sintering (SLS) – SLA is based on the power- bed inject 3DP. This is superior used approach as the capability of chemical demotion of the material is extreme. Fabrication of tablets by SLA utilized pharmaceutical polymer was newly described. ^[18-19] The first utilization of SLA for pharmaceutical betterment with inside the fabrication of polycaprolactone primarily based totally drug delivery devices. Rather of resin, power bed is expanded as thin layer and radiation is used to fuse them and sinter the bed layer by layer. ^[20-21]

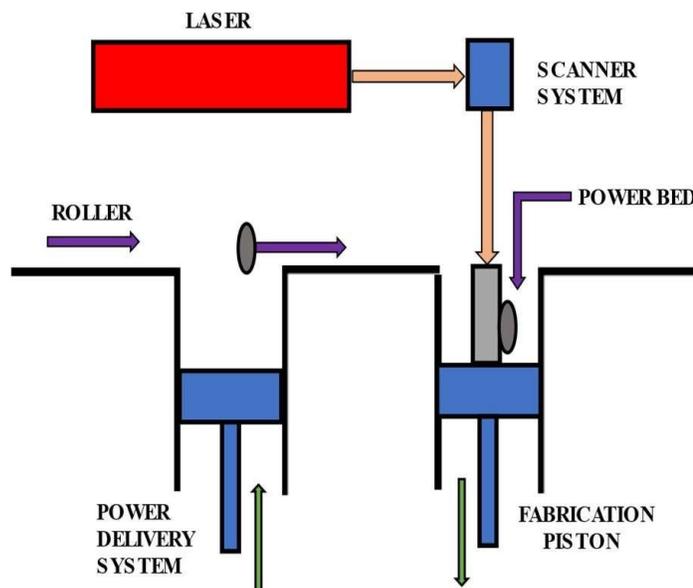


Figure 3. Selective laser sintering (SLS)

2.2 Stereolithography (SLA) - SLA turned into the first commercially technology and turned into the inception of solid unfastened fabrication invented via way of means of Charles et al. SLA is a mater that's used to construct a medical and computer part (hardware) and which is very costly. ^[22-23] SLA technique associate the use of photopolymerization to fruitage a 3DP design. A concentrated ultraviolet laser over the photopolymerization liquid in a floor-by-floor fashion, prompt a chemical reaction is that causes gelatin of the display area. Floor upon floor recurrence of this process produces an entire design. The resin used should be Food and Drug Administration (FDA) approved for human use and be compelled have the capability to solidify upon susceptibility to ultraviolet. ^[24-25]

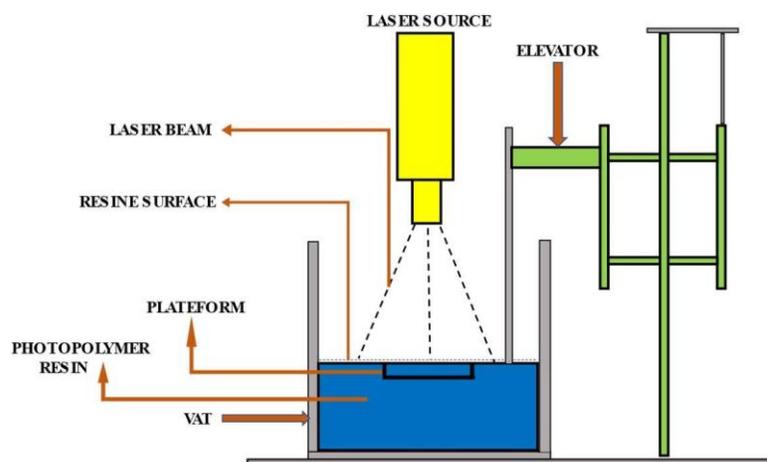
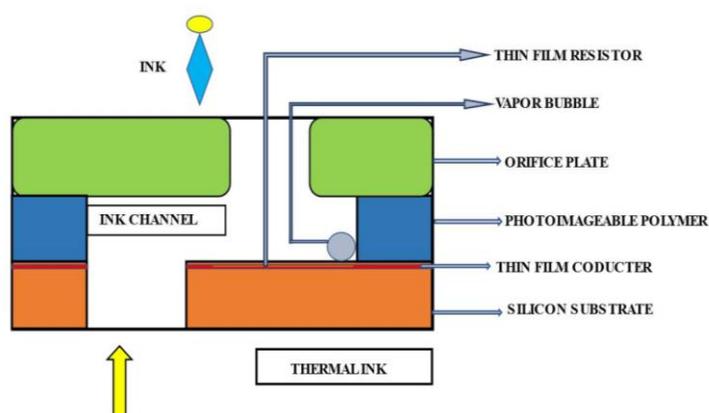


