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A review of hot melt extrusion paired fused deposition modeling three-dimensional printing for developing patient centric dosage forms

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Abstract

In recent years, the demand for developing patient-centric dosage forms is increasing enormously with the increasing patient population. Much research is ongoing exploring various additive manufacturing techniques for developing pharmaceutical medications. Poor solubility of drug substances and underdeveloped manufacturing strategies are majorly affecting the pharmaceutical industry's revenue. Developing intravenous dosage forms for drug substances with poor solubility will affect the revenue of the pharmaceutical industries. Thus, improving solubility remains to be the major prerequisite for the developmental scientist. In addition to improving solubility, establishing a robust manufacturing process with commercial viability is also essential. In recent years hot melt extrusion (HME) has been most widely investigated for developing amorphous solid dispersions (ASDs) over other techniques such as spray drying and Kinetisol®. The process of HME can be coupled with the fused deposition modeling (FDM) three-dimensional (3D) printing technique which is capable of fabricating on-demand patient-centric dosage forms. A continuous manufacturing line can be established by painting HME and FDM 3D printing processes. The quality of the product can be controlled and monitored by employing suitable process analytical technology (PAT) tools. Though the process of the HME-paired FDM 3D printing process has resulted in various advantages compared to the conventional manufacturing process, still many limitations, such as the limited number of polymers, reproducibility, and stability, need to be addressed.

Keywords: Hot melt extrusion; Fused deposition modeling; Amorphous solid dispersion; Patient-centric dosage forms; Continuous manufacturing; Process analytical technology

1. Introduction

In today's world, the poor solubility of drug substances is one of the significant issues that is haunting the pharmaceutical industry and impacting its revenue. The demand for pharmaceutical medications is increasing rapidly with an increasing patient population[1–3]. The pharmaceutical industries continuously fail to meet market demands due to the poor solubility of drug substances and underdeveloped manufacturing technologies. Around 70-80% of the new chemical entities within the developmental pipeline are claimed to be poorly soluble, affecting oral bioavailability. The conventional manufacturing strategies, such as high shear granulation, roller compaction, and fluid bed granulation, are limited to batch processing. In addition, the conventional manufacturing process involves several unit operations, which are time-consuming. Following the manufacturing process, the finished drug product requires complete testing to ensure the product is safe for human administration, which delays the product from getting into the market. Among various routes of administration, the oral route is the most preferred due to its easy administration, low cost, and self-administration[4–6]. Within various oral medications such as solids (tablets, capsules) and liquid (solutions, suspensions) dosage forms, tablets and capsules are most preferred attributing to low manufacturing, packaging, and

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transportation cost. However, any drug substance administered orally should dissolve and present in solution form for absorption into the blood circulation. As mentioned earlier, the poor solubility of drug substances limits the manufacturing of oral solid dosage forms. Thus, based on the above facts, improving solubility and establishing a robust continuous manufacturing process is the primary prerequisite for developmental scientists. In recent years, continuous manufacturing has attracted people from various avenues of the pharmaceutical sector, including regulatory bodies. Within continuous manufacturing, the batch size is not limited by the size of manufacturing equipment. A small-scale continuous manufacturing line can also be utilized for commercial-scale manufacturing where the feed time of material can be increased[7–10]. Employing the developmental scale instrument to manufacture commercials will prevent scaleup-related issues and save time and capital for the pharmaceutical industries. In fact, within continuous manufacturing, the quality of products can be continuously monitored and controlled by mounting suitable process analytical technology (PAT) tools[11, 12]. Any discrepancies triggered during the continuous run do not require quarantine of the entire batch. A part of the affected batch can be destroyed, which saves the unfed material for usage. Transforming from batch manufacturing to continuous manufacturing has several advantages in terms of manufacturing time, quality of product, and investment.

For the last three decades, various approaches such as amorphous solid dispersion, cocrystals, co-amorphous systems, pharmaceutical salts, lipid-based formulations, solid crystal suspensions, pH modification, and cyclodextrin complexation have been investigated for improving the solubility of drug substances by various researchers [13–15]. Among the various approaches, amorphous solid dispersions (ASDs) have gained a tremendous response for improving solubility. Within ASDs, the drug is dissolved and dispersed in a molecular state within a crystalline or amorphous polymeric carrier[16–20]. The molecularly dispersed drug improves wetting properties, resulting in improved solubility. Earlier the ASDs were manufactured either by conventional melt techniques or by solvent evaporation using a rotaflash evaporator. However, the conventional manufacturing strategies have limited the advancement of ASDs development, attributing to the difficulty in scaleup of the process to the commercial scale[21–24]. Recently, novel manufacturing strategies such as hot melt extrusion (HME), spray drying, electrospinning, and Kinetisol are being investigated to develop ASDs.

