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Coupling Hot Melt Extrusion and Fused Deposition Modeling: Critical Properties for Successful Performance

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Abstract

Interest in 3D printing for pharmaceutical applications has increased in recent years. Compared to other 3D printing techniques, hot melt extrusion (HME)-based fused deposition modeling (FDM) 3D printing has been the most extensively investigated for patient-focused dosage. HME technology can be coupled with FDM 3D printing as a continuous manufacturing process. However, the crucial pharmaceutical polymers, formulation and process parameters must be investigated to establish HME-coupled FDM 3D printing. These advancements will lead the way towards developing continuous drug delivery systems for personalized therapy. This brief overview classifies pharmaceutical additive manufacturing, Hot Melt Extrusion, and Fused Deposition Modeling 3D printing techniques with a focus on coupling HME and FDM 3D printing processes. It also provides insights on the critical material properties, process and equipment parameters and limitations of successful HME-coupled FDM systems.

Keywords

Additive Manufacturing; Continuous Manufacturing; Coupling; Fused Deposition Modeling; Hot Melt Extrusion; 3D Printing; Process Analytical Technology

1. Introduction

Over the last few decades, numerous studies on hot-melt extrusion (HME) have been published [1,2]. HME technology has several advantages over conventional techniques [3]. It is solvent-free and has few processing steps and downstream operations. Indeed it may generate amorphous solid dispersions [4–6]. HME is a “green” technology and can solve

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Conflicts of Interest

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many of the fabrication issues in the pharmaceutical industry. It is an essential tool for the improvement of oral bioavailability of drugs with poor water solubility. The use of HME has been largely relegated to preparing solid dispersions. However, other uses for HME continue to be discovered and implemented in product development [3,7,8].

As HME is flexible and produces distinct dosage forms, researchers have evaluated it in various drug delivery applications. Uses of HME described in the literature include the fabrication of amorphous solid dispersions [9–11], immediate-, delayed-, pulsatile-, and sustained-release/extended release products [12–14], transmucosal, transdermal, transungual, ocular, orodispersible delivery systems [15–18], implants and abuse deterrent products [19–21]. HME has been considered for pharmaceutical cocrystals, co-amorphous systems [22–26], twin screw melt and dry granulation [27], chronotherapeutic formulations, semisolid dosage forms, self-emulsifying systems, solid lipid nanoparticles, nanostructured lipid carriers (NLC), and fused filament fabrication (FFF) or fused deposition modeling (FDM) three-dimensional (3D) printing [3,7,28–31]. Interest in additive manufacturing (AM) and 3D printing for pharmaceutical applications markedly increased after FDA approval of the first 3D printed product and confirmation of the benefits of AM [32,33]. The Hot Melt Extrusion (HME)-Based Fused Deposition Modeling (FDM) 3D printing technique one of the additive manufacturing techniques was explored to develop various geometric dosage forms [34,35]. Figure 1 shows the abundance of publications on HME-based FDM 3D printing for the development of diverse drug delivery applications as of November 2020. The advancement of complex, patient-focused drug delivery is a new objective in the pharmaceutical industry. HME coupled with FDM 3D printing might efficiently and economically generate personalized, patient-focused complex drug products [36–38].

In 2004, the United States Food and Drug Administration (USFDA) inducted process analytical technology (PAT) tools and quality by design (QbD). Since that time, these concepts were also considered for the design and development of continuous manufacturing (CM). PAT tools and QbD elucidated the processes by which quality products can be manufactured [39–41]. They also facilitated inline and online tracking of every stage in the fabrication of these products. The use and applications of PAT tools in HME-based FDM 3D printing techniques is illustrated below. In this review, authors present and classify pharmaceutical additive manufacturing, critical HME, and FDM 3D printing parameters. We also describe the prospects and critical aspects of coupling HME and FDM 3D printing using PATs and their limitations and regulatory issues.

1.1 Additive manufacturing/3D printing process

The additive manufacturing (AM) process comprises conceptualization, 3D design, .stl file creation, G code production, 3D printing, and downstream processing and evaluation [32,42]. The 3D printing process sequence is illustrated in Figure 2. HME-based 3D printing entails formulation mixture extrusion and alignment of the feedstock product with a 3D printer to manufacture the desired 3D model [43].

The different AM techniques considered for pharmaceutical product design include inkjet printing (IP) and nozzle- and laser-based printing. IP is further classified as continuous IP

and drop-on-demand (DOD) IP. Nozzle-based printing is subdivided into fused deposition modeling/fused filament fabrication and pressure-assisted microsyringe (PAM) or semi-solid extrusion. Laser-based printing comprises stereolithography (SLA) and selective laser sintering (SLS) (Figure 3) [44–48]. HME-based FDM 3D printing has been extensively assessed as a batch process. However, HME technology could also be coupled with FDM 3D printing for continuous manufacturing (CM) [43,49,50]. Further research is warranted to screen polymers and polymer combinations and address formulation, process, and engineering parameters in order to couple HME and FDM 3D printing and generate an advanced continuous manufacturing process. As interest in advanced continuous manufacturing processes and complex dosage forms globally expands, further developments in 3D printing-based additive manufacturing are expected over the next few years.

2. Hot melt extrusion

HME is a standalone method of producing suitable filaments (feedstock) for FDM 3D printing. In HME, materials at the required temperature are pumped with rotating screws on a shaft through an extruder barrel. The mixture in the barrel is passed through a die and the extrudate forms the intended product. The HME extrudate for AM is a uniform flexible filament whose diameter depends on the type of 3D printer used [1,2]. A detailed illustration of HME process in manufacturing of filaments is shown in Figure 4.

2.1 Critical HME parameters

Material, process, and equipment attributes critically influence extrusion process performance. Active pharmaceutical ingredients (APIs) and polymers play important roles in successful HME. Thermal polymer and API properties, thermal material expansion, API and polymer miscibility, and extrudate uniformity influence this process. Feedstock quality is affected by screw configuration and speed, die shape and diameter, feed rate, temperature, pressure, and torque.

