RESEARCH ARTICLE

Formulation and *In-vitro* Evaluation of Rivaroxaban Tablet by Fused Deposition Modelling 3D Printing Technique

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ABSTRACT

The primary aim of this work is to use fused deposition modelling (FDM) 3D printing technique in the formulation of immediate-release tablets of Rivaroxaban, an oral anticoagulant that acts by directly inhibiting Factor Xa. FDM is one of the 3D printing techniques with the advantage of formation of amorphous solid dispersion during the process of hot-melt extrusion (HME) required for filament production preceding the FDM printing. Rivaroxaban is insoluble in water, and the combination of HME and FDM 3D printing was successfully employed to enhance the solubility and dissolution of the drug through the formation of amorphous solid dispersion and modifying the design of tablets where 50% infill tablets showed faster dissolution compared to 100% infill tablets. Four formulas were selected for characterization, where Soluplus and Kollidon VA 64 were the main polymers employed with different plasticizers and different drug loading (2.5%, 10%, 20%) were tested. F14 with 50% infill released 95% of the drug in 45 min while F15 with 100% infill released 95% of the drug in 90 min, where both formulas containing 10% drug. Differential Scanning Calorimetry and X-Ray Powder Diffraction confirmed the conversion of Rivaroxaban from the crystalline state to the amorphous state.

Keywords: 3D printing, FDM, HME, Immediate release, Rivaroxaban.

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INTRODUCTION

3D printing (3DP), also known as Additive manufacturing, is considered an emerging technology in the field of drug delivery systems and medical devices. It's a manufacturing technique where three-dimensional objects are created layer by layer according to the 3D digital object that can be designed through computer-aided design (CAD) software.[1] The introduction of 3DP technology in the pharmaceutical field has revolutionized since 2015 when the US Food and Drug Administration (FDA) approved the first 3D printed drug SPRITAM, an orally disintegrating tablet of levetiracetam manufactured by the ZipDose Technology (Aprecia Pharmaceuticals, Langhorne, PA, USA).[2] Different 3DP technologies have been developed and used in pharmaceutical research such as Stereolithography,[3] Powder bed 3DP,[4] Inkjet 3DP,[5] and Fused Deposition Modeling (FDM)[6] which is the most common technology due to its low cost and easily accessible.[7] FDM is based on the extrusion of thermoplastic polymer filaments through a high-temperature nozzle that moves in the X and Y axis while deposition and solidification of the melted filament layer by layer occur on a build plate that moves in the Z-axis.[7]

Drug loading into the polymeric filaments can be done by two methods. The first one, which is the simplest, is the soaking method, where filaments used for FDM printers are soaked into concentrated drug solution to allow drug diffusion into the filaments.[8] However, this method has several drawbacks such as limited drug loading capacity, time-consuming, and limited availability of suitable pharmaceutical-grade filaments.[9] The second method, which is widely used and studied recently is Hot-Melt Extrusion (HME) technology, where heat and pressure are applied to melt the materials which usually consist of polymeric blend and active pharmaceutical ingredients (API) and extrude it through a nozzle with defined shape and diameter, forming a filament suitable for the FDM printers.[7] HME role in solubility and bioavailability enhancement of poorly water-soluble drugs, through the formation of amorphous solid dispersion, has been extensively researched recently, in addition to its application in taste masking, and modifying the release profile of available dosage forms.[10] The combination of HME and FDM 3DP will allow the formation of personalized dosage forms with the required dose, shape, and release profile.[6] The formulation of immediate-release tablets

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with enhanced solubility and dissolution of poorly water-soluble drugs using FDM 3DP remains a challenge, mainly because of the mechanism of FDM printers which forms a rigid structure by the deposition of the polymeric filament layer by layer which slows tablet disintegration and dissolution, also, limited availability of biodegradable thermoplastic polymers suitable for HME and formulation of filaments with sufficient mechanical properties required by the FDM printers renders this dosage form formulation more challenging.[11,12]

This research aims to formulate an immediate release FDM 3D printed tablet of Rivaroxaban (RXB) and study the effect of different polymeric blends on the mechanical properties of the extruded filaments, and the effect of HME and FDM 3DP on the solubility and dissolution of RXB.

