

Three Dimensional Printing by Hot-Melt Extrusion; New Era for Development of Personalized Medicines and Continuous Manufacturing of Pharmaceuticals

Amit Chivate^{1,2}, Atul Garkal¹, Namdev Dhas¹, Tejal Mehta^{1,*}

¹Department of Pharmaceutics, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, INDIA.

²Area Marketing Manager, Roquette India Private Limited, Mumbai, Maharashtra, INDIA.

ABSTRACT

The three-dimensional printing is a growing field in engineering, civil constructions and pharmaceutical development. The three-dimensional printing is a one-step continuous process. However, conventional manufacturing is batch by batch process hence the three-dimensional manufacturing is advantageous over conventional manufacturing. The three-dimensional technique is cost effective and time-saving process. The three-dimensional printing is a rising era in the development and manufacturing of pharmaceuticals such as medical devices, oral dosage forms and some modified-release products. The personalized dose adjustment as per patient requirement is easier due to three dimensional printing. Hence, the personalized dosage forms are more preferable for potent drugs to avoid the adverse drug reactions and accuracy of a therapeutic drug. The three-dimensional technique equipped with hot-melt extrusion is recently used for the development of various pharmaceutical products. The fused disposition model is commonly employed for the development of layer by layer products. However, the hot-melt extrusion was previously used in pharmaceuticals for solubility enhancement. Currently ample of applications of hot-melt extrusion is explored in research

and one of them is the manufacturing of personalized pharmaceuticals. The dose adjustment and personalized pharmaceutical development will be achieved by three dimensional technique equipped with hot-melt extrusion. There is a wide range of polymeric materials with superior properties available for three-dimensional printing of pharmaceuticals. This review briefly discussed the applications of three-dimensional techniques for pharmaceutical development with suitable examples. The current scenario of the techniques and future perspectives are also discussed.

Key words: Personalized dosage forms, Hot-melt extrusion, Three Dimensional printing, Fabrication of dosage forms, Fused-deposition modeling.

Correspondence

Dr. Tejal Mehta

Professor and Head-Pharmaceutics, Institute of Pharmacy, Nirma University, S.G. Highway, Chharodi Ahmedabad-382481, Gujarat, INDIA.

Phone no: +91 9879357584

Email: tjshah3@gmail.com

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INTRODUCTION

The early 1980s Three Dimensional (3D) printing technology was used in chemistry, robotics and optics research. Presently, it is also explored in the development of medical and pharmaceutical products. The first powder based 3D printing technique was used in 1993.¹

THREE DIMENSIONAL PRINTING OF PHARMACEUTICALS

Pharmaceutical manufacturing is batch to batch process and it is lengthy and costly process. However 3D printing is continuous process of manufacturing of pharmaceuticals and it is cost effective and time saving. It is having industrial scalability and thus, could be useful in development of several personalized pharmaceutical dosage forms. The fabrication of novel design is achieved as per the patient requirement via 3D printing easily.² 3D printing is currently used for development of human organ and tissue and printing of medical devices. 3D printing is growing field and having rising applications. ZipDose® technology is based on the deposition of solid by drops. It introduces the first 3D printed orally disintegrating tablet of drug-levetiracetam (Spritam®) in 2016.¹ ZipDose® technology having advantages over conventional techniques such as high dose loading capacity (1000 mg/ tablet), a wide range of taste masking capacity and rapid disintegration within second.³

3D printing technique is very simple and robust technique. It is cheaper than the conventional manufacturing process for development of pharmaceutical products. 3D printing is used for development of customized designed products as per patient requirement i.e. Development of personalized dosage forms.² 3D printing is a flexible alternate technique to the conventional method of tablet compression. There are different printing techniques such as i) 3D printing inkjet printing, ii) thermal inkjet printing, iii) selective laser sintering, iv) stereolithography v) syringe or extrusion 3D printing.³ 3D printing is preferred in manufacturing of aerospace, automotive and consumer goods industries. In 2015 first drug manufactured by using 3D printing is approved by the FDA.⁴ This is strong proof for development of new pharmaceutical products using 3D printing. It is also called as solid form of fabrication/ rapid prototyping/ additive manufacturing. Unprinted material may be reused in continuous processing.⁵

Three Dimensional Printing manufacturing technology vs traditional manufacturing

As compared to conventional methods of product development 3D printing is flexible. It creates personalized complex products.¹ In Raw material Printing, the raw material is poured layer by layer as per the defined design and automatically solidified to get the desired product.