2.1.1 Material properties

2.1.1.1 Thermal properties of API and polymers: The glass transition temperature of API and polymer, regulation of melting, and degradation temperature is crucial for fabricating FDM 3D printing feedstock with consistent high quality. Tg (glass transition temperature), melting point, and material degradation are evaluated by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA).

2.1.1.2. Thermal expansion: Thermal expansion is filament (feedstock) swelling after extrusion. Thermal expansion of the polymer and API passing through the extruder die impacts feedstock suitability for FDM 3D printing. High thermal expansion of the filament increases its diameter and may hinder its processing in a 3D printer. Extrudate contraction reduces filament diameter and results in brittle feedstock that may be unfit for printing. Thus, selection of polymers or polymer blends compatible with the API is essential for feedstock manufacturing. The nature of the feedstock obtained from HME also affects 3D printing. Soft filaments may not be fed into the printer or may even clog it. Brittle filaments

may break inside the extruder. Hence, the filaments must have the appropriate flexibility/rigidity for successful batch or continuous 3D printing [51,52].

2.1.1.3. Polymer and API miscibility: Miscibility of the polymer and the API influences the surface properties of the filaments produced by HME. Immiscible API and polymers may result in rough filaments that may impede 3D printing and have heterogeneous content. Miscible API and polymer generate smooth filaments that are easily processed in 3D printers. Feedstock miscibility and nature of components can be assessed offline or inline by Fourier transform infrared spectroscopy (FTIR), Raman spectroscopy, or Fourier transform near-infrared spectroscopy [53].

2.1.1.4. Viscosity: Viscosity plays a crucial role in successful HME and 3D printing. Most polymers are thixotropic and their viscosity decreases with increasing process temperature. For smooth extrusion, a process temperature should be selected that ensures low viscosity of the formulation blend. Thermosensitive materials may degrade at high process temperatures. Thus, appropriate formulation blends are required to reduce melt viscosity and permit extrusion to be performed at lower operating temperatures. Certain API acting as plasticizers decrease torque with increasing drug load and enable further barrel temperature reductions. Melt rheology is a pre-formulation tool that predicts suitable process temperatures [54,55].

2.1.1.5. Drug load: Drug load determines the mechanical properties of the feedstock (filaments). Increasing the concentration of certain drugs has a plasticizing effect. Okwuosa et al. [56] reported that theophylline and dipyridamole plasticize PVP (Povidone) filaments and lower the PVP glass transition temperature from 93 °C to 69 °C and 73 °C, respectively. Yang et al. [57] reported that filament stiffness (load:deformation ratio) decreased with increasing ibuprofen concentration. However, other drugs make filaments brittle, render them unfit for 3D printing, and necessitate the addition of plasticizers. Sadia et al. [58] reported that Eudragit® E PO filaments are too brittle for 3D printing. Plasticizing aids HME and 3D printing by reducing melt viscosity and allowing extrusion to occur at lower processing temperatures. Thus, plasticizers improve process and filament quality and make the process suitable for drugs and materials that degrade at high temperatures. Nevertheless, compatibility among the constituents in a formulation blend is vital to stable product fabrication.

2.1.2. Process and equipment parameters—HME equipment and process parameters that influence successful extrusion and FDM 3D printing feedstock production include screw configuration, elements, and speed, die shape and size, torque, pressure, temperature, and feed rate.

2.1.2.1. Screw configuration and elements: Screw configuration, screw element type, and number of kneading zones significantly affect extrusion. There are conveying and kneading screw elements. The screw configurations and conveying and kneading element combinations vary with the API and polymer properties and are also determined by API-polymer mixture flow properties and extruder throughput. Conveying elements transport the material from the feed zone to the mixing zones and thence to the discharge point. Quality of the conveying properties of the mixing elements decreases while material residence time in

the barrel increases with increasing offset angle. Long processing material residence times affect the barrel fill levels, which in turn, increase the torque. Low offset angles result in poor mixing properties and negatively impact filament quality [59]. For successful extrusion of drug-loaded filaments, the screw configuration must be optimized.

2.1.2.2. Die shape and diameter: A circular die is often used to manufacture feedstock or filament for FDM 3D printing. The diameter of the die used for extrusion determines the type of 3D printer required. Filament diameter may vary with 3D printer model but is generally either 1.75 mm or 2.85 mm. The die diameter is set according to the nature and thermal expansion of the feedstock. Materials that tend to swell require relatively narrower die diameters than those normally used for 3D printing [51,52].

2.1.2.3. Torque and pressure: Torque is the amount of energy required to rotate the twin screws within the extruder barrel. An increase in process temperature decreases torque by reducing melt viscosity. However, process temperature must not rise above the formulant degradation temperatures. Incorporation of plasticizers may help lower melt viscosity and process temperatures. Feed rate, temperature, screw speed, and viscosity are directly or indirectly related to torque. An increase in torque may also occur as a consequence of pressure elevation during extrusion [60,61].

2.1.2.4. Process temperature: The appropriate process temperature is vital for the extrusion of stable formulations. The optimum processing temperature ensures low melt viscosity for the physical formulation mixture. In general, the process temperature is maintained at 20–30 °C below the degradation temperature. The processing material melt temperature differs from the barrel temperature. The temperature of the material inside the barrel may be high because of the mechanical shear imposed by mixing and extrusion. Plasticizers reduce melt viscosity and permit extrusion at lower temperatures. Typical plasticizers include polyethylene glycol (PEG), triethyl citrate (TEC), and poloxamers 188 and 407. The extruder barrel is divided into zones that are temperature-regulated according to the extruder [55]. The correct barrel temperature is vital to product quality.

2.1.2.5. Feed rate and screw speed: Feed rate and screw speed also critically influence extrusion. Screw speed, conveying element pitch, and feed rate are interrelated. The barrel fill level increases with feed rate, which in turn, increases torque and influences the mechanical shear generated during the process. A low screw speed increases material residence time in the extruder and affects extrudate quality. Hence, feed rate and screw speed during extrusion must be optimized to obtain feedstock suitable for 3D printing. These parameters also significantly influence extruder throughput and HME coupling to FDM 3D printing [62,63].