Among various novel approaches, HME has gained the interest of researchers from academia, industries, and regulatory bodies attributing to its various advantages[25]. The HME is a single-step thermal manufacturing process and utilizes no solvent making it suitable for continuous manufacturing processes[26–29]. This review article mainly focuses on the detailed note of the HME process, instrumentation, and downstream processing of the extruded filaments or extrudates. In addition, a small note on the advantages and limitations of pairing the HME process with the additive manufacturing process is also discussed.

2. Hot melt extrusion

In the early 1930s, the HME was originally employed in the plastic, rubber, and food industries. During the 1980s, the suitability of HME for developing pharmaceutical medications was investigated for the first time. HME is well known for developing various formulations, among which ASDs have gained a tremendous response. Other formulations developed using HME include cocrystals, coamorphous systems, pharmaceutical salts, cyclodextrin complexation, and solid crystal suspensions[30–34]. A single piece of the instrument can be employed for various applications, resulting in a revolutionary achievement within the pharmaceutical sector.

The process of HME involves a controlled/metered feeding of a physical mixture consisting of drug, polymer, and any additive (if required) into the feed zone of the heated barrel. The barrel consists of enclosed co-rotating or counter-rotating screws that convey the material across the barrel and between the mixing zones. The screw configuration mainly consists of a combination of conveying and mixing elements. The main function of the conveying elements is to convey the materials with no mixing property[35–38]. A set of mixing elements constitutes a mixing zone. The mixing elements impart distributive and dispersive mixing onto the processing material and have no conveying property. The mixing elements can be configured at 0, 30, 60, and 90 degrees offset angles. With increasing offset angle, the amount of mechanical shear imposed on the processing material and the residence time of the material inside the extruder barrel will also increase. During the process of HME, the material gets exposed to thermal and mechanical shear. The number of elements and offset angle of the mixing zones mainly depend on the melt viscosity of the processing material. The mixing zones can be customized as required depending on the amount of shear that needs to be imparted onto the processing material[39–45]. Apart from the conveying and mixing elements, the other elements include comb mixing, cutter element, and narrow-toothed mixing elements, which have not been investigated for developing ASDs. The molten formulation material inside the extruder barrel is conveyed and pumped outside the barrel as cylindrical filaments through a die connected at the discharge point. The collected filaments/extrudates can be subjected to various

downstream processing based on the type of dosage form being developed. The downstream processing of the extrudates, along with the potential challenges, are further discussed below.

The major process parameters involved in the process of HME include screw speed, feed rate, barrel temperature, process torque, die pressure, and melt temperature. The process parameters play an important role in successful extrusion. Knowledge of all the process parameters is required to develop a robust manufacturing process since adjusting one process parameter alone requires the adjustment of other dependent parameters[46, 47]. For instance, an increase in the feed rate also requires the screw speed to be increased to maintain uniform barrel fill levels and process torque conditions. The HME can also be employed for performing granulations called "twin screw granulation." The die needs to be disconnected for the granulation process. Based on the physical state of the formulation components, the twin screw granulation is categorized as twin screw melt granulation (TSMG), twin screw dry granulation (TSDG), and twin screw wet granulation (TSWG). In TSMG, the process is carried at a temperature greater than the melting point of the binder, whereas in TSWG, the process is carried at a temperature below the melting point or the glass transition of the binder. In the TSWG process, the binder solution is sprayed onto the processing material using an external peristaltic pump[48–53]. The process's scaleup remains simple since the small-scale extruder employed for early development studies can also be utilized to manufacture commercial products by increasing the processing time. The product quality can also be monitored continuously by mounting suitable process analytical technology tools (PAT). This HME process has gained tremendous recognition within the pharmaceutical industry. A schematic representation of HME is shown in Figure 1.

