



A Review on 3D Printing Technologies in Pharmaceutical Science

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ABSTRACT

3D printing known formally as Additive Manufacturing began in the late 1980s. It is a digital manufacturing process that creates 3D objects by fusing or depositing material such as variety of polymers, metals, and ceramics in successive layers laid down under computer control. This objects can be of almost any shape or geometry & are produced from a 3D model as defined in a Computer- aided design(CAD). A variety of 3D printing technologies have been developed to fabricate novel solid dosage forms which are among the most renowned & distinct products today. The present review focused on briefing various techniques, applications in Pharmaceutical technology.

Keywords: 3D Printing Technology, Polypill concept, Thermal-Inkjet Printing, Binder Deposition, Stereo lithography, Democratization.

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INTRODUCTION

The 3D Printing technology has caught the attention of medical devices industry and pharmaceutical industry due to its application on various platform in health care industry. 3D printing technology promises a future of drugs & medicine printed on demand, personalized with customized doses. The potential of 3D printing is about being able to deliver what you want, how much & when you want. This technology will definitely help Doctors & pharmacists to provide "Tailor made" medicine for each patient [1, 7].

3D printing in pharmaceutical drug delivery would excel greatly in the domain of personalized medicine, where the medication could be customized as per the need of treatment, & not "one fits all" approach. 3D printing can play a significant role in multiple active ingredients dosage forms, where the formulations can be as a single blend or multilayer printed tablets with sustained release properties. This reduces the frequency and no. of dosage forms units consumed by the patient on a daily routine. 3D printing technology has high potential in individualized dosage forms concept called the polypill concept. This brings about the possibility of all the drugs required for the therapy into a single dosage form unit [8].

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 [2].

3D printing relies on computer aided designs to achieve almost flexibility, time saving, & exceptional manufacturing capability of pharmaceutical medicines which can be utilized in personalized and programmable medicine.

ADVANTAGES OF 3D PRINTED DRUG DELIVERY [2-4, 15]

- High drug loading ability when compared to conventional dosage forms.
- Accurate and precise dosing of potent drugs which are administered at small doses.
- Reduce cost of production due to lesser material wastage.
- Suitable drug delivery for difficult to formulate active ingredients like poor water soluble drug.
- Narrow therapeutic window as well as increase complexity.

- 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 CR 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.
- Avoid batch –to –batch variation seen in bulk manufacturing of conventional dosage forms.
- 3D printers occupy minimal space and are affordable.
- Manufacture of small batches is feasible and the process can be completed in a single run. On demand manufacturing is occur.
- Easy to used, no skilled person needed.

WORKING OF 3D PRINTER [11-14]

The basic process involves 3D prototyping of layer by layer fabrication to drug excipients to formulate into the desired dosage form. It begins with making a virtual design is for instance a CAD (Computer aided Design) file. This CAD file is created using a 3D modelling application or with a 3D scanner (to copy an existing object). A 3D scanner can make a 3D digital copy of an object

Steps involved in 3D printing:

Design: The intended product design is digitally rendered. Design can be rendered in 3 dimensional with Computer Aided Design Software (CAD)



Conversion of the design to a machine readable: 3D design are typically converted to the STL file format, which describe the external surface of a 3D model.



Raw material processing: Raw material may be proceed into granules filaments, or binder solution to facilitate the printing process.



Printing: Raw materials are added and solidified in an automatic, layer –by-layer manner to produce the desired product.



Removable & post processing: After printing products may require drying, sintering, polishing or other post processing steps.

TECHNIQUES IN 3D PRINTING:

3D printing includes a wide variety of manufacturing techniques, which are based on digitally – controlled depositing of material (layer- by – layer) to create freeform geometries.