3. Fused Deposition Modeling (FDM) 3D printing

Fused Deposition Modeling (FDM) is a nozzle-based system requiring drug-loaded filaments. HME is the only reliable technique for drug incorporation into filaments. An alternative filament production involves soaking commercially available filaments in saturated drug solutions (impregnation) followed by filament drying and 3D printing. The

major disadvantages of this technique include solvent use and low drug loading. Skowyra et al. [47] evaluated commercially available polyvinyl alcohol (PVA) filaments charged with saturated methanolic prednisolone solutions. The drug load was 1.9% (w/w). Solvent selection was the critical step here. The solvent must solubilize the drug without altering the properties of the filament. HME is a standalone technique for producing suitable filaments for FDM 3D printing. In FDM 3D printing, the filaments are run through the gear rollers of the printer feeder head, melted in the heating zone, and extruded through the nozzle. The extruded molten mass is printed in the x, y, and z planes on the build platform. The deposited material is cooled and solidifies immediately and the next layer can be deposited [64]. The printed FDM formulations require no downstream cooling. Selection of the correct feedstock polymer plays an important role in extrusion and 3D printing. Schematic representation of FDM 3D printing process is illustrated in Figure 5.

3.1. Critical parameters of FDM 3D printing

The critical process parameters in FDM 3D printing are equipment, process, or material-specific. Equipment-specific parameters include nozzle size and number of feeder heads. Process-specific parameters include nozzle and build platform temperature, infill density, print speed and pattern, and layer height. Material-specific parameters include filament mechanical properties and surface morphology.

3.1.1. Material properties

3.1.1.1. Mechanical characteristics of feedstock: The mechanical properties of feedstock determine the suitability of filaments for FDM 3D printing. Filaments produced from HME must be able to withstand the mechanical stress that occurs during loading and printing. Filaments with poor mechanical properties may break and block the nozzle. Filament assessment before printing will save fabrication time and prevent nozzle blockage. Zhang et al. [65] used a texture analyzer to evaluate the mechanical properties of filaments manufactured by HME. Filament flexibility, brittleness, and stiffness were determined by the Repka-Zhang test and compared against commercially available poly lactic acid(PLA) filaments. Extrusion at high torque and die pressure produced stiff filaments. High polymer blend viscosity generated filaments with rough surfaces that blocked the printer nozzle. Soft filaments formed a molten mass that could not be extruded from the printer nozzle. Filaments with large breaking distance and force were compatible with the FDM 3D printer. Nasereddin et al. [66] evaluated the suitability of thermal analyzers for predicting HME filament flexibility and comparing them against commercially available filaments. The author used HME to produce filaments whose mechanical properties resembled those of commercially available filaments. All HME-generated filaments had suitable feeding and printing characteristics. Filament properties could be altered by changing the formulant ratios or selecting other excipients. Table 1 shows the characterization methods and processing window values that can help researchers design formulations and determine the suitability of filaments for FDM 3D printing.

3.1.1.2. Melt viscosity: Feedstock melt viscosity also determines the suitability of filaments for 3D printing. Formulants with high melt viscosity cannot be extruded through a 3D printer nozzle because the molten material has poor flow. The addition of plasticizers

reduces the viscosity and improves molten mass extrudability. An increase in 3D printer nozzle temperature may reduce viscosity but could also affect material degradation.

3.1.1.3. Surface morphology: Filament surface morphology determines how efficiently filaments can be processed for 3D printing. Zhang et al. [65] reported that rough or stiff filaments with high viscosity adversely affect 3D tablet printing. Chai et al. [72] revealed that hydroxypropylcellulose (HPC) filaments loaded with domperidone were smooth and successfully formed 3D-printed tablets but $BaSO_4$ incorporation resulted in rough filaments and tablets.

3.1.2. Critical process and equipment parameters—Process and equipment parameters affecting 3D printing processability include nozzle and build platform temperature, infill density, print speed and pattern, layer height, nozzle size, and number of feeder heads.

3.1.2.1. 3D printer nozzle size: Nozzle size affects filament printability in a 3D printer. Filaments 1.75 mm in diameter are generally used in FDM 3D printing. Few materials extruded as filaments, with diametric swelling characteristic feature renders them unsuitable for FDM 3D printers. Printers with customizable nozzle size can accommodate filaments with varying diameters. Printers fitted with multiple feeder heads can generate complex dosage forms and multiple filaments containing mixtures of incompatible drugs can be fabricated. A 3D printer with multiple feeders can create barrier layers around tablet cores and protect them from the gastric environment and moisture. Selection of the appropriate 3D printer influences complex dosage form production [73].

3.1.2.2. Process parameters in FDM 3D printing: Various process parameters play key roles in successful filament printing and 3D printed product quality. Alhijjaj et al. [74] evaluated the effects of FDM process parameters on polycaprolactone filaments incorporated with acetylsalicylic acid. Printing speed and nozzle temperature affected dosage form weight. Tablet weight decreased with increasing printing speed. Melt rheology changed and tablet weight increased with increasing nozzle temperature. Dosage form weight was more strongly influenced by printing speed than nozzle temperature. Melt viscosity and molten mass spread on the build platform decreased and thickness increased with decreasing nozzle temperature. Viscosity influences filament extrusion which is vital to FDM 3D printing. The viscosity of the molten filament mass plays an important role in printer nozzle extrusion. Most materials are thixotropic; their viscosity decreases with increasing temperature. Nozzle temperature must be optimized to extrude the molten mass without affecting printability. Formulant melt rheology must be thoroughly understood for extrusion-based preparations.