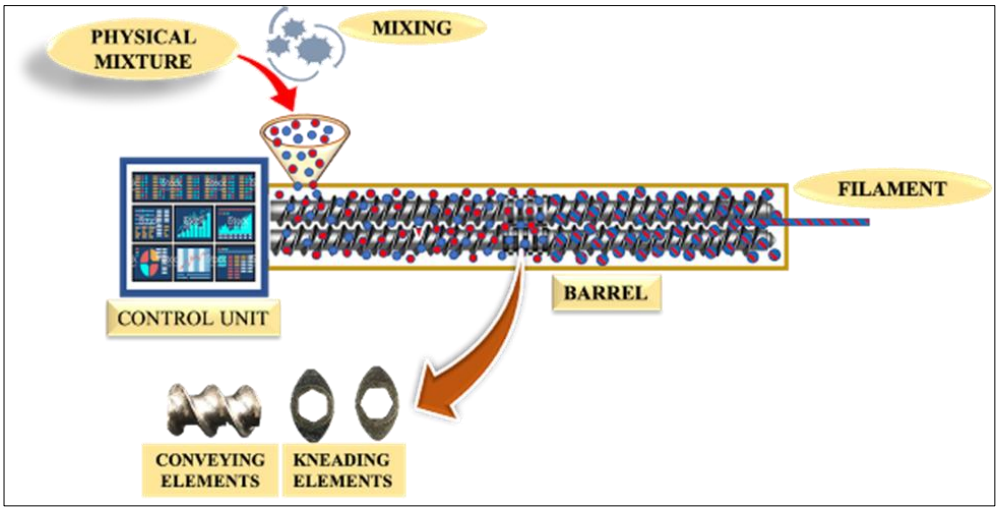

Figure 1 A schematic representation of hot melt extruder

3. Evolution of HME

As mentioned, HME was initially employed in the plastic and rubber industries to melt and extrude the product. The earlier version of HME is the RAM extruder. Initially, RAM extruders were introduced for developing pharmaceutical medications. The instrumentation of the RAM extruder consists of a cylindrical barrel with a piston. The material loaded into the barrel is melted and extruded outside the barrel using the piston by applying an external energy source. However, the residence of material inside the barrel is comparatively high, resulting in the degradation of the material. In addition to the degradation, the formulations extruded using a RAM extruder have resulted in a non-homogeneous distribution attributing to the absence of mixing property. Later the RAM extruders were replaced with single screw extruders (SSE) with predesigned mixing zones. Implementing a single screw extruder has improved the mixing efficiency but the longer residence time of the material inside the barrel remained unaddressed[54, 55]. To address the challenges of poor mixing and residence time, the SSE was replaced with a newer version of twin screw extruders (TSE). The implementation of TSE has improved the material's mixing property and residence time. In terms of homogeneity, the quality of formulations developed by TSE is superior to that developed by SSE and RAM technologies. The implementation of TSE has bought a revolutionary change in hot melt extrusion since various advancements related to instrumentation and screw configuration have been achieved. The screw configuration within the TSE can be customized, and the mixing zones can be arranged as required depending on the melt rheology of the formulation components. The rotation of screws inside the barrel can be either co-rotating or counter-rotating. Counter rotation of screws imparts relatively higher amounts of shear onto the processing material and is beneficial for the extruders with

no mixing zones. The counter-rotating screw configuration is unsuitable for highly viscous materials and materials sensitive to mechanical stress. The screw configuration can be majorly divided into self-cleansing and non-self-cleansing. Within the self-cleansing type of screw configuration, the flight of one screw overlaps with the pitch of the other screw, thereby preventing the longer exposure of the materials to thermal energy[56, 57]. In recent years, multiple extruders have been brought together and connected to a single die for the extrusion of multiple-layer films or for developing medical devices. Implementing multiple extruder technology will provide an advanced platform for developing fixed-dose combination products with multiple layers with incompatible drugs. In addition, the technology of multiple extruders will also be suitable for developing buccal films with backing membranes since the release of drugs from the films has to be unidirectional. The advancement in the instrumentation of TSE has also provided the flexibility to employ process analytical technology tools (PAT) for monitoring and controlling the drug's physical state and the formulation's quality. Among various PAT tools, near-infrared (NIR) and Raman spectroscopy have been most widely investigated in monitoring and controlling the quality of the products[58, 59]. The NIR is mainly employed for monitoring the uniform distribution of the activities within the formulations. In contrast, Raman spectroscopy was employed for monitoring the drug crystallinity, which plays an important role in developing ASDs.

4. Downstream processing of HME filaments

Once the filaments come out of the HME, they cool down and become either brittle or elastic, depending on the type of polymers used. Once the filaments cool down, they are sent downstream to processing to manufacture tablets. The most common techniques for downstream processing are direct compression, roller compaction, and FDM-3D printing. In the case of direct compression, the filaments are initially cryo-milled and sieved to get the desired mean particle size and size distribution. Traditional mills are not suitable for HME filaments since they are elastic in nature. In the case of brittle filaments, the milled particles are highly static, resulting in handling issues during downstream processing[60–62]. The milled filaments are blended with extra granular excipients like disintegrants, lubricants, etc., and then sent for direct compression. If the milled filaments have poor compressibility, in that case, roller compaction will be performed using highly compressible excipients. While this is the most commonly used approach for downstream processing of HME, it is often challenging and results in a high pill burden. Recently, injection molding and FDM-3D printing have attracted huge attention as an alternative to traditional downstream processing techniques. In injection molding, the HME filaments are directly molded into a tablet with a predefined size and shape. HME with injection molding is still in the development phase and requires much research to make the process commercially viable. On the other hand, FDM-3D printing gained popularity among many research groups as a potential downstream processing of HME with commercial viability. In FDM-3D printing, the HME filaments can be directly printed into desired pill size and shape to achieve the required release profile. The total number of unit operations involved in FDM-3D printing is significantly lower than direct compression or roller compaction, making it the most economical manufacturing technique with the potential for continuous manufacturing. Since no additional excipients are required for FDM-3D printing, the total pill size will be low, making it a suitable technique for high-drug-loaded HME formulations[63, 64]. A schematic representation of downstream processing of extruded filaments is shown in Figure 2.