Figure 4. Stereolithography (SLA)**2.3 Thermal inject printing**

In thermal inject printing a proposal to a customized medicine essence from the process of computer operated thermal inject printing and carry of thermal inject printers.^[26] Thermal inject printing use thermal radiation, piezo effect to deposit small bead of “ink” on to the medium conformity with the load direction fed to the printer. The ink is discharge from the nozzle applying consolidation. One major drawback of thermal inject printing it is excessive temperature carried out might also additionally probably cause degrade. (Heat labile API and excipients used limited in pharmaceutical).^[27]

**Figure 5.** Thermal inject printing**2.4 Fused deposition modeling**

Fused deposition modeling (FDM) is likewise acknowledged as fused filament fabrication (FFF). Fused deposition modeling is help in manufacturing of delayed release print without an outlying gastro resistance coating. And they are also help in tailor dose medication.^[28,29] Fused deposition modeling is a most familiar and economical type of printer. Fused deposition modeling is a most familiar and economical type of printer. Fused deposition modeling is analogous to the thermal inject printer. They are used for thermoplastic material.^[30] Fused deposition modeling may be enforced to severa dosage shape which are tailored in polymer as a part of the groundwork similarly, implants, zero-order release tablet, surrounding coated Cora tablets, orally disintegrating tablet. In the technique the polymer is deliquesced and eject via a transportable heated nozzle. Fused deposition modeling has many drawbacks like lack suitable polymer, incomplete drug release.^[31-32]

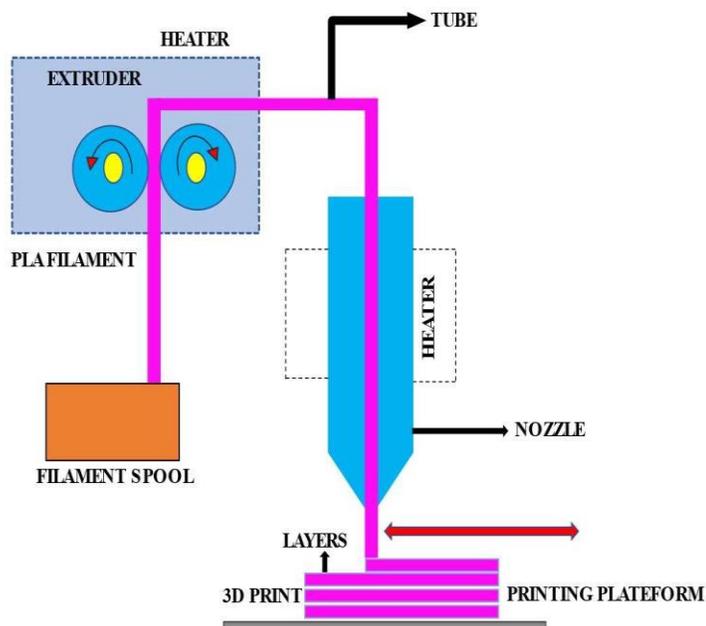


Figure 6. Fused deposition modeling

2.5 Power bed inject printing

Power bed inject printing may be a speedy prototyping additive producing technology for creating object represented by digital knowledge similar to CAD file. The objects are fancied by spreading a skinny of a fine material that is then sure in elite region by printing a binder solution using an inject type nozzle.^[33] This can be a quick and sophisticated methodology which needed the fusion of high and low temperature binder using produce by a laser beam.

They are divided into two technique-

1. **Continuous jet printing (CJ)**
2. **Drop on demand printing (DOD)**

In CJ printing a stream of ink droplets continually ejected by a nozzle. Ink column under pressure. Charge droplets deflected and positioned using electric field. Remaining droplet collected by a gutter and recycled.