FDM 3D printing is flexible and can fabricate simple and complex dosage forms. Several trials must be conducted to optimize drug release from the dosage form by conventional methods. For HME and 3D printing, dosage form drug release properties may be optimized by varying the infill density and dosage form size, shape, and volume. Thakkar et al. [75] assessed the effects of infill density on ibuprofen release profiles. HPMC-AS filaments were prepared using 20% drug load and HME at 130 °C processing temperature. The tablets were FDM 3D-printed at infill densities in the range of 20–80%. For all formulations, the

dissolution rates increased with decreasing infill density. Sadia et al. [76] investigated the roles of infill density on increasing the dissolution rate of 3D printed tablets containing hydrochlorothiazide (HCT). Filaments containing HCT were prepared by HME using Eudragit® E, triethyl citrate (TEC), tricalcium phosphate (TCP), and the disintegrants Ac-Di-Sol®, Primellose®, Primojel®, Explotab®, and Polyplasdone™-XL. The 3D-printed tablets with 100% infill density slowly released the drug. However, drug release and surface area exposed to the dissolution media increased with decreasing infill density. Developing various shaped dosage forms by conventional powder compaction techniques depends on die and punch size and shape and is relatively labor-intensive. Goyanes et al. [77] developed cubic, pyramidal, cylindrical, spherical, and toroid dosage forms for 3D printing using polyvinyl alcohol (PVA) filaments loaded with paracetamol. The surface-to-volume ratio (S/V) influenced the tablet drug release profiles. FDM 3D printer can print different geometries and complex dosage forms such as controlled release [43,50,78], delayed release [79,80], orally disintegrating formulations [81], bilayered/multilayered tablets [82], chewable tablets [83], floating systems [52,72,84] and encapsulated liquid formulations [79].

3.2. Personalized patient-focused drug delivery

Collaboration between compounding pharmacies and the pharmaceutical industry would result in the development of personalized medications. FDM 3D printing could efficiently fabricate personalized patient-focused dosage forms. Further research into various polymers and the establishment of standard evaluation methods will help develop a continuous process in community pharmacies. Drug-loaded filaments could be manufactured by the pharmaceutical industry and supplied as intermediate products. Compounding pharmacies could print medications according to patient requirements. HME coupled with FDM 3D printing is an efficient and economical method of developing personalized, patient-focused drug products. Moreover, advanced HME-based FDM 3D printing could furnish drug delivery systems to remote areas in emergency situations. The critical understanding of above mentioned HME and FDM 3D printing parameters influence the establishment of HME based FDM 3D printing techniques as an advanced continuous manufacturing process.

4. Coupling HME with FDM 3D printing

Coupling HME with FDM 3D printing as a continuous manufacturing process requires real-time monitoring and control to ensure that both steps are synchronized. Recently, various spectroscopic techniques such as Raman, NIR, MIR, FTIR, and UV/VIS have been explored as PAT tools for HME. However, application of these tools in FDM 3D pharmaceutical printing is limited. PAT tools are non-destructive and provide continuous, high-throughput material screening during drug product manufacturing [85–90].

Though HME and FDM 3D printing are two separate techniques, interruption of one disrupts the other and alters the critical quality attributes (CQA) of a drug product. PAT tools rapidly and non-invasively collect and analyze data. Hence, their use could enhance the robustness and efficiency of HME coupled 3D printing as a CM technique for the fabrication of high-quality customized drug products. Integration of PAT tools with quality by design (QbD) will determine the CQA for drug products.

The CQA for final drug products manufactured by HME-coupled 3D printing include API concentration, solid state, API distribution and texture of filaments diameter, melt viscosity, mechanical properties of feedstock and 3D printing characteristics in a 3D printer. PAT tools should be applied at various points in HME-coupled 3D printing for real-time CQA monitoring and process control. Zhang et al., 2017, investigated suitability of coupling HME with FDM 3D printing techniques, where the authors made an attempt for developing extended-release formulations of acetaminophen using various grades of HPC, HPMC polymers, Eudragit L100, Soluplus, and ethylcellulose N14. Tablets manufactured by FDM 3D printing demonstrated desired extended drug release characteristics compared with tablets manufactured by direct compression [43]. Recently, Tan D. K. et al. in 2018 has reviewed the literature for the suitability of coupling HME with FDM 3D printing techniques [49]. Similarly Pereira GG et al. (2020) has discussed various polymers that are suitable for HME coupled FDM 3D printing processes [91]. These few reports available in the literature provide insights about coupling HME with FDM 3D printing and about polymers and PAT tools utilized for developing HME and FDM 3D printing as a continuous process.

4.1. In-line API quantitation and detection of spatial distribution

Polymers and APIs are exposed to high temperatures during HME. The stability of these materials at high processing temperatures must be established. To check API quality and quantity in drug products, samples must be analyzed by HPLC or UV/VIS spectroscopy. However, implementation of these analytical methods results in a time-consuming batch manufacturing process. Dadou et al. [86] recently developed and validated a QbD-based in-line PAT tool to quantitate API during HME. QbD revealed that feed rate and processing temperature influenced API stability. The authors developed a Raman-based partial least square (PLS) model to quantitate API and validate the model. QbD was integrated with the PAT model to optimize formulation and process variables and control API quality and quantity during HME. Khorasani et al. [92] used near-infrared chemical imaging (NIR-CI) plus multivariate curve resolution-alternating least squares (MCR-ALS) to predict the spatial distribution of indomethacin and polycaprolactone in HME filaments and 3D-printed solid dosage forms. The authors concluded that NIR-CI chemically maps active and inert ingredients and detects solid-state [53] changes during manufacturing. The aforementioned studies demonstrated the feasibility of coupling HME with FDM 3D printing by using appropriate validated methods.

4.2. In-line filament diameter and texture detection

Filament diameter is a CQA affecting mechanical resilience of filaments and influencing printed dosage form accuracy. Most commercial FDM 3D printers use filaments with a diameter of either 1.75 ± 0.1 mm or 2.85 ± 0.1 mm as feedstock. Production of filaments with suitable diameters is necessary for successful 3D printing [71]. An in-line PAT tool to determine HME filament diameter reduces process time and keeps it continuous. Korte et al. [71] used a laser-based diameter measurement module (Laser 2025 T, Sikora, Bremen, Germany) at the end of the conveyor belt for inline filament size determination at 1 Hz. The authors used design of experiments (DoE) to analyze the effects of feed rate, screw speed, extrusion temperature, and conveyor belt speed on filament diameter. Filament diameter

depended on the feed rate and conveyor belt speed. Ponsar et al. [93] also used the Laser 2025 T (Sikora, Bremen, Germany) as an in-line PAT tool for determining filament diameter. Specific feed loads (SFL) > 0.04 produced filaments with acceptable diameters and enabled the production of high-quality dosage forms. Inputs from the proposed PAT tools will facilitate to control feed rate, screw RPM, extrusion temperature, and conveyor belt speed to obtain filaments with the desired diameter.