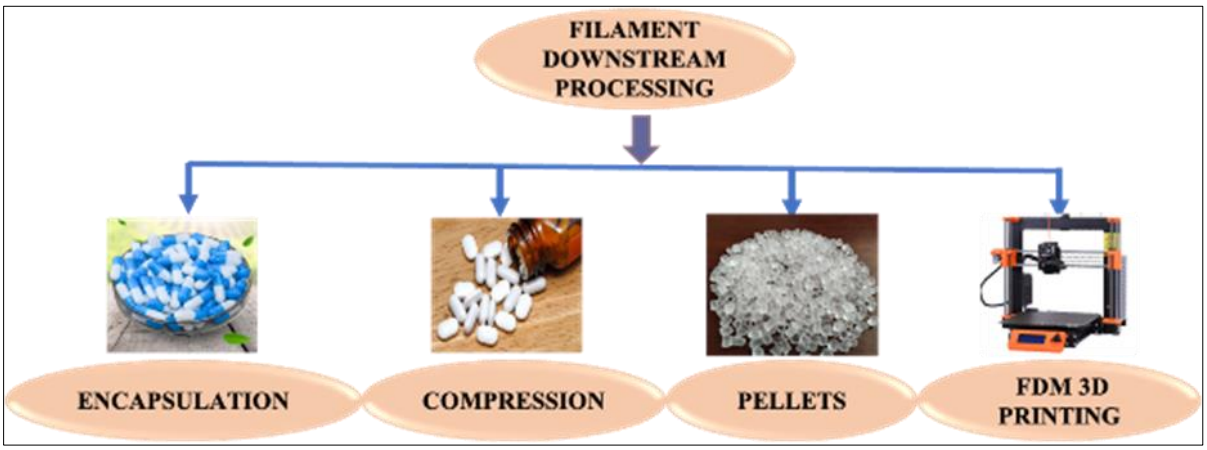

Figure 2 Downstream processing of filaments developed by hot melt extrusion process

5. Fused deposition modeling 3D printing

Fused deposition modeling (FDM) three-dimensional (3D) printing has gained tremendous recognition among other types of additive manufacturing techniques. FDM 3D printing is cost-effective, user-friendly, portable, and easy to operate compared to other 3D printing techniques. The process of FDM 3D printing requires a continuous feeding of drug-loaded filaments. The filament is directed to the heating zone through a narrow gap between the toothed gear rollers. The filament is melted in the heating zone, and the molten mass is extruded through a small orifice onto the build platform where the 3D object is formed[65, 66]. The filament inside the printer head acts as a piston to extrude the molten mass outside the nozzle. The mechanical properties, dimensions, melt rheology, and surface morphology of filaments play an important role in the successful fabrication of dosage forms. The various process parameters involved in the FDM 3D printing process include printing speed, cooling fan speed, printing nozzle temperature, and build platform temperature. A schematic representation of FDM 3D printer is shown in Figure 3. Various sequences of steps involved in the process of FDM 3D printing are described below:

- Generation of drug-loaded polymeric filaments by hot melt extrusion
- Creation of a 3D digital design
- Loading of 3D design file into the printer software
- Heating of FDM 3D printer and loading of drug-loaded filament.
- Melting and deposition of molten filament onto the build platform.
- Curing and ejection of 3D objects.