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Later, the printing designed products may be further processed like polishing, drying, sintering.⁵

STEPS INVOLVED IN HOT-MELT EXTRUSION THREE DIMENSIONAL PRINTING

- Dosage form design:** Computer design aided software is used for designing expected objects. The selected design need to be as a machine-readable format.^{1,5}
- Preparation of raw materials:** Raw material processed maybe in the form of powders, particles, pastes, filaments, binder solution or granules.^{1,5}
- Hot-melt extruded filaments preparation:** The polymer and drug heated specific temperature to produces melted filament. The melted filament is moldable as per the design.
- 3D printing:** The material poured layer by layer as per the defined design and automatically solidified to get the desired product.^{1,5}
- Finishing:** Later the printing designed products may be further processed like polishing, drying, sintering.^{1,5}

FUSED DISPOSITION MODELING

Fused disposition modeling (FDM) is a leading 3D technique employed in the continuous manufacturing of pharmaceutical products and it works based on HME. It is also named as fused filament fabrication (FFF) because the filament of printing material was poured into the hot nozzle followed by depositing the layer by layer on the printing table. It is suitable for various s printing materials and can be molded in specific size and shape. FDM is applicable for manufacturing of tablets, films, implants, etc. Numerous polymers are recommended as film formers, some suitable examples includes methacrylic acid copolymers such as (Eudragit® RL, Eudragit® L, Eudragit® RL-PO), cellulose derivatives (HPMC, HPC, HPMCAS), polyvinyl alcohol (PVA), Soluplus®-polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer using HME. Water-soluble polymers are generally used for the improvement of bioavailability of poorly soluble drugs (BCS class II and IV).⁶ FDM is mostly used for the development of porous scaffolds for biomedical applications.⁷ In FDM, the melted polymer deposited layer by layer in predefined manner working on the principle of the melted polymer where deposited layer by layer in a predefined manner. FDM heated polymeric material is extruded through a small orifice normally 50-100 µm. followed by cooling and solidified on the build plate.⁸

PHARMACEUTICAL APPLICATIONS OF THREE DIMENSIONAL PRINTING

3D printing has a wide range of pharmaceutical applications. It is not only limited to the development of pharmaceutical drug products but also preferred in tissue culture and medical devices. (Table 1 and Figure 1)⁵

a. Manufacturing of Oral tablets

Pietrzak, I *et al.* Prepared flexible-dose of immediate-release and extended-release tablets by using FDM 3D printing and HME. The designed tablets are genuine and easy to swallow. The crystalline thermo-stable theophylline was loaded in 3D printed polymeric tablet matrix.³

b. Orodispersible films

Orodispersible films are solid films that rapidly disintegrate and dissolve in the mouth. It has recommended to those patients who have swelling problems and want to improve patient compliance. It is also having advantages over conventional tablets like avoidance of drug first-pass

metabolism.⁶ Musazzi *et al.* prepared personalized orodispersible films of paracetamol maltodextrins by using HME 3D printing technology. The RMA extruder was preferred for the extrusion of materials. Maltodextrins plus paracetamol was mixed and glycerin is used as a wetting agent. Wetted material was extruded by using RAM extruder followed by 3D printing of orodispersible films on packing material.⁹⁻¹⁴ Jamróz *et al.* prepared an orodispersible film of poorly water-soluble drug-aripiprazole for improvement of dissolution rate. After the processing, aripiprazole is converted into amorphous form in product as confirmed by XRD data. The designed film is porous in nature hence an increased dissolution rate. This study proves that the FDM is a suitable technique for the preparation of orodispersible films. PVA was used as a polymer for drug loading. PVA is a water-soluble polymer having matrix-forming capacity by HME. From this case, the study author concludes that FDM is a suitable method for the fabrication of orodispersible films by using 3D printing and HME.^{6,15}

c. Medical Devices

Common methods for the preparation of medical devices: injection molding, melt-extrusion, freeze-drying, solvent casting and compression molding.^{7,16,17}

d. Implants

3D printing using FDM is recently developed for the manufacturing of implantable drug delivery devices. This technique is commonly used for the preparation of intravaginal rings, subcutaneous rods, intrauterine devices, etc.

e. Gastro retentive drug delivery systems

Dumpa, Bandari and Repka designed core-shell gastro retentive pulsatile tablets of theophylline by using HME fused with FDM 3D printing techniques. The filament generated through HME fused with FDM 3D printing was used for direct compression and the final product was core-shell tablets.^{10,18,19}