The widely used 3D printing technologies are as follows:-

1. Thermal inkjet printing.
2. Inkjet printing
3. Fused Deposition Modeling
4. Extrusion 3D printing
5. 3D printer
6. Hot Melt Extrusion(HME)
7. Powder bed 3D printing.
8. Stereo-lithographic 3D printing

1. THERMAL INKJET PRINTING

In thermal inkjet printing, the aqueous ink fluid is converted to vapour form through heat and expands to push the ink drops out of a nozzle. It is used in the preparation of drug loaded biodegradable

microspheres, drug loaded liposomes, patterning microelectrode arrays coating and loading drug eluting stents. It is also an efficient and practical method of producing films of biologics without compressing activity [18-20].

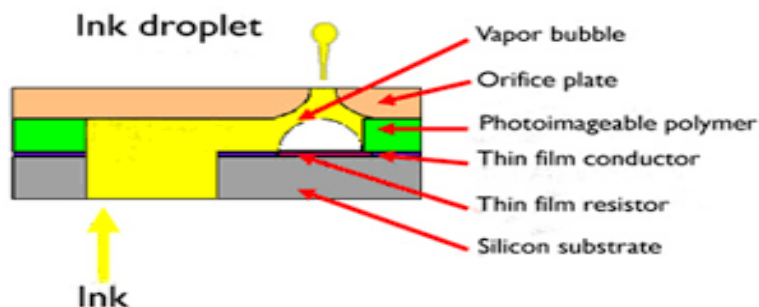


Fig. 1: Thermal Inkjet Printing

Table 1- Some of the drug prepared by Thermal Inkjet Printing

Sr.No.	Drug	Dosage form	Application
1	Prednisolone	Tablet	Anti-inflammatory Immunosuppressant
2	Folic acid	Nano suspension	Anaemia
3	Salbutamol sulphate	Solution	Bronchodilators
4	Carbamazepine	Co-crystals	Antiepileptic drug
5	Felodipine	Solid dispersion	Antihypertensive

2. INKJET PRINTING

Inkjet printing is also called as ‘mask-less’ or ‘tool-less’ approach because the formation of desired structure mainly depends upon the movement of inkjet nozzles or movement of the substrate for an accurate & reproducible formation. In this technique, the ink is deposited onto a substrate either in the form of Continuous Inkjet Printing (CIJ) or Drop on Demand (DOD) printing, hence it provides a high resolution printing capability [2].

Advantages of inkjet printing is that it has low processing cost, rapid processing rates, generation of minimal waste, it gives CAD information in a ‘direct write’ manner & it process material over large areas with minimal contamination [3].

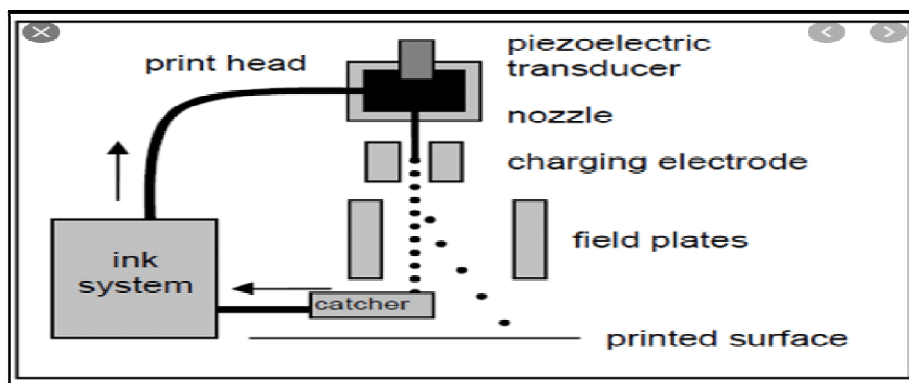


Fig. 2: Inkjet printer

Table 2 -Some of the drug prepared by Inkjet Printing

Sr. No.	Drug	Dosage form	Application
1	Polyvinyl-Pyrrolidone(PVP)	Micro needle	Excipients
2	Insulin	Micro needle	Antihyperglycemia
3	5-flurouracil, curcumin, cisplatin	Micro needle	Anticancer
4	Paclitaxel	Micro particles	Anticancer
5	Caffeine	Tablet / Capsule	CNS stimulants
6	Lysozyme & Rionuclease-A	Film	NSAIDs
7	Rifampicin	Implant & Nanoparticles	Antibiotic

3. FUSED DEPOSITION MODELLING [4-10]

It is a commonly used technique in 3D printing, in which the materials are softened or melted by heat to create objects during printing. There are several dosage forms available by using FDM.