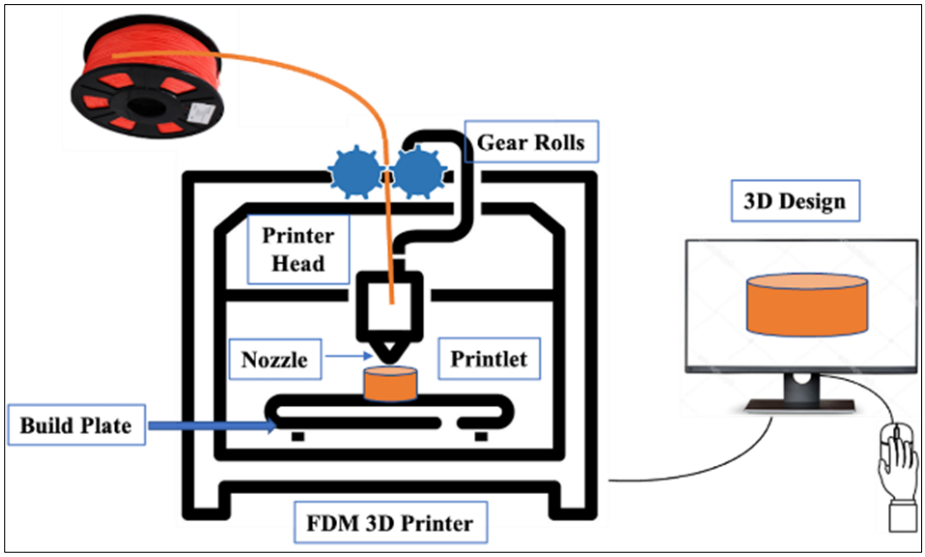

Figure 3 A schematic representation of fused deposition modeling 3D printer

6. Various critical filament properties

6.1. Mechanical Properties

During the process of FDM 3D printing, the filament experiences varied degrees of mechanical stress. Thus, the mechanical properties of filament play an important role. Filament with brittle nature gets damaged, and the flexible filaments get coiled inside the printer head, interrupting the printing process. Thus to be suitable for the FDM 3D printing process, a balance must be maintained between brittleness and flexibility. Similarly, the dimensions of the filament also play an important role.

6.2. Filament dimensions

The major component of the filament is a polymer. The polymer chains relax soon after extruding from the die of the extruder and result in the swelling of the filament, which is referred to as “Die Swell” behavior. Each type of FDM 3D printer can accommodate a suitable diameter of the filament. Most of the FDM 3D printers available in the market can accommodate filaments with either 1.75 mm or 2.50 mm diameters. Polymers experiencing die-swell behavior and resulting in a filament diameter greater than the dimensions the printer can accommodate are considered unsuitable

for the FDM 3D printing process[67, 68]. Thus, utmost care must be taken while screening polymers and selecting the appropriate die size for the extrusion process.

6.2.1. Melt rheology

FDM 3D printing is a thermal process that involves the melting and extrusion of drug-loaded filaments. Most polymers exhibit thixotropic behavior where the melting viscosity of the processing materials will decrease with increasing temperature. Thus understanding the melt rheology of the formulation components concerning the temperature provides useful information for developing the process for HME and FDM 3D printing. Filaments with high melt viscosity require either higher pressure levels for extruding the mass outside the printer nozzle or higher processing temperatures to reduce the melt viscosity. Since the filament acts as a piston to extrude the molten mass outside the extruder, the brittle filaments are unsuitable for extruding highly viscous materials, which might damage the filament[69, 70]. Thus increasing the temperature to reduce the melt viscosity can be investigated however, the degradation temperature of the formulation components needs to be taken into consideration. Increasing temperature reduces the melt viscosity, but the flow of the material from the printer nozzle and the drying time must also be considered. Materials which exhibit very low viscous properties are not suitable for the FDM 3D printing process since the structure of the 3D printed object might be affected, attributing to the low viscosity.

6.2.2. Surface morphology

The surface morphology of the filament plays an essential role in successfully printing the dosage forms. The extrusion process parameters affect the quality of the filament. The filaments with rough surface morphology are unsuitable for FDM 3D printers since they get damaged within the printer head. The process temperature, screw speed, and feed rate of the HME process majorly affect the quality of the filament. Feeding material into the extruder barrel at higher feed rates and higher screw speeds will provide shorter residence time for the material inside the barrel, providing insufficient time to melt and distribute homogeneously. The presence of undissolved particles or unmelted particles will affect the quality of the filaments resulting in rough surface morphology. The recrystallization of the drug on the surface of the ASD filaments will also result in rough surface morphology[71, 72]. Extrusion of formulation components at a lower temperature than the glass transition temperature will carry the material in an undissolved state, leading to rough surface morphology. Thus the process of HME needs to be optimized for developing filaments with suitable quality for the FDM 3D printing process. In addition, the surface morphology of the extrudates obtained from the nozzle of the FDM 3D printer affects the quality and resolution of the 3D object. Thus, suitable printing temperature and speed need to be employed, providing sufficient time for the filament to melt entirely before being extruded onto the build platform.

7. Coupling of HME and FDM 3D printing process

In today's world, with the increasing patient population, the demand for pharmaceutical medications is increasing enormously. However, attributing to the underdeveloped batch manufacturing process, the pharmaceutical industries are failing to meet the market demands. The batch manufacturing process involves a series of unit operations, making the process to be time-consuming. The scaleup of the batch manufacturing process requires a lot of large-scale equipment involving colossal capital and time for optimizing the process for each unit operation. Any unexpected discrepancies within the process will affect the quality of entire batch materials within the batch manufacturing process. The batch manufacturing process involves testing various in-process or intermediate products to ensure the quality of the product[73–75]. The finished product manufactured by batch manufacturing requires complete testing and release of the product from the quarantine before being distributed into the market. Continuous manufacturing processes can save both time and investment for the pharmaceutical industries with assured product quality. The drug product quality can be continuously monitored within the continuous manufacturing process by employing a suitable process analytical technology tool (PAT)[76, 77]. Any discrepancy, if noticed during the manufacturing process, will automatically discontinue, thereby saving the unprocessed physical mixture from being discarded. Various PAT tools have been investigated to monitor the impurities, uniformity of drug distribution, and physical state of the drug within the formulation. Employing PAT tools will reduce the number of destructive and non-destructive tests, thereby reducing the time for getting the product into the market soon after manufacturing.

