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Formulation Development Studies of Three-Dimensional Printable Filaments Containing Eudragit S100 Polymer with High-Glass Transition Temperature

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Abstract

The aim of this study is to examine the formulation, process, and equipment conditions to obtain printable filaments for fused-deposition modelling three-dimensional printing (FDM-3DP) using Eudragit-S100 polymer, which is widely used in the pharmaceutical field and has a high glass transition temperature (Tg).

The filaments were extruded by a modified simple single screw extruder. The influence of powder preparation processes such as pre-plastification, sieving, drying, and the formulation factors, such as types and amounts of excipients on the quality of filaments were evaluated. The mechanical properties of filaments were determined manually. Structural integrity and homogeneity of filaments and the printed tablets were demonstrated by SEM. Finally, the printability of the filaments was shown by producing the tablets using an FDM-3D Printer.

When combining triacetin and citric acid, extrudable formulations with an adequate plastification were obtained. Magnesium stearate increased the output speed of the filament through the nozzle of the extruder. Furthermore, it was seen that simple modifications on the extruder and powder preparation process improved the printability of the filaments. A higher screw speed accelerated the output of the filaments while minimizing the filament diameter variability, which is a requirement for providing uninterrupted printing.

In conclusion, the filaments containing Eudragit S100 were successfully and reproducibly printed into round-shaped tablets after modification of the extruder and improvement of the formulation development processes.

1. Introduction

Three-dimensional printing (3DP) technology has increasingly been used in different industries such as dentistry, construction, automotive, aerospace, and tissue engineering. Nonetheless, the use of 3DP in pharmaceutical applications has exploded since the Food and Drug Administration approved a 3D pharmaceutical product (Spritam®) in 2015 (Elkasabgy et al., 2020). 3DP technology offers a unique opportunity for individualized treatment, enabling patient-specific doses instead of a single and standard dosage unit for every patient (Beck et al., 2017). Furthermore, 3DP methods are adaptable for dosage forms with different sizes, complicated shapes, different release kinetics, and variable infill patterns that are not easy to apply for conventional methods (Chai et al., 2017).

Fused-deposition modelling (FDM) is the most popular method in 3DP due to its low cost, simplicity, lack of solvent requirement, ability to fabricate complex dosage forms, and wide variety of applications (Beck et al., 2017). It is an extrusion-based 3DP method that deposits layer-by-layer after melting feed material to produce digitally designed objects. FDM-3D printers require filaments as feedstock material. Recently, hot-melt extrusion (HME) has become the most used method for producing drug-loaded filaments. Despite the fact that a wide range of pharmaceutical-grade polymers is available, many of them have poor thermal and mechanical properties, making them inappropriate for extrusion and printing processes. Therefore, there has been a lot of interest and research on utilizing HME to produce drug-loaded printable filaments using pharmaceutical polymers, such as cellulose-based polymers, methacrylate derivatives, polyvinylpyrrolidone, and ethylene vinyl acetate (Goyanes et al., 2015; Genina et al., 2016; Pietrzak et al., 2015). Despite the growing number of studies on FDM-3DP, there are still significant obstacles to printing pharmaceutical polymers with a high glass-transition temperature (Tg). The higher Tg of polymers, the higher extrusion and printing temperatures are required for the process. Applying high temperatures in FDM is a massive problem for the drugs and polymers with lower degradation temperatures (Td) (Kollamaram et al., 2018).

The object of this study is to investigate the printability of the filaments prepared by Eudragit S100 (EudS100) polymer which has a high Tg and to offer suggestions associated with the formulation, process, and equipment to eliminate the problems encountered in the early stages of formulation development.

2. Materials and Methods

2.1. Materials

Citric acid monohydrate (CAMH), magnesium stearate (MGS), and talc were donated by Drogsan Pharmaceuticals. Eudragit S100 (EudS100) was kindly provided by Evonik. Triacetin (TA) was gifted from BASF. Glyceryl monostearate (GMS) was a kind gift from Gattefosse. Triethyl citrate (TEC) was supplied from Sigma-Aldrich.

2.2. Preparation of filaments

When preparing the initial formulations (F1-F15), EudS100 and the other excipients were weighed in the ratios shown in Table 1.