FDM 3D printing helps in manufacturing delayed release printlets without an outer enteric coating, & also provides personalized dosed medicines.

Limitations – FDM 3D printing indicates several limitations of the system,

- Lack of suitable polymers
- Slow & often incomplete drug release because the drug remains trapped in the polymers & the miscibility of the drug & additives with the polymers used was not evaluated.

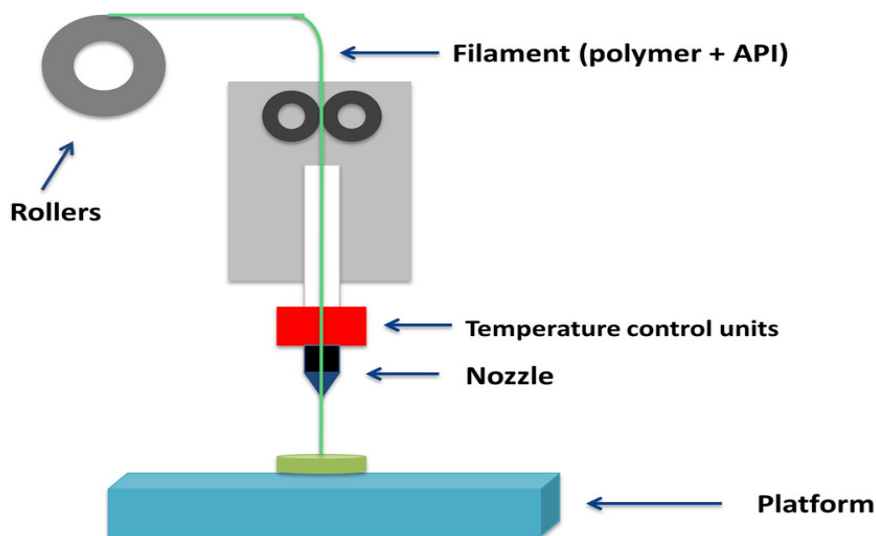


Fig.3: Fused Deposition Modeling (FDM)

Table 3 – Some of the drug prepared by Fused Deposition Modelling (FDM)

Sr. No.	Drug	Dosage form	Application
1	Metformin, Glimepiride	Tablet	Ant diabetic
2	Theophylline	Tablet / Capsule	Lung disease
3	Diclofenac	Controlled release tablet	Ulcerative colitis
4	Prednisolone	Extended release tablet	Immunosuppressant
5	Gentamicin sulphate, Methotrexate	General device	Antibiotic & Anticancer

4. EXTRUSION 3D PRINTING [7-8]

Extrusion is the most widely used 3D printing technology. In an extrusion process, material is extruded from robotically –actuated nozzles. Unlike binder deposition, which requires a powder bed, extrusion methods can print on any substrate. A variety of materials can be extruded for 3D printing, including molten polymers, pastes & colloidal suspension, silicones, & other semisolids.

A particularly common type of extrusion printing is fused filament fabrication (FFF). It is only used to fabricate tablet containing Guaifenesin as expectorant.

Table 4- Some of the drug prepared by Extrusion 3D printing

Sr. No.	Drug	Dosage form	Application
1	Captopril	Tablet	Antihypertensive
2	Dexamethasone	Drug encapsulated film of PLGA & PVA	Arthritis
3	Atenolol	Polypill (multi active solid dosage form)	Angina
4	Pravastatin	Polypill	Cardio-vascular disease

5. 3D PRINTER :

3D printer is a valuable tool which is used to create customized medication with tailored release profiles & the medication is changed as per the patient comfort.