Considering the facts associated with the continuous manufacturing process, pairing HME and FDM 3D printing is advantageous for developing ASD-based digital pills. Manufacturing solid oral dosage forms by conventional manufacturing techniques such as high-shear wet granulation, roller compaction, fluid bed granulation, and direct compression requires free-flowing running powder for developing capsules and tablets. In addition, the final lubricated blend should also possess good compressibility properties for developing tablet formulations. Most drug substances exhibit poor flow and compressibility, requiring adapting the granulation process for developing the dosage forms[75,

78]. The granulation process involves a series of manufacturing steps compared with the direct compression process. The direct compression process also results in the capping and lamination of tablets attributed to the entrapped air within the final lubricated blend. Employing the HME-paired FDM 3D printing process will overcome all of the limitations associated with conventional manufacturing techniques. However, the physical mixtures of drug-polymer result in poor flow behavior, a homogeneous and uniform feeding of material into the extruder barrel can be achieved by employing loss in weight feeders. The extruded filaments of the drug can be directly utilized without any intermediate processing steps for the printing dosage forms. A single drug-loaded filament can be utilized for developing dosage forms with multiple strengths. Depending on the state of disease, age, and sex of the patient population, the release profiles can also be adjusted by altering the infill density of the tablets. Even the filaments can be directly sent to the pharmacies to fabricate on-demand medications for patients experiencing emergency conditions[67, 79, 80]. Thus, the HME and FDM 3D printing process has potential commercial viability for developing on-demand, patient-centric dosage forms. A schematic representation of pairing HME and FDM 3D printer is shown in Figure 4.

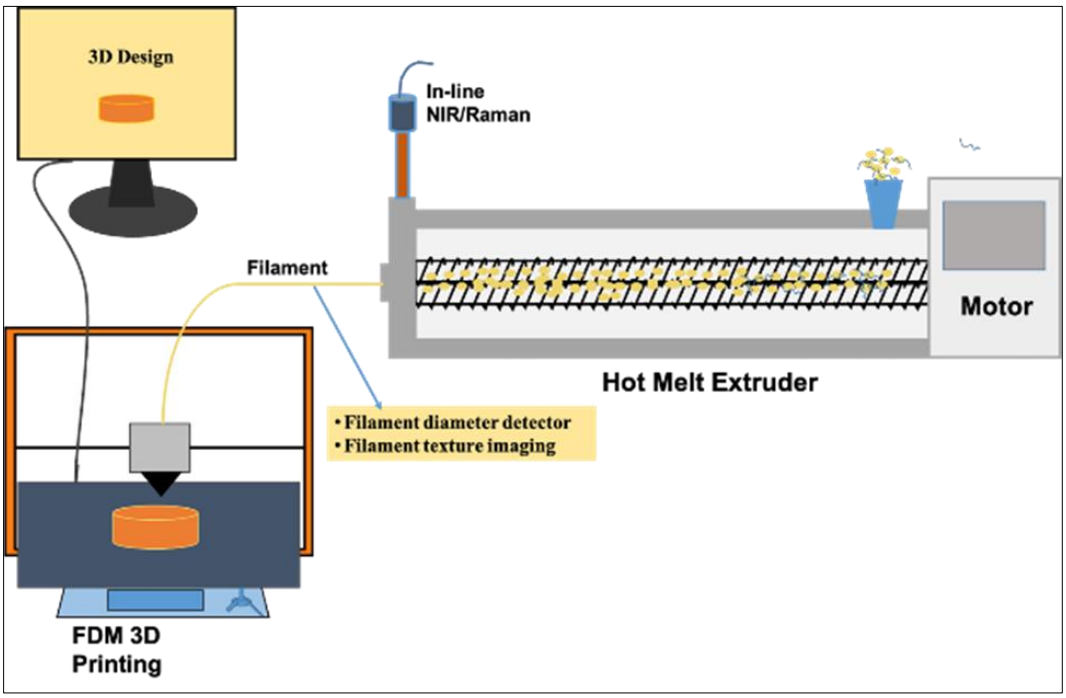

Figure 4 A schematic representation of a continuous manufacturing line by pairing HME with FDM 3D printing

7.1. Advantages

The process of HME-paired FDM 3D printing has several advantages when compared to conventional manufacturing techniques. A few of the advantages are discussed below.