Table 1. Filament formulations containing EudS100 as the primary polymer

Code	EudS100	TEC	TA	P:P	CAMH	MGS	Talc	GMS	T (°C)
F1	65	35	-	1,9	-	-	-	-	135
F2	50	25	-	2	-	-	25	-	135
F3	60	30	-	2	-	-	10	-	130
F4	64	32	-	2	-	-	4	-	130
F5	64	32	-	2	-	-	-	4	130
F6	60	30	-	2	-	-	-	10	120
F7	54	27	-	2	15	-	-	4	125
F8	56	28	-	2	16	-	-	-	125
F9	50	25	-	2	15	5	-	5	120
F10	50	25	-	2	15	10	-	-	120
F11	54	27	-	2	15	4	-	-	125
F12	54	-	27	2	15	4	-	-	115
F13	50	-	25	2	15	-	10	-	120
F14	50	-	25	2	15	5	5	-	110
F15	50	-	25	2	15	10	-	-	110

P:P: polymer:plasticizer ratio, EudS100: Eudragit S100, TEC: Triethyl citrate, TA: Triacetin, CAMH: Citric acid monohydrate, MGS: Magnesium stearate, GMS: Glyceryl monostearate, T: Extrusion temperature

Next, the powder mixture was taken into a mortar, and the liquid plasticizer was added in a drop-wise manner with constant mixing through a pestle. Finally, the obtained powder mixture was extruded using a single-screw extruder (SSE) with a 1.75 mm-diameter nozzle (Noztek Pro, UK) (Figure 1a). The extrusion temperatures were also given in Table 1.

The improved preparation method which was applied to the final formulation (F15) was as follows: The polymer was taken into a mortar. Then the plasticizer was dropped and constantly mixed with a pestle. The prepared blend was left overnight. The next day, the plasticized polymer was passed through 18 meshes and kept in an oven at 55°C for 2 hours with other excipients. Finally, the powder was mixed until homogeneity in a mortar according to a 'geometric dilution' protocol. The mixture was extruded using the modified equipment (Figure 1b).

2.3. Characterization of filaments

2.3.1. Diameters of the filaments

Diameters of the filaments were randomly measured at six points using a digital caliper (Dasqua, Italy). The measured values were aimed to be in the range of 1.70-1.80 mm.

2.3.2. Morphological properties of the filaments

Filaments were assessed visually according to their colors, whether being opaque or transparent, and their surface properties such as roughness, smoothness, and stickiness. Furthermore, the

morphological properties of printable F15 filament were examined by a Scanning Electron Microscopy (SEM, FEI Quanta 250 FEG, Netherlands). SEM imaging at different magnifications was conducted to observe the surface and cross-section of printable filament.

2.3.3. Mechanical properties of the filaments

Mechanical properties such as flexibility, stiffness, and brittleness of the produced filaments were evaluated manually by stretching filaments and twisting them into a spiral.

2.4. Printability of filaments

The final filament (F15) was printed as round-shaped model tablets with a dual FDM 3D printer (CraftBot3, Hungary) with a 0.4 mm diameter nozzle. The setting parameters of printing are given in Table 2.

Table 2: The setting parameters of model tablets printed with Eudragit S100-based filament

Setting Parameters	
Nozzle temperature (°C)	165
Bed temperature (°C)	50
Printing speed (mm/s)	20
Movement speed (mm/s)	120
Layer height (mm)	0.2

2.5. Morphological properties of tablets

The morphological features of 3D printed tablets were assessed using a SEM (FEI Quanta 250 FEG, Netherlands). The images were taken from the surface and the side view of the tablets at different magnifications.

3. Results

Among fifteen formulations, only F15 filament was suitable for printability. However, it was observed that the F15 formulation did not result in the same quality filament in each time when re-extruded at different periods. While some of them were printable, some failed in the 3D printer. In addition, the low filament yield and the extremely slow powder flow from the hopper to the screw during extrusion were the other issues arisen from the F15 formulation. These issues were eliminated when F15 filaments reproduced after the modification of the powder preparation process and equipment. The F15 filament reproduced by the modified method was named as “final filament”.