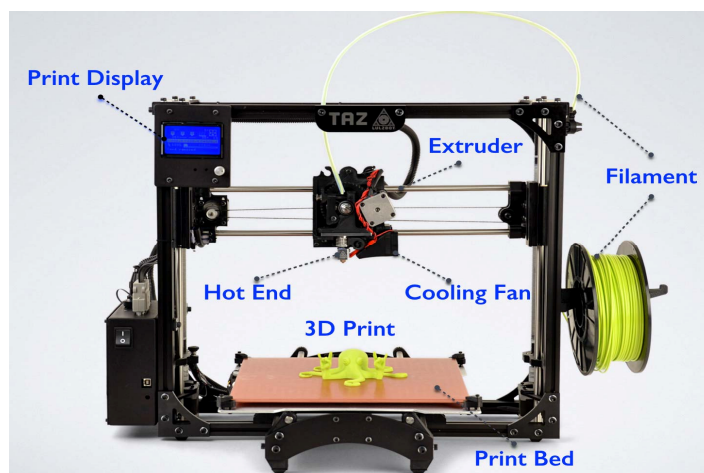


Fig.4: 3D Printer.

Examples: Table 5- Some of the drug prepared by 3D printer technology

Sr. No.	Drug	Dosage form	Application
1	Paracetamol	Fast disintegrating tablet	Analgesic
2	Polycaprolactone	Biodegradable patch	Manufacture specially of polyurethanes
3	Nitrofurantoin	Biofilm disk	Urinary tract infections
4	Chlorpheniramine	Tablet	Antihistamine

6. HOT MELT EXTRUSION(HME) [9-11]:

Hot melt extrusion is the process of melting polymer & drug at high temperature & the pressure is applied in the instrument continuously for blending. It is a continuous manufacturing process that includes several operations such as feeding, heating, mixing, & shaping.

In recent years, it has proved that HME has the ability to improve the solubility & BA of poorly soluble drugs.

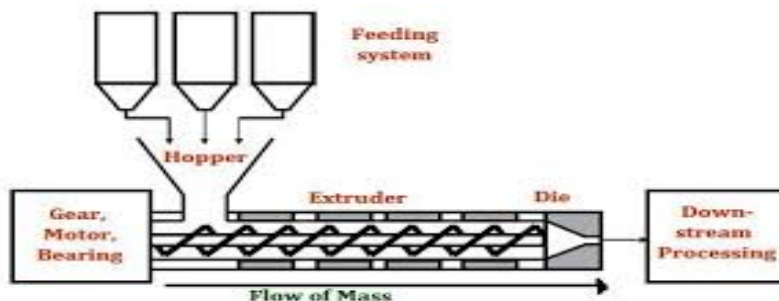


Fig.5 - Hot Melt Extrusion

Table 6 - some of the drug prepared by HME

Sr. No.	Drug	Dosage forms	Applications
1	Isoniazid	Compartmentalized shells	Tuberculosis infections
2	Indomethacin	Subcutaneous rods	NSAIDs
3	Ethylene vinyl acetate (EVA) copolymers	T-shaped prototype of intrauterine system	Hot melt adhesion

7. POWDER BED 3D PRINTING:

In that technique powder jetting or power bed is used to spread thin layer of power and simultaneously applying liquid binder drops with the help of inkjet printers. The ink (binders & APIs binder solution) is sprinkled over a powder bed in 2D fashion to make the final product in a layer-by-layer fashion [5-6].

The adaption of this technique into pharmaceutical manufacturing is easier than other techniques as powder and binder solution are widely used in the pharmaceutical industry.

This method is has its own disadvantages as follows-

- Additional drying is required to remove solvent residues.
- Excess powder accumulates during printing leading to wastage.