Filament texture affects printability. Rough filaments create friction between gears during feeding. Changes in formulation composition may make filaments smooth [43]. In-line high-speed cameras can monitor filament surfaces. Hagrasy et al. [94] used an in-line 3D high-speed camera (Eyecon™; Horiba Ltd., Kyoto, Japan) to monitor real-time process control for twin screw melt granulation. In HME-coupled 3D printing, cameras could monitor filament texture during production and keep the process continuous. They could also detect unintentional formulation changes and ensure filament texture consistency.

4.3. PAT tools for pharmaceutical 3D printing

PAT tools have been successfully utilized in other applications. They could also be used to facilitate HME-based FDM 3D printing, monitor, and establish CM, and fabricate the intended drug product. Yang et al. [95] used acoustic emission (AE) to monitor filament breakage in FDM 3D printing. They claimed that the same technique can assess nozzle clogging, geometrical misalignments, and manufacturing failure. Li et al. [96] used vibrational sensors to detect machine failure and product defects. They used least squares support vector machine (LS-SVM) and back-propagation neural network (BPNN) algorithms and returned a detection accuracy of > 90%. Coogan et al. [95] designed a modified FDM 3D printer head nozzle and incorporated a thermocouple and pressure transducer to monitor in-line melt temperature and filament rheology. They reported excellent agreement between in-line and off-line rheometry and proposed that the in-line rheometer they developed could be a PAT tool for real-time monitoring and process control. Tlegenov et al. [97] used a dynamic model to monitor nozzle clogging in FDM 3D printers. The aforementioned studies demonstrated the feasibility of PAT tools in the establishment of HME-coupled 3D printing as a CM technique. They also showed that interruptions in manufacturing can be detected in real time so that the process and material parameters may be effectively controlled, and quality products can be continuously generated.

The various PAT tools are investigated for HME and FDM 3D printing techniques. Table 2 summarizes the various PAT tools that could be applied towards HME and 3D printing.

4.4. Critical aspects of successful HME coupling to FDM 3D printing

Integration of HME and 3D printing requires optimal startup and shutdown procedures, material traceability, residence time distribution (RTD), and analytical methods assuring high-quality pharmaceutical products. Combining HME and 3D printing could produce safe, efficient, and cost-effective dosage forms. Using PAT tools for real-time monitoring is a viable option for designing CM techniques. Control strategies for integrated continuous manufacturing are necessary for robust pharmaceutical quality systems. Figure 6 proposes

the HME-coupled FDM 3D printing model. Critical parameters for implementation of HME-coupled FDM 3D printing include the following.

4.4.1. PAT tool selection—Appropriate PAT tools must be identified for HME and FDM 3D printing in order to couple these techniques as a continuous manufacturing process. Various PAT tools were investigated for HME and FDM 3D printing. NIR/Raman spectroscopy elucidates the nature of the materials used in HME and high-definition cameras observe the feedstock. Filament diameter must be measured and rheometry and NIR/Raman spectroscopy must be implemented in FDM 3D printing. These PATs must be integrated into HME-coupled FDM 3D printing for continuous manufacturing.

4.4.2. PAT tool alignment at appropriate locations—The correct PAT tool location is imperative for the accurate evaluation of the feedstock, process parameters, and material traceability in HME and FDM 3D printing. Further, appropriate locations need to be investigated and established for continuous manufacturing of quality product.

4.4.3. Synchronization of HME output to 3D printing speed—Filament extrusion from the HME die must be synchronized with 3D printing to prevent filament breakage during high relative HME output or incompletely printed dosage forms during low relative HME output. As a rule, FDM 3D printing speed is kept low and a filament roller is interposed between the HME and the 3D printer to collect excess filament.

4.4.4. Integration of HME and 3D printing—Integration of HME and FDM 3D printing requires optimal startup and shutdown procedures to assess product traceability. Filament coolers, collectors, and rollers along the process chain are also necessary to establish a CM technique. The various material, process and equipment related attributes involved in HME and FDM 3D printing process are represented in Figure 7.

5. Limitations and regulatory considerations

Continuous manufacturing processes such as HME-coupled 3D printing require the operation of equipment for extended periods of time to assess their robustness. To this end, it is necessary to set up control systems that identify disturbances, nonlinearities, constraints, and uncertainties in each operation and assess the risk of failure or delay in the process. Disturbance studies on CM systems determine manufacturing process robustness. HME and FDM 3D printing involve the exposure of APIs, and other excipients to high temperatures. Some of these materials are thermolabile and cannot, therefore, be used with these techniques. There are comparatively few available pharmaceutical-grade polymers with suitable rheological and mechanical characteristics for the production of 3D printing feedstock. Hence, identification of suitable polymers and polymer properties require further analysis to broaden their applications. Loading large quantities of drug into polymers with suitable characteristics for FDM 3D printing alters the mechanical and rheological properties of filaments. Thus, it is arduous to produce feedstock filaments with large drug loads. Engineering and monitoring HME-coupled 3D printing for continuous drug product manufacturing is an intensive process because changes in even a single process parameter can interrupt the entire production cycle [100].

The manufacture of 3D-printed medical devices such as cranial implants, external prosthetics, and dental restorations are regulated by the Center for Devices and Radiological Health (CDRH). However, there are no published regulatory guidelines for other 3D-printed products [101,102]. In 2016, draft guidelines for technical considerations of additive manufactured devices was issued by the FDA. Nevertheless, public feedback on it has not yet been compiled. As with other pharmaceutical manufacturing equipment, 3D printers and related devices used in AM must comply with CFR 21 Part 211. Pharmaceutical companies are reluctant to use 3D printing technology because of the limited availability of cGMP-compliant 3D printers [103]. In 2014, the FDA convened an AM working group comprising all stakeholders from academia and industry, field experts, and early adopting clinicians. They discussed various challenges and best practices that must be implemented in AM of medical products. The CDRH and other centers closely trace the provision of innovative, effective, and safe drug products that have been generated by AM or 3D printing technology [104].