The diameters of the final filament were 1.73 ± 0.02 mm, and the mechanical properties (Figure 2) were suitable in terms of the resistant to manual stressing and bending.

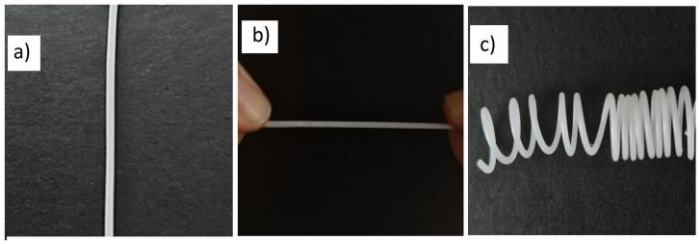

Figure 2. Images (a), stretching tests (b), and twisting tests (c) of the final filament

The surfaces of the filaments were smooth and homogenous. SEM images of the final filament were given in Figure 3. The filaments had no defects, pores, or bubbles in their inner structure and outer surface.

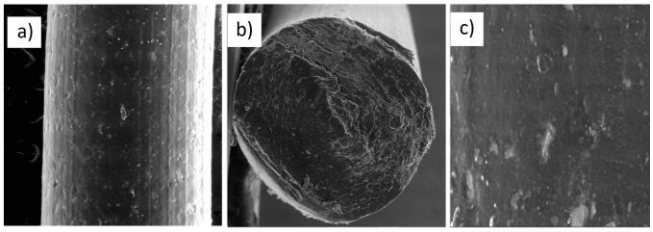

Figure 3. SEM images of the final filament containing EudS100.

The final filaments were printed on the FDM-3D printer using the process settings listed in Table 3 to produce the tablets shown in Figure 4. The 3D-printed tablets had an excellent appearance, with minimal variances in their diameter, thickness, and weight (Figure 4a). SEM images of the tablets also confirmed their morphological quality. SEM images of the surfaces of the 3D tablets have shown that extruded strands bonded with each other without any gaps between them (Figure 4b). Furthermore, SEM images of the 3D tablets' side view exhibited no cracks or holes between the layers of 3D tablets, which were firmly adhered to each other (Figure 4c).

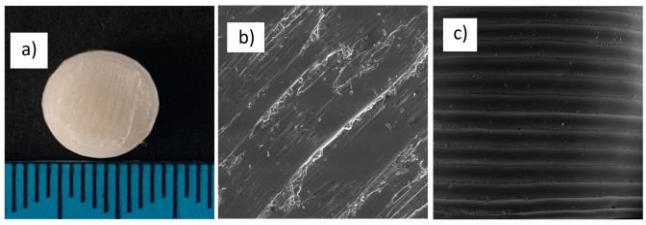

Figure 4. Images of 3D printed tablets

4. Discussion

Generally, polymers with Tg values ranging from 100°C to 170°C are considered suitable for the HME process (Pereira et al., 2020). However, because the temperatures required for FDM are nearly 20-30˚C greater than those needed for extrusion, the temperature in the HME stage should be kept as low as possible. Since 3DP requires higher temperatures than Tg of polymers, EudS100 with a Tg of 173 ºC, which is also its Td, is inappropriate for many drugs (Okwuosa et al., 2016). In most cases, the researchers have reduced the high Tg of the polymers by using plasticizers or mixing them with other thermoplastic polymers with lower molecular weight (Sadia et al., 2016; Carlier et al., 2019). Gioumouxouzis et al. were successful in extruding EudS100 at 165 °C using 35 % triethyl citrate (TEC); nevertheless, the printing temperature of 182 °C was higher than the Td of the polymer (Gioumouxouzis et al., 2018). In our study, this formulation, given as F1 in Table 1, was tried first. Although this formulation was initially extruded at 165 °C, a very tiny amount of filament was obtained at a slow extrusion speed. Additionally, owing to the low output speed of the filament, which extends its time in contact with the heat, after a while, a change in the filament's color and bubbles on its surface were observed, which indicated that the filament had degraded. Although the authors reported that the filaments they extruded had superior printability to PLA filaments, our filament was not even printable. We attributed this inconsistency to the use of different extruders because while Gioumouxouzis et al. used a twin-screw extruder, we produced the filaments with the most basic SSE (Gioumouxouzis et al., 2018). Besides, a polymer with a convenient Tg is not the only determining factor for obtaining a printable filament. Every filament extruded by HME may not be suitable for the FDM printers in terms of their mechanical, morphological, and rheological properties. Furthermore, only 1% of materials available for HME-based procedures are appropriate for FDM-3DP (Carlier et al., 2019).