Polypill concept [11-13]

The polypill is also known as “zip dose”. It refers to a single tablet that includes the combination of several drugs. This concept is highly beneficial for geriatric population, as patient of this age category are prone to multiple disorders and hence multiple therapy.

The technology has been realised through the research of Khalid *et al*, where 5 different active pharmaceutical ingredients (APIs) with different release profiles have been formulated in a single 3D dosage form. Three drugs (pravastatin, atenolol, & ramipril) were printed in the extended release compartment. The drugs were physically separated by a permeable membrane of hydrophobic cellulose acetate.

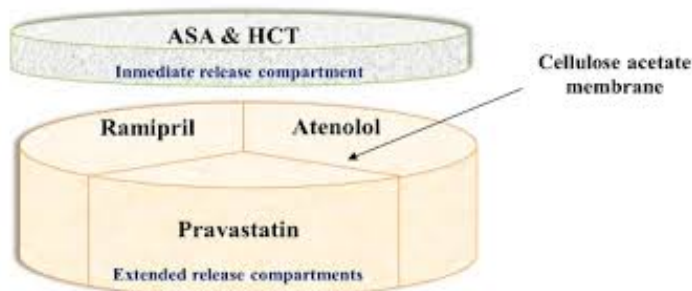


Fig.6: 3D printed polypill

An immediate release compartment containing aspirin and hydrochlorothiazide was deposited on top of the extended release compartment.

8. STEREO-LITHOGRAPHIC 3D PRINTING

This technique involves the curing of photosensitive materials (photo polymerization to produce a 3D object. Scanning a focused UV laser over the top of a photopolymerisable 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 part 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 insuring adhesion & therefore, layer formation is done. Post printing processing is usually required to further curve the final product, to improve its mechanical integrity & to polish or remove the attached supports to the fabricated objects [12, 13].

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 UV light beam, in the form of a laser, which transfer the energy into a liquid photopolymerisable resin. The UV light beam is aided by baffles, axis X&Y, to transverse the surface of the liquid resin, in order to accurately represent the 3D model, previously designed. When a layer solidifies, the lifting platform descends its position to the night of a new layer of a liquid resin, again beginning the procedure, until the manufacturing of the 3D product is finished in a layer -by-layer way. Here thickness of the cured layers depends upon the energy of the UV light to which resin exposed. The resin should be FDA approved for human use with the ability to solidify upon exposure to laser beam [14].

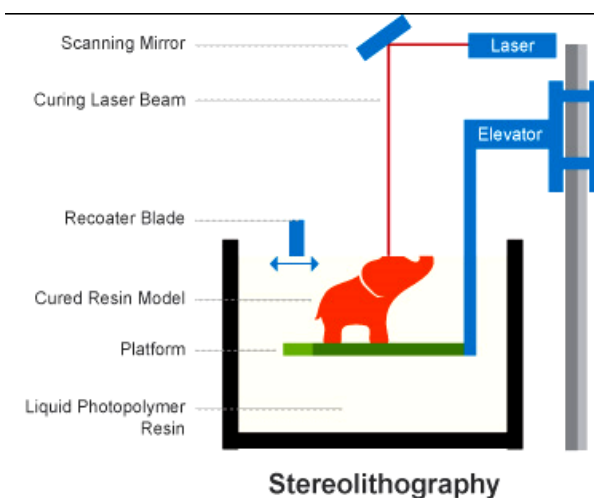


Fig.7: Stereo lithographic 3D printing

Obstacles & Challenges:

- Huge scale of investment is required.
- Actual implementation of application.
- Safety and security concern.
- Lack of regulation of 3D printing.
- Selection of appropriate polymer & excipients.
- Post treatment methods and optimization.

Applications of 3D Printing Technology

Manufacturing industries have been using 3D printers for more than decades, but mostly to make prototypes rapidly & cheaply. The majority are used as functional models, prototypes, & casting patterns, or for presentation models.