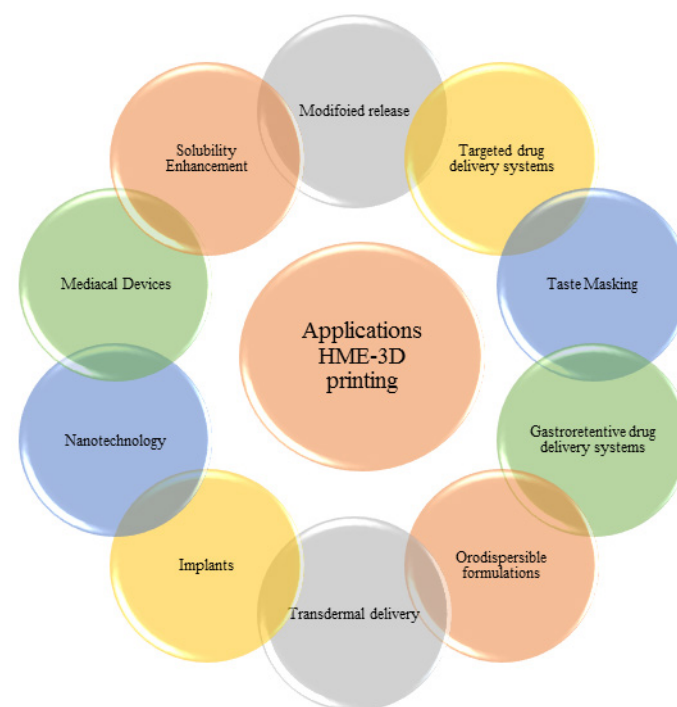


Figure 1: Different Applications of HME-3D printing.

Table 1: Different products developed by using 3D printing with HME.

Formulation	Route of administration	Drug	Excipients	Application	Technology	Reference
Orodispersible films	Oral	Paracetamol	Maltodextrins	Personalized orodispersible films	HME 3D printing	9
Orodispersible films	Oral	aripiprazole	PVA	Solubility enhancement	FDM	6
Tablets	Oral	fluorescein	PVA	Personalized Controlled release tablet	Fused-filament 3D printing	1
Tablets	Oral	theophylline	Hydroxypropyl cellulose, ethyl cellulose	Gastroretentive and pulsatile drug delivery systems	HME and FDM 3D Printing	10

f. Polymers

Properties of superior polymers for 3D printing by using HME; It should be thermoplastic, it should be sufficient rigidity to mould and allow to form a filament of specific predefined dimensions before printing. Cyclodextrin- water-soluble polymer used for improvement of solubility. PVA has the capacity to form a matrix as well as it is water-soluble hence used for the improvement of drug solubility.^{6,19}

DISCUSSION

3D printing is advanced technology and it forms the object as per requirement by layer-by-layer technique During the development of pharmaceutical dosage forms, the continuous manufacturing is a very important consideration because of cost-effectiveness and increase productivity. In the current manufacturing process, the pharmaceuticals are manufactured in lots or batches. However, it varies the product specifications and quality. But the formulations developed using novel 3D printing technology is a continuous process and it would be cost-effective and produces uniform quality products. Recently it is applied in several areas like engineering, construction, aerospace, automotive, medical and pharmaceutical sectors. More specifically in the pharmaceuticals it is applicable for the manufacturing of medical devices and some complicated pharmaceutical products. However, the scope of these techniques is increasing towards the productions of personalized dosage forms. The need for personalized dosage forms may fulfill by 3D printing with HME. The manufacturing of pharmaceutical tablets was achieved by 3D printing in the future. The 3D printing is approved by the FDA and the first ZipDose® technology successfully works on the basis deposition of solids by drops. In the view of simplicity, robustness and cost-effectiveness and thus. Advantageous over the commercial manufacturing of pharmaceutical products. It is a promising flexible technology that offers the design of formulations, which is complicated to develop by conventional technique. Moreover, it allows the preparation of various dosage forms with high accuracy of Active Pharmaceutical Ingredient and excipients concentrations, as compared to the traditional pharmaceutical manufacturing process. It allows for creating multifunctional multidrug devices, drug delivery systems and drug dosage formulations for personalized use.

CONCLUSION

The formulation of medical devices and pharmaceutical products using 3D printing technology is a promising new era worldwide. The majority of patients prefer the personalized dosage forms of medicines however the manufacturing of personalized medicine is only feasible using the 3D printing techniques. The hot-melt extrusion is the advanced, industrially scalable and cost-effective method for 3D printing of materials. Looking to the ample of opportunities and versatility, it is predicted that the

conventional techniques of manufacturing of pharmaceutical dosage forms will be augmented by 3D printing in near future.

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CONFLICT OF INTEREST

Authors report no conflict of interest.

ABBREVIATIONS

3D: Three dimensional; **HME:** Hot-Melt Extrusion; **FDA:** Food and Drug Administration; **FDM:** Fused deposition modeling; **FFF:** Fused filament fabrication; **BCS:** Biopharmaceutical Classification Systems.

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