6. Conclusion

Over the past few years, numerous studies have explored the potential use of HME in various drug delivery applications. The recent development of complex patient-focused dosage forms has interested regulatory bodies. Academic and industrial researchers have investigated HME-based FDM 3D printing for dosage form fabrication. This process could be an efficient and economical method for the development of patient-focused drug products. FDM 3D printing could be extended towards the production of novel drug delivery systems. The use of PAT tools in HME and FDM 3D printing can transform these innovative technologies into CM processes. However, progress in the development of HME and FDM 3D printing as an advanced batch process is limited. To unlock the potential of these techniques, research is warranted in the design and implementation of new analytical and integration methods to develop a robust manufacturing setup. Appropriate controls must also be established to integrate and synchronize HME and FDM 3D printing as a CM technique. These innovations might advance drug delivery technologies and expand and evolve the pharmaceutical industry.

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Abbreviations:

3D	three-dimensional
AE	acoustic emission
AM	additive manufacturing
API	active pharmaceutical ingredients

BPNN	back-propagation neural network
CDRH	Center for Devices and Radiological Health
CM	continuous manufacturing
CQA	critical quality attributes
DOD	drop-on-demand
DOE	design of experiments
DSC	differential scanning calorimetry
FDM	fused deposition modelling
FFF	fused filament fabrication
FTIR	Fourier transform infrared spectroscopy
HCT	hydrochlorothiazide
HME	hot melt extrusion
HPC	hydroxypropylcellulose
HPMC-AS	hydroxypropylmethylcellulose acetate succinate
IP	inkjet printing
LS-SVM	least squares support vector machine
MCR-ALS	multivariate curve resolution-alternating least squares
NFAH	nitrofurantoin anhydrate
NFMH	nitrofurantoin monohydrate
NIR-CI	near-infrared chemical imaging
NLC	nanostructured lipid carriers
PAM	pressure-assisted microsyringe
PAT	process analytical technology
PLA	polylactide
PLS	partial least square
PVA	polyvinyl alcohol
QbD	quality by design
RTD	residence time distribution
SFL	specific feed load

SLA	stereolithography
SLS	selective laser sintering
TA	thermal analyser
TEC	triethyl citrate
TCP	tricalcium phosphate
TGA	thermogravimetric analysis
USFDA	United States Food and Drug Administration

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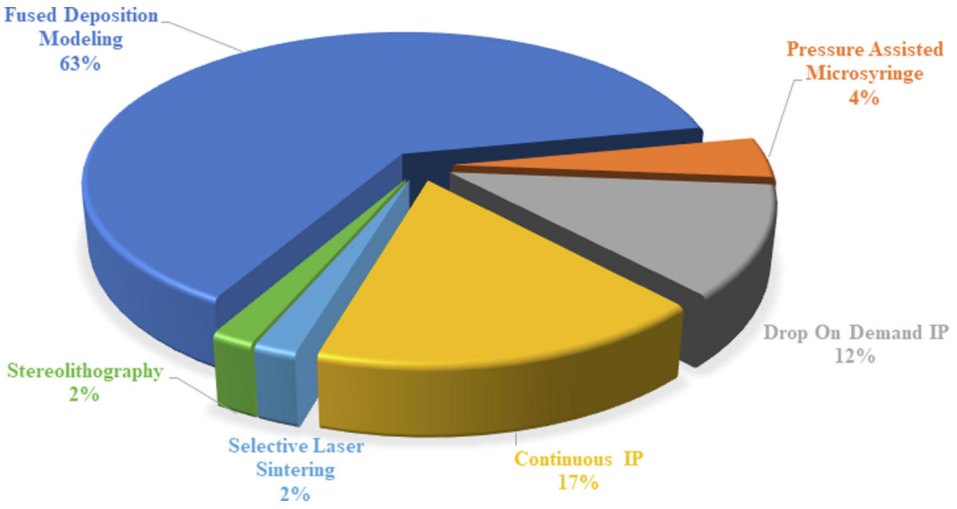

Figure 1.

Pie chart demonstrating the volume of research publications on various pharmaceutical 3D printing techniques over the last 5 years (Pubmed) IP- Inkjet Printing