In DOD printing is high cost then CJ printing because it produces droplets which are dispensed only when required, this result in less wastage.^[34]

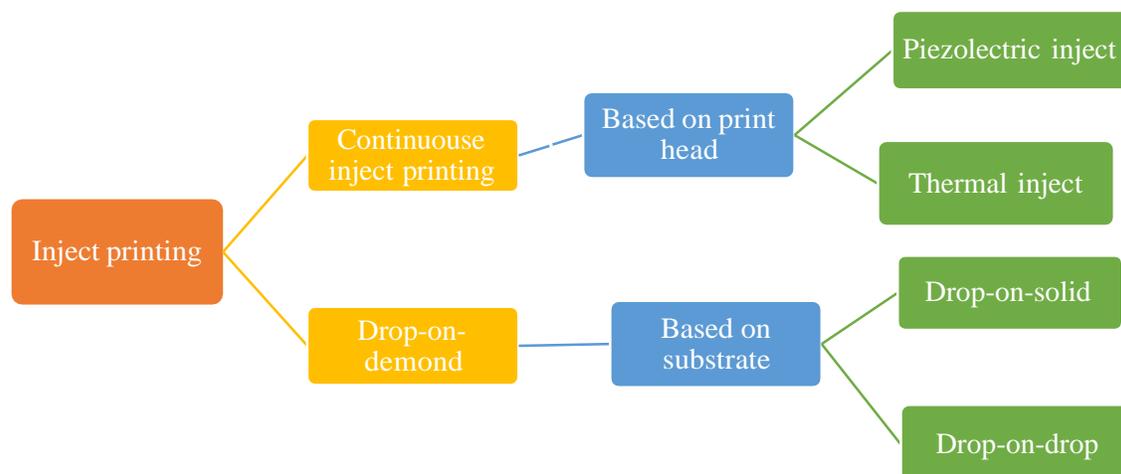


Figure 7. Inject Printing

3. CURRENT 3DP TECHNOLOGIES AND PHARMACEUTICAL FORMULATION FOR DRUG DELIVERY

The current 3DP technology and pharmaceutical formulation is shown on table no. 3 [35-41]

Table 3. Types of 3DP technique dosage form and its active polymers

Types of 3DP technique	Dosage form	Active polymer	References
FDM 3DP	Tablet	Felodipine, Tween 80, Eudragit EPO, PEG	35
3DP	Biodegradable patch	Polycaprolactone, 5-fluorouracil	36
Inject 3DP	Tablet	PEGDA, ropinirole	37
Thermal inject printing	Solid dosage forms	rasagiline mesylate	38
SLA	Hydrogel	polyethylene glycol, diacrylate, ibuprofen	40
FDM	Tablet	Hydrochlorothiazide	41