7.1.1. Simple manufacturing process

Compared with conventional manufacturing techniques, the HME and FDM 3D printing process involves two unit operations, which include the extrusion of drug-loaded filament and fabrication of the 3D objects. In terms of cost, establishing a manufacturing line consisting of HME and FDM 3D printers is economical compared to conventional manufacturing instruments. Since the process of HME and FDM 3D printing involves fewer steps, it saves industries a lot of time and workforce. The scaleup of the HME-paired FDM 3D printing process remains simple, and even the bench scale instrument can be employed for developing commercial products[81, 82]. Establishing a continuous manufacturing line of HME and FDM 3D printing will save the industries a lot of time and revenue.

7.1.2. Patient-centric dosage forms

It is well known that one dose will not fit all the age groups of the patient population. Depending on age, sex, race, disease state, and biological factors, each patient requires a different dose of drugs with different release profile patterns. Conventionally, the tablets are supplied with a score line to break them into two equal doses for the pediatric patient population. However, preserving the other half of the medication where the core is exposed to the external environment

is critical and harmful for moisture-sensitive drugs. The dose division is possible only for immediate-release dosage forms but not for modified-release medications. The division of doses is complicated and impossible for capsule medications. By adapting to additive manufacturing techniques, physicians can prescribe a dose based on the patient's condition rather than depending on the dose established by pharmaceutical industries[83, 84]. The majority of the geriatric patient population is required to administer multiple drugs each day. For the geriatric patient population, pills that can accommodate multiple drugs can be fabricated, making their life esay. By employing conventional manufacturing techniques, dose adjustment is impossible. Thus, adapting to additive manufacturing techniques will provide the opportunity for developing patient-centric dosage forms.

7.1.3. Complex medications

Developing bilayer medications or fixed-dose combination products by adapting to conventional manufacturing techniques is challenging and time-consuming. Few patients require to administer multiple medications each day[85]. In such cases, patients experiencing dysphagia face difficulty swallowing the medications, eventually making them discontinue the prescription drugs. Within the United States, 30-40% of the patient population each year discontinues the medication due to difficulty in swallowing. Thus, by adapting the additive manufacturing process, bi-layered tablets and polypills can be developed easily compared to conventional manufacturing techniques. Conventionally, for developing bilayered tablets, both the layers should be compatible and compressible and remain intact throughout the product's shelf life[86]. Even complex medications encapsulating the powdered physical mixtures into a core shell or encapsulating liquid or semisolid materials can easily be achieved by adapting to additive manufacturing techniques.

7.1.4. Improved bioavailability

Poor solubility and bioavailability are the major issues haunting the pharmaceutical industries. Especially for the drug substances belonging to the biological classification system (BCS) class II, where the drug is poorly soluble and highly permeable, the bioavailability of the drug is affected by the poor solubility. Improving the solubility of the drug substances where dissolution is the rate-limiting step results in improved oral bioavailability[87]. Among various solubility enhancement techniques, ASD has gained a tremendous response for improving solubility. The ASDs can be manufactured by HME, spray drying, and Kinetisol techniques. However, developing ASDs by HME has been most widely adapted since it is a solvent-free green technique, and the extruder filaments with the amorphous drug can be utilized by the FDM 3D printing technique for developing patient-centric dosage forms[88, 89]. Thus, employing the HME-paired additive manufacturing technique will improve the solubility and oral bioavailability of poorly soluble drug substances.

7.1.5. Dose and design flexibility

The major advantage of adapting to the additive manufacturing technique is fabricating on-demand, patient-centric dosage forms. By employing the FDM 3D printing process, the medications can be fabricated for any dose and shape. Even the release profiles of the tablets can be controlled by adjusting the infill density. A 3D-printed tablet with 100% infill density has no pores or openings, and all the successive layers are tightly packed. With decreasing infill density, the tablet will possess network-like openings where the dissolution media can penetrate rapidly into the tablet matrix resulting in faster release profiles. However, with decreasing infill density, the amount of dose the tablet can accommodate will decrease[90, 91]. Thus the additive manufacturing technique is suitable for fabricating low-infill tablets with smaller therapeutic doses. Still, much research is warranted to improve the drug-loading capacity of the medications. In addition, the additive manufacturing process will also provide the flexibility to fabricate the tablets in different shapes to attract the pediatric patient population and make them adhere to the medications.

8. Limitations

Apart from the advantages discussed above, the additive manufacturing process has a few unresolved limitations. Since the additive manufacturing technique has been recently introduced into pharmaceutical industries for developing medications, much research is warranted in this area before making the process available for developing commercial medications. A few limitations associated with HME paired FDM 3D printing process are discussed below.