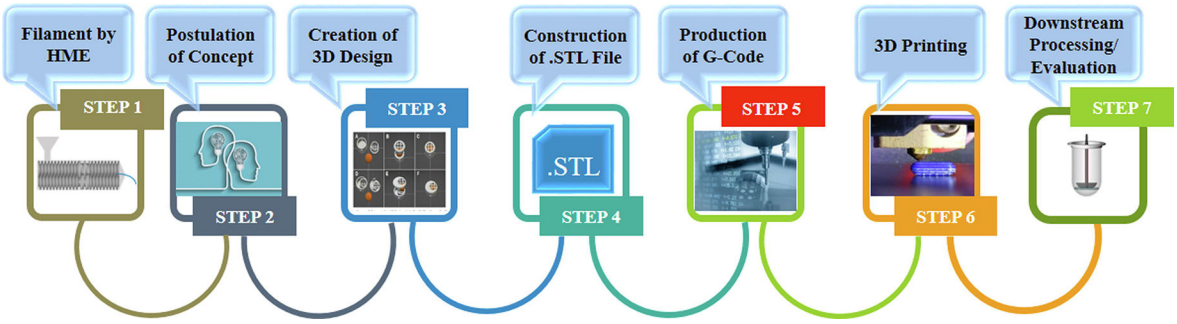

Figure 2.
Additive manufacturing process flow

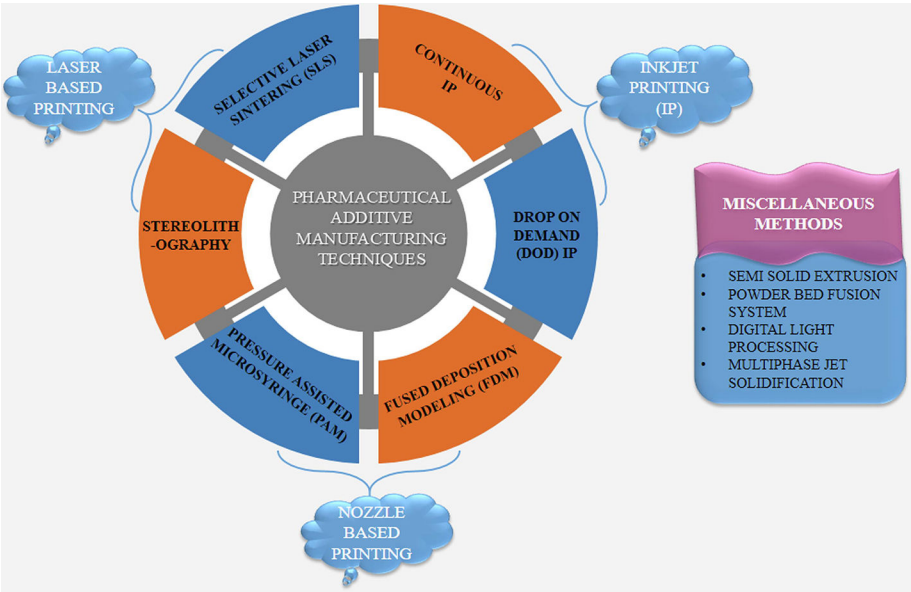

Figure 3.
Pharmaceutical 3D printing processes

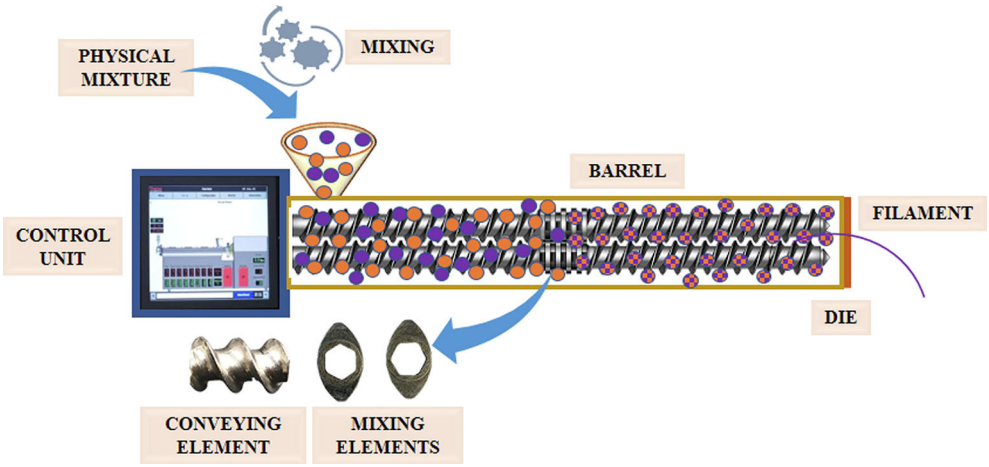

Figure 4.
HME filament manufacture

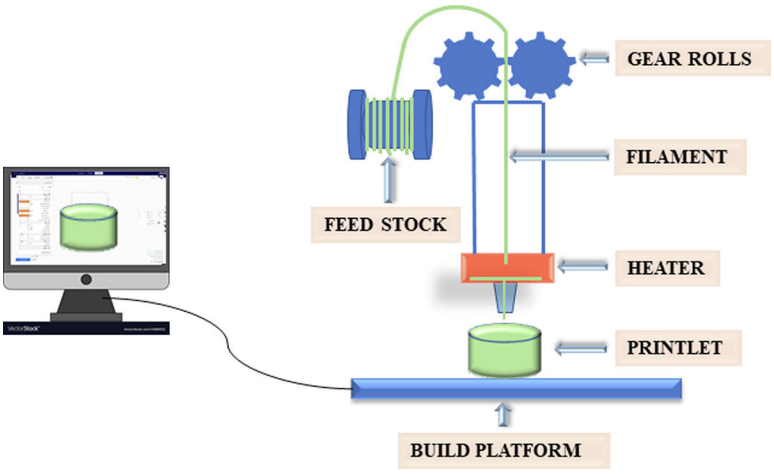

Figure 5.
FDM 3D printing

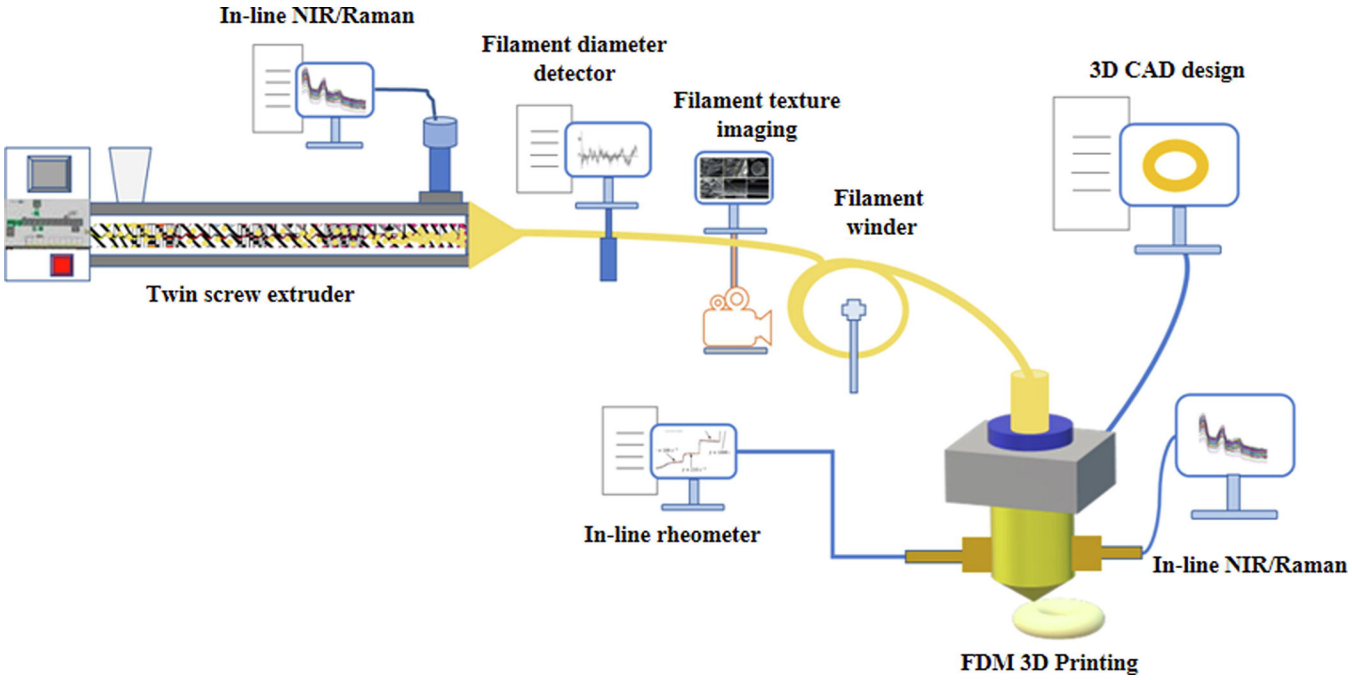

Figure 6.
Coupling HME and FDM 3D printing with PAT tools

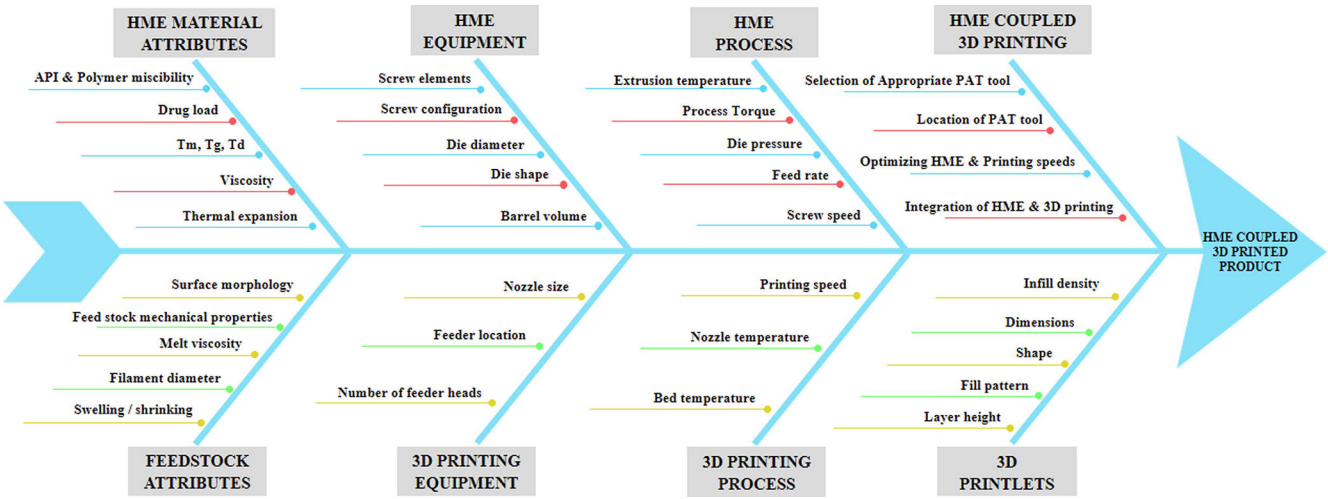

Figure 7.
Material, process and equipment related attributes in HME and FDM 3D printing

Table 1.

Characterization methods to assess the suitability of feedstock filaments for FDM 3D printing

Characterization method	Parameters studied	Printer type	Processing window	Reference
Three-point bend test	Brittleness	Prusa i3	Breaking stress > 2,941 g/mm^2, breaking distance > 1 mm	[43]
Repka-Zhang test	Brittleness/stiffness	Prusa i3	Stiffness > 20, 758 g/mm^2	[65]
Stiffness test	Toughness	Prusa i3	Toughness > 80 g/mm^2	[67]
Hooke's law	Constant "k"	Prusa i3	"K" value > 40 g/mm^3	[68]
FDM feedability testing	Flexibility	Makerbot® Replicator 2X	Correlation score > 0.5	[66]
Dry spaghetti fracturability test	Flexibility	Makerbot® Replicator 2X	N/A	[69]
Dynamic mechanical analysis	Brittleness	Makerbot® Replicator 2X	Brittleness > 0.0002%Pa	[70]