By using 3D printing technology, better things are being printed as finished goods, around 28% of the output of 3D printers is now final products rather than prototypes, & this is expected rise to 80% in 2020. Hearing aids 3D printing technology for manufacturing hearing aids was introduced a decade ago & it has shortened the manufacturing process to three steps: scanning, modelling, & printing. Printers can print 65 hearing aids shells & 47 hearing aid moulds within 60 -90 min. the printing speed helps manufacturers to adjust demand to supply.

3D printing technology is also used in Automobile industry for making metallic parts components, also useful for making aircraft components (European aeronautic defence & Space Company has developed the aircraft machine parts by 3D printing technology). It is also used to make Weapons, also to produce parts of sports gadgets or wearing sports things like shoes etc.

Medical application: 3D printing has been applied in medicine since the early 2000s. When the technology was first used to make dental implants & custom prosthetics. Since then, the medical applications for 3D printing have evolved concededly. Recently published reviews describes the use of 3D printing to produce bones, ears, exoskeleton, windpipes, jawbones, eye glasses, cell cultures, stem cells, blood vessels, vascular networks, tissues, & organs as well as novel dosage forms & drug delivery devices. It is also used in Dentistry to make dental device.

Pharmaceutical applications: Pharmaceutical application for 3D printing are expanding rapidly & are expected to revolutionize health care. 3D printing technologies are already being used in pharmaceutical research & fabrication. Advantages of 3D printing includes precise control of droplets size & dose, high reproducibility, & the ability to produce dosage forms with complex drug release profiles.

3D printing technology makes complex drug manufacturing process more standardised, simpler & more viable. 3D printing technology is also valuable tool in the development of personalised medicines. 3D printing technologies allows drug dosage forms, release profiles & dispensing to be customized for each patient. 3D printing can lead of drugs actually manufactured by “precision drug dispensing”. The drug themselves could be tailored to meet various précised specifications & address the unique needs of individuals taking them.

Application of 3D printing technology in pharmaceutical manufacturing could have following potential benefits.

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.

- 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.

Need of 3D printing:

The use of 3D printing in pharmaceutical science can provide many benefits which includes – cost effectiveness; increased productivity; the democratization of design & manufacturing & enhanced collaboration.

Cost efficiency: The most important benefits offered by 3D printing is the ability to produce items cheaply. Conventional method of drug manufacturing are less cost effective than 3D printing technology, because conventional methods use a lot of process for manufacturing (mixing, milling, dry or wet granulation, compression or moulding etc.)

Enhanced Productivity: traditional method of drug manufacturing uses various processes such as mixing, milling, dry or wet granulation, compression or molding that makes it time consuming. But 3D printing technology is much faster than traditional method of drug manufacturing because it does not have various processes like traditional manufacturing. In addition to speed, other qualities, such as resolution, accuracy, reliability & repeatability of 3D printing technologies, are also improving.

Environment friendly: 3D printing technology claims to have more environmental benefits than traditional drug manufacturing which needs huge setup to manufacture a pill.

Another beneficial feature offered by 3D printing is the democratization of the design & manufacturing of goods.

FUTURE PROSPECTS

New possibilities in 3D printing may open up whole new opportunities for pharmaceutical research & Bio-technology applications. In the new future 3D printing approach will be utilized in many ways such as fabricate and engineer various novel dosage forms, achieved optimized drug release profiles, development of new excipients, avoid incompatibilities between multiple drugs, drug dosage forms, supporting delivery, limits degradation of biological molecules or helping to research cures. 3D printing could add a whole new dimension of possibilities to personalized medicines.

On demand printing of drug product can be implemented for drugs with limited shelf life or for patient specific medication, offering, and an alternative to traditional compounding pharmacies. In the future it may lead to the innovation in garage biology. As the technology is still so new, there's a lack of regulation, safety, and security concern of 3D printing. So these problems can be overcome in the early future.

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. 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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