Okwuosa et al. extruded the EudS100 at 120˚C in an SSE (Filabot) by adding 22.5% TEC and 25% talc into the formulation and they successfully printed the

extruded filament. However, the printing temperature was extremely high (190˚C) (Okwuosa et al., 2021). We prepared a different formulation similar to Okwuosa's formulation by just reducing the polymer to plasticizer ratio from 2.2 to 2 to lower the printing temperature (F2). This formulation could not be extruded since the prepared powder mixture remained unmelted in the extruder even though the extrusion temperature was raised from 135 ºC to 165 ºC. This may be related to the high ratio of talc in formulation, which has a relatively high melting temperature. The F3 and F4 formulations, in which 10% and 4% talc were added in order to improve the flow of the powder and prevent the molten mass from sticking to the inner walls of the extruder, were also insufficient in terms of filament yield, and the filament output speed was very low, as in the F1 formulation.

In an HME study, where EudS100 and TEC were formulated in the ratio of 2:1, different formulations were developed with the addition of GMS (5-6 %) as a lubricant and CAMH (10%) as a co-plasticizer. Although this was not an FDM-3DP study, it is clear that filaments with improved extrusion will enhance printability. Accordingly, we have utilized GMS as a lubricant in two different ratios of 4 % and 10 % in F5 and F6, respectively. In the higher ratio (10%) of GMS, the powder could not be extruded properly and oil dripped from the nozzle of the extruder at 120˚C. However, the inclusion of 4% GMS resulted in a filament with a very low output rate from the nozzle. A filament (F7) with a higher output rate was produced at 125°C when 15% CAMH was added to this formulation while keeping the polymer to plasticizer ratio constant at 2:1. Despite the fact that this filament was not homogeneous, it was shown that the addition of a co-plasticizer such as CAMH improves the filament extrusion. However, when CAMH was used without any lubricant (F8), the output rate of the filament was very low. Thus, it was decided to combine CAMH with an appropriate lubricant in the formulation. Since MGS is the most commonly used lubricant in the production of solid dosage forms, MGS and GMS were used separately or together, keeping the amounts of CAMH, and polymer to plasticizer ratio in the formulations constant (F7, F9-F11). When GMS and MGS were used together (F9), extrusion was not achieved. When 10% MGS was used as the lubricant (F10), twisted and very flexible filaments were obtained. When the MGS ratio was reduced to 4% (F11), filaments with better mechanical properties were obtained but they were still unsuitable for printing in terms of filament diameter (1.80-2.00 mm). Even though the initial formulations (F1-F11) in which TEC was used as a primary plasticizer were very similar or identical to the published ones (Gioumouxouzis et al., 2018; Bruce et al, 2005), none of them resulted in a printable filament.

Therefore, we decided to change the plasticizer, and TA was included in the formulations as the primary plasticizer alternative to TEC. EudS100 plasticized with TA in a 2:1 ratio was formulated with CAMH (10–15%), MGS (0–10%), and talc (0–10%) and extruded the powder mixtures at lower temperatures than TEC formulations (F12–F15). A filament (F12) with a suitable diameter was obtained when TA was used instead of TEC in the F11 formulation, but its output rate was still insufficient. The filament output rate dramatically decreased when only 10% talc was included in the formulation as a lubricant (F13). However, when the talc ratio was lowered to 5% and

MGS was added in the same proportion, the filament's output rate modestly increased (F14). MGS-containing formulations generally had a relatively higher output speed. That could be due to the co-plasticizer effect of MGS, which Goyanes et al. previously stated (Goyanes et al., 2017). Then, a successful extrusion was achieved at 110ºC with the obtaining of a filament (F15) with suitable brittleness, stiffness, and diameter by excluding talc from this formulation and increasing the magnesium stearate to 10%. However, it was observed that the F15 formulation did not yield the same quality filament when re-extruded at different times. While some of them were printable, some failed in the 3D printer. In addition, the low filament yield and the extremely slow powder flow from the hopper to the screw during extrusion were other issues with the F15 formulation. These inconsistent results may arise from the differences in equipment or powder preparation processes (Roulon et al., 2021; Bruce et al., 2005). The above-mentioned issues are eliminated in F15 filaments obtained after the modification of the powder preparation process and equipment.