4. 3DP TECHNOLOGY

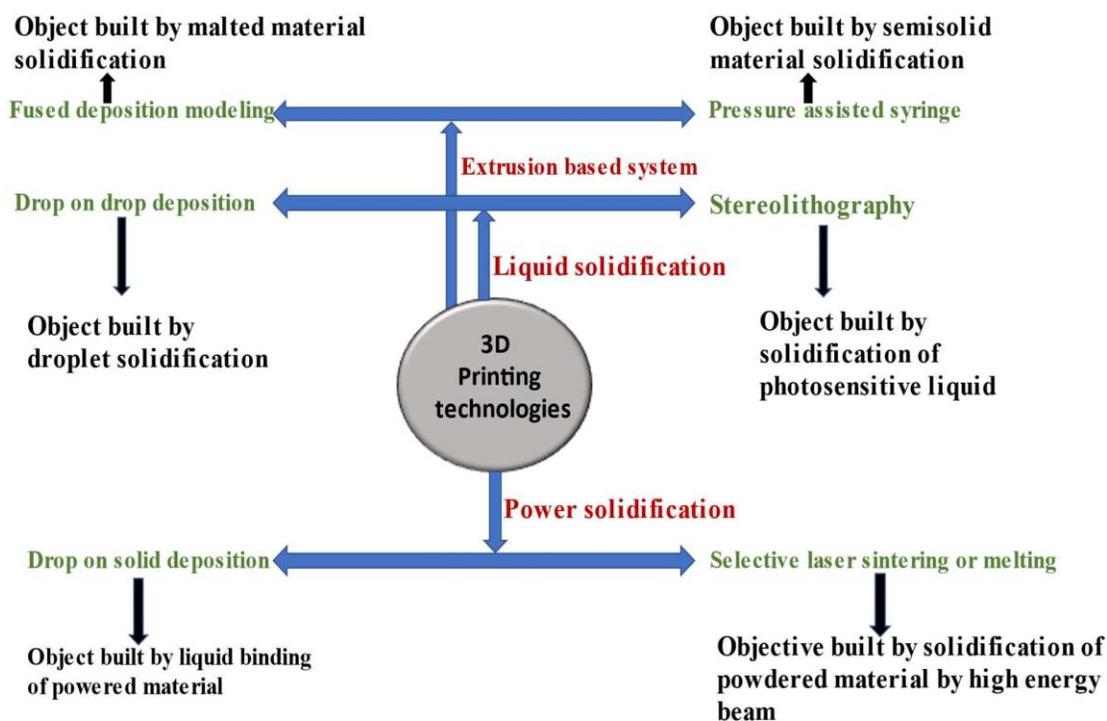


Figure 8. 3DP technologies

5. STEPS INVOLVED IN A 3DP DOSAGE FORM

Many steps involved in 3DP dosage form [42,43]

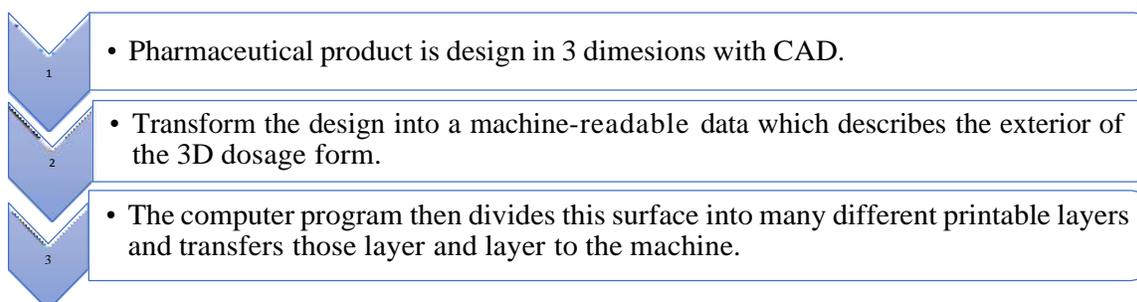


Figure 9. Steps of 3DP**6. BENEFITS AND DRAWBACKS OF 3DP TECHNOLOGIES**

Different types of 3DP technologies and its benefits & drawbacks [44-52]

Table 4. Benefits and drawbacks of 3DP technologies

3DP technologies	Benefits	Drawbacks	References
Thermal inject printing	Raised three-dimensional resolution can be achieved.	The printing period is raised.	44,45
Stereolithography	High resolution and accuracy	Treat is required after deposition. A residual exploration is needed for pharmaceutical usage.	46,47
Fused deposition modelling	Products are economical. Provide a high level of accuracy.	Depending on nozzle magnitude, low resolution limit is needed.	48,49,50,51
Power bed injected 3DP	It is over 10 times more inexpensive and very effective.	Demand the fusion of extreme & low melting point binder.	52

7. APPRAISEMENT PARAMETER

There are many Evaluations parameter of 3DP dosage form

Table 5. Evaluation parameter

S. No.	Parameter
1.	Tablet's shape and dimensions.
2.	Weight variation.
3.	Breaking force.
4.	Friability.
5.	Drug dissolution testing.

6.	X-ray powder diffraction.
7.	Dimensions of 3D printed tablet.
8.	Differential scanning calorimetry.

8. APPLICATION OF 3DP

8.1 Commercially accessible 3DP drugs- Spritam is shown with the aid of using Aprelia Pharmaceutical adopting the Zip Dose technique primarily based totally on power bed inject printing. Spritam fashioned with the aid of using the layer-with the aid of using-layer production device. The pharmacological effectiveness of Spritam changed into assemble to be proportionate to conventional tablets. ^[53]

8.2 Cancer treatment- Chemotherapy has typically enforced withinside the most cancer treatments however chemotherapy typically reasons aspect effects. Chemotherapeutic drug terrible solubility in aqueous media; thus, they may be administering via a different. Currently, the PCL, poly (lactic-co-glycolic acid), and 5- fluorouracil-loaded patches have been appropriately printed and inserted directly into pancreatic tumours. ^[54-56]