Tensile test and three-point bend test	Young's modulus and distance at break	XXL Pro, Prodim International	Young's modulus > 300 N/mm^2; distance at break > 1.125 mm	[71]

Table 2.

Potential PAT tools for HME and 3D printing

PAT tool	Location	Applications	Advantages	Reference
Raman spectroscopy	Extruder barrel or die	API quantitation	API degradation can be detected in-line	[88]
NIR-CI	Extruder die	Chemical mapping of API and excipients	Uniformity of API and excipients in extrudates can be detected	[91]
High speed camera	Between extruder and 3D printer	Filament texture analysis	Ensures smooth feeding of filaments into 3D printer	[93]
Laser-based diameter measurement module	Between extruder and 3D printer	Filament diameter detection	Improves dosing accuracy and mechanical resilience of filaments	[71,92]
Acoustic emission technique	3D Printer print head	Filament breakage monitoring	Avoids interruptions in printing	[97]
In-line rheometer	3D Printer nozzle	Viscosity measurement	Avoids printer nozzle clogging	[97]
Vibrational sensor-based monitoring	3D Printer print head	Detects machine failure and product quality defects	High-quality drug products can be generated	[95]
Heterogeneous sensor-based monitoring	3D Printer print head	Detects drifts in printing process	Prevents fabrication of non-uniform drug products	[98]