In terms of standard and reproducible production, powder preparation process was rarely discussed in the literature; however, it was experienced in our study. The method which was applied the F1-F15 formulations may suitable in twin screw extruder; however, it did not provide sufficient standardization in a basic SSE. Indeed, the polymers should be exposed to the plasticizer for a specific amount of time to allow the plasticizer to penetrate the polymer (Carlier et al., 2019). In terms of efficiently lowering the processing temperature, the pre-plastification step is essential for polymers with high Tg. Accordingly, in this study, F15 formulation was reproduced by the improved method given in the Section 2.2.

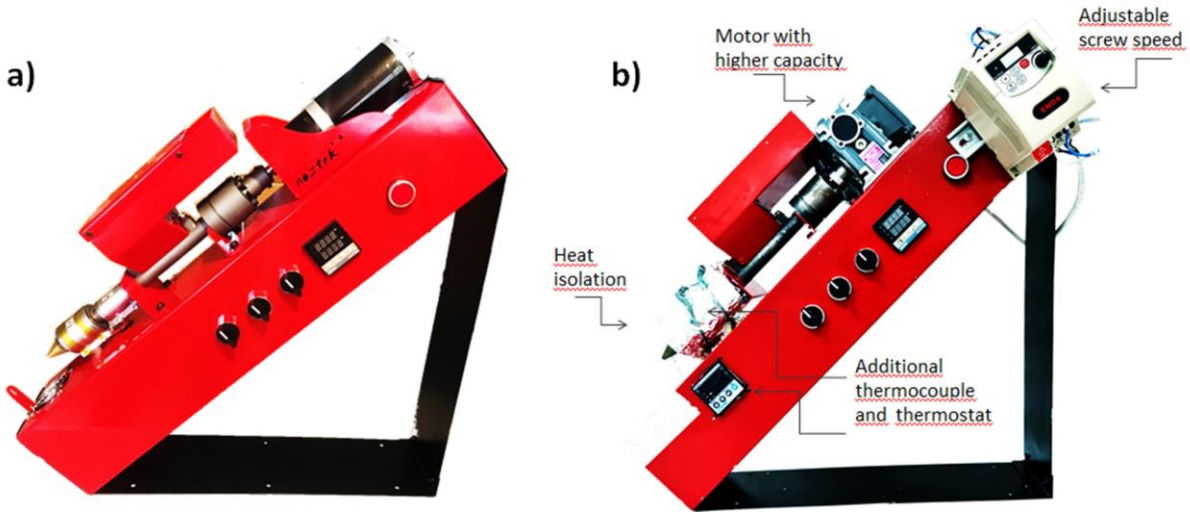

Figure 1. Unmodified (a) and modified (b) extruders

Aside from the formulation process the extruder was also modified (Figure 1). A higher capacity motor and a speed control unit were added to the extruder, allowing the screw to operate at a rotational speed of 0-70 rpm. In addition, the extruder was outfitted with an extra thermocouple and thermostat. Following these modifications, a higher screw speed accelerated the output of the filament, which minimized filament

diameter variability. Extruder modification helped to obtain filaments with the targeted quality and overcome the critical problems encountered.

5. Conclusion

In this study, a filament formulation containing EudS100 polymer, which has high Tg value, was successfully developed and demonstrated to be printable for the FDM 3D method. This study emphasized the importance of parameters associated with extruder, formulation, and process in producing a reproducible filament with printable quality. In the future, various drugs can be loaded into this filament to obtain delayed-release tablets.

Conflicts of interest

The authors declare no conflicts of interest.

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