8.3 Novel Dosage Form and Drug Delivery Devices- Expanding implantable drug transport systems with different drug release characteristics may be possible with 3DP Technology. For instance, bone disease needs for on-site medication treatment. Similarly, the surgical defect must be filled in order to successfully treat osteoarticular tuberculosis surgically. ^[57] Microcapsules, nanosuspensions, synthetic extracellular matrices, antibiotic printed micropatterns, mesoporous bioactive glass scaffolds, and exclusive type of multi-layered drug delivery devices are only a few examples of the novel dosage forms printed using 3DP technology. In order to produce paclitaxel microparticles with precisely defined and controlled forms, Lee and colleagues used a piezoelectric inject printing system. ^[58]

8.4 3D Printed polypill- The method polypill illustrated an aggregate of certain drug in a single customized tablet. It affords gain over poly medicated affected person which includes elder person. Divergent polypills the use of 3-D extrusion printing had been properly constructed. As an example, Captopril and Nifedipine used withinside the treatment of hypertension and Glipizide used withinside the treatment of type 2 diabetes. ^[59]

Personalized treatments- Salicylic acid-filled nose-shaped mask for anti-acne treatment had been quickly and confidently introduced. The subject's face was scanned, and the capture images were then projected into the Auto CAD application, where the nose segment was then chosen. SLA changed into the maximum correct technology for mask manufacturing. ^[60-61] Personalising medical products included feature such as size, shape, texture, colour and flavour of oral dosage shape, all of which may have an effect on patient's acceptability criteria. ^[62-64]

9. FUTURE EXPECTED OF 3DP

The future and advancement of pharmaceutical betterments is depiction by 3DP drug assembling technology. 3DP technology may want to permit on-Demand for manufacturing of products with personalised dosages, drug combinations, geometries and release distinctive not afforded by existing conventional production technology like tableting and encapsulation. 3DP performs a crucial and efficacious role in the field of personalised medicine. Drug accomplishment and distribution is a pricey in the pharmaceutical industry. 3DP used in alter nutritional products, organ, and drugs. It is also help in the manufacturing of medication with constant research. ^[65-66] 3DP technology can make evolve in pharmacy practices by acquiesce particularly to each patient, even though specialised and compliance difficulty remain. In 2015, the FDA corporation granted the approval of Spritam, the primary 3DP tablet for the treatment of epileptic seizure. 3DP technique with ultraviolet deal with changed into and is utilized by Glaxo Smith Kline to fabricate for treatment of Parkinson's disease. They have the capability. ^[67-68]

10. CHALLENGES IN 3DP

The technology is still in the infancy as the importance parameters remain unresolved. These demanding situations consist of the optimization of the optimization of the process, enhancing the overall performance and choice of excipients. Drop on demand printer heads display the problem of nozzle clogging. To carry out the best 3DP products the compactivity of excipients and binder wants to be addressed. It is also essential to study the rheological properties of the binder polymer. There are some drawbacks withinside the commercialization of 3DP, withinside the market place along with the raised price in developing new components of new formulation thru 3DP, choice of proper excipients, and preservation of pharmaco-technical properties of very last products. ^[69-70] There are many types of 3DP to be had has its personal set of advantages and demanding situations.

For example, the considerable demanding situations in exploiting stereolithography to manufacturing modify product have interaction considerable regulatory troubles and implementation of manufacturing fashions to efficiently produce person healing desires into small batches of drug merchandise of stander best.^[71] Different 3DP technology produce 3DP tablet of many mechanical resistance. Although Fused deposition modelling can produce highly resistant drugs.^[72]

11. CONCLUSION

3DP has become convenient for the pharmaceutical sector, exceptional to personalised medication specializes in the patients. The scope of 3DP technology has still its own disadvantages. The new FDA approval of the first 3DP tablet Spritam changed into a massive milestone on this technology history. 3DP is expected to maintain hastily evolving over the next decade. In the close to future this technology has the ability to take the industry closer to the affected person for the manufacturing and drug delivery. Ever for the reason that FDA permitted the producing of 3DP technology, the research at the improvement of oral dosage form has elevated immensely. To ensure the optimum release rate and to maximise therapeutic efficacy, the oral dose forms for children and the elderly should be improved as one of the extra benefits of 3DP drug delivery. Drug manufacture frequently use 3DP techniques such laser-based writing, thermal inject printing, fused deposition modelling, and power bed inject painting. The use of 3DP enables the creation of oral drug delivery systems that improve the release and solubility of insoluble medications. The use of 3DP in drug delivery systems is currently on the rise, creating the possibility that 3DP and traditional pharmaceutical technology will one day be combined to expand the areas in which it can be used.

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