8.1. High processing temperatures and limited polymers

The process of HME and FDM 3D printing involves the application of thermal energy. Polymer remains to be the major component of the extrusion process. The majority of the pharmaceutical grade polymers that are suitable for HME and FDM 3D printing process exhibit high melt viscosity and require high processing temperatures for extrusion and 3D printing. The formulation components exhibit thixotropic behavior, where the melt viscosity reduces with increasing temperature. However, the processing temperature needs to be maintained at least 30 degrees below the degradation point of the formulation components. The temperature inside the extruder barrel remains 10-15 degrees higher than

the set temperature attributing to the generation of additional heat due to applied mechanical shear. The load of the Drug substances with plasticizing properties can be increased to reduce the melt viscosity and conduct the extrusion and 3D printing process at lower temperatures[92, 93]. However, the effect of drug load on the mechanical properties of the filaments needs to be investigated since it plays an important role in successfully fabricating the dosage form. In addition, for drug substances with anti-plasticizing properties, incorporating an additive plasticizer will reduce the melt viscosity and processing temperatures. Again, the effect of plasticizers on the stability and mechanical properties of the filaments needs to be investigated right in the early phases of product development. The number of solid plasticizers that can be utilized to develop drug-loaded filaments is limited. The solid plasticizers that have been investigated include polyethylene glycol and poloxamers[94–97]. In addition, a very limited number of pharmaceutical-grade polymers which can be processed at lower temperatures with suitable mechanical properties for the FDM 3D printing process are available in the market. Among various polymers, Kollicoat IR, Kollidon VA64, Kollidon 12 PF, Soluplus, hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) have been most widely investigated and employed for developing digital pills using FDM 3D printing process. Thus, developing novel polymers that can be processed at lower temperatures is needed, and making them suitable for thermosensitive drug substances is warranted.

8.2. Shelf life of filaments

The drug-loaded filaments are considered intermediate products. In the future, compounding pharmacies will be transformed into digital pharmacies where the on-demand manufacturing of patient-centric dosage forms will be executed. In such cases, the pharmacies will receive the drug-loaded filaments, which will be utilized to fabricate medications when required. Thus, the filaments considered the intermediate product need to be stable throughout the shelf life without changing the quality and mechanical properties of the filament. Thus, much research still needs to be conducted to establish the filaments' storage conditions and hold time. Nyavanandi et al.[98] for the first, have investigated the hold time study for the cocrystal-loaded filaments of hydrochlorothiazide and nicotinamide. The investigation employed Kollicoat IR and Kollidon VA64 as backbone polymers[99–101]. The filaments developed by the HME process were stored at ambient room temperature, long-term stability conditions, desiccator, and refrigerator conditions. Among all the storage conditions, the filaments stored in the desiccator were stable for thirty days compared to those stored at other conditions, which failed to retain their mechanical properties even for one week. The filaments stored in the desiccator were fabricated into a dosage form. Upon characterization for release profiles, the formulation of stored filaments exhibited similar behavior to that of the initial samples. With this research, Nyavanandi et al.[98] have laid a way forward for future investigations to establish the shelf life of the filaments.

8.3. Cyber risk

With increasing technology, cybercrime is also increasing enormously. In the future, digital pharmacies will receive electronic prescriptions from physicians with all the necessary information to fabricate the patient dosage form. Here comes the risk of cyber security in the picture. The electronic prescription might be compromised, altering drug, dose, and release profiles. In the case of potent drug substances, any instances of cyber-attack might even result in the death of patients[102, 103]. Thus, the utmost care and preventive measures must be taken before transforming compounding pharmacies into digital pharmacies and replacing paper-based prescriptions with electronic versions.

9. Conclusion

In recent years, after the approval of the first commercial 3D printed product SPRITRAM, the demand for an investigation of additive manufacturing has increased enormously. The pharmaceutical industries fail to meet market demand due to poor solubility and underdeveloped manufacturing techniques. Hot melt extrusion has gained a tremendous response for developing ASDs of poorly water-soluble drugs over other manufacturing technologies such as spray drying and Kinetisol. Initially, the downstream processing of the extrudates obtained from the HME process was difficult, attributed to the poor compressibility of milled extrudates into tablets. However, pairing the process of HME with FDM 3D printing has provided the platform for developing on-demand patient-centric dosage forms. The process of HME and FDM 3D printing has viability for establishing a continuous manufacturing line with suitable PAT tools where the quality of the product can be assured. Though coupling HME with the FDM 3D printing process has several advantages over conventional manufacturing technologies, many limitations remain unanswered. Before replacing conventional manufacturing technologies with the additive manufacturing process, much research must be conducted.

Compliance with ethical standards

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Disclosure of conflict of interest

The author declare that they have no conflict of interest.

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