RXB is an oral anticoagulant act by directly inhibiting Factor Xa, used in the treatment and prevention of venous thromboembolism (VTE) and Pulmonary Embolism (PE) in adult patients.[13] RXB is practically insoluble in water with pH-independent solubility of 5–7 mg/L at 25°C and belongs to the biopharmaceutical classification system II (BCS class II) with limited aqueous solubility and high permeability across the gastrointestinal tract.[14] RXB is available in the market as a film-coated immediate-release tablet under the brand name (Xarelto; Bayer Healthcare AG) in 2.5, 10, 15, and 20 mg doses with the bioavailability ranging from (80–100%) for the 10 mg dose to (66%) for the 20 mg dose.[13,14]

Several techniques have been utilized to solve the problem of poor aqueous solubility of RXB including the preparation of polymeric amorphous solid dispersion, cyclodextrin inclusions, and Self-nano emulsifying drug delivery system (SNEDDS).[14-19]

In this study, HME combined with FDM 3DP was used to prepare RXB immediate-release tablets with enhanced solubility and dissolution profile through the formation of amorphous solid dispersion. Among the different thermoplastic polymers studied, Soluplus and Kollidone® VA 64 was the main polymers that were used in HME to prepare drug-loaded filaments, however, they are not suitable for FDM printing on their own, and other additives are required, which are mainly plasticizers, to prepare filaments with suitable mechanical properties. The effect of drug loading capacity, different dimensions, and infill % of the 3D printed tablet were also studied to evaluate the feasibility of using FDM 3D printers in the formulation of personalized dosage forms with the required release profile.

MATERIALS AND METHODS

Materials

Rivaroxaban and Polyethylene Oxide 100 K (PEO Mw 100,000) were purchased from Baoji Guokang Bio-Technology Co Ltd (Baoji, China). Kollidon® VA 64 (Vinylpyrrolidone-vinyl acetate copolymer), Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer), Kollidon® 30 (Polyvinylpyrrolidone K30), and Kollidon® 12 PF (Polyvinylpyrrolidone K12) were donated by BASF Co (Ludwigshafen, Germany). PEG 400, PEG 4000 (Polyethylene glycol), and Mannitol were purchased from Himedia Laboratories Co Ltd (Mumbai, India). Poloxamer 407 was purchased from Guangdong Yumay Chemical Co., Ltd. (China). Sodium starch glycolate and Croscarmellose sodium were received as a gift from Sama Alfayhaa Pharmaceutical Industries (Basrah, Iraq). Other chemicals such as solvents and buffering materials were of analytical grade.

Preparation of Drug-loaded Filaments by Hot-melt Extrusion (HME)

The composition of the formulations is illustrated in Table 1. RXB and other powdered excipients in 30 gm batches were mixed using mortar and pestle for 15 min to ensure a homogeneous mixture with fine particle size, formulas containing liquid PEG 400 were added to the powdered mixture and mixed for a further 5 minutes. The mixture was extruded using a single-screw Noztek Pro Filament Extruder (Noztek, Shoreham, UK) through a nozzle with a diameter of 1.75 at a screw speed of 15 rpm, extrusion temperature of each formula is shown in Table 2. The extruder was placed at a height to ensure constant gravity enough to pull the filament, and the diameter was adjusted by controlling the temperature,

Table 1. Composition of the formulations

Formulation component (% w/w)	*F 1*	*F 2*	*F 3*	*F 4*	*F 5*	*F 6*	*F 7*	*F 8*	*F 9*	*F 10*	*F 11*	*F 12*	*F 13*	*F 14*	*F 15*	*F 16*	*F 17*
Rivaroxaban	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	20	2.5
Soluplus					30	75	50	50	50	40	40	50	50	50	45	45	50
Kollidon VA 64	25	35	20	30			25		20	25	20	15	10	20	25	15	27.5
PVP K30								25									
PVP K12	25	20															
PEO 100,000	15	15	60	40	40					5	5	10	10	5	5	5	5
PEG 400						5	5	5	5	5	5	5	5	5	5	5	5
PEG 4000	15	10	10	10	10	5	5	5	5	5	5	5	5	5	5	5	5
Poloxamer 407									5								
Mannitol	5									5	10						
Sodium Starch Glycolate				5	5	5	5	5	5	5	5	5	10	5	5	5	5
Croscarmellose sodium	5	10	10	5	5												

Table 2. Printable formulas, HME temperature, Printing temperature, Bed temperature, and Filament diameter (mean ± SD, n=3).

Formula	*Printed*	*HME Temp. °C*	*Printing Temp. °C*	*Bed Temp. °C*	*Filament diameter*
F 1	No	105			1.74 ± 0.03
F 2	No	125			1.67 ± 0.05
F 3	Yes	160	220	60	1.73 ± 0.01
F 4	Yes	120	200	60	1.72 ± 0.02
F 5	Yes	105	190	60	1.7 ± 0.01
F 6	Yes	115	190	60	1.73 ± 0.07
F 7	Yes	105	180	50	1.73 ± 0.05
F 8	Yes	110	190	50	1.75 ± 0.005
F 9	Yes	90	180	50	1.7 ± 0.04
F 10	Yes	110	180	50	1.72 ± 0.02
F 11	Yes	100	180	50	1.63 ± 0.02
F 12	Yes	105	190	50	1.68 ± 0.05
F 13	Yes	100	190	60	1.72 ± 0.07
F 14	Yes	110	180	60	1.72 ± 0.01
F 15	Yes	110	180	60	1.73 ± 0.005
F 16	Yes	115	180	60	1.6 ± 0.02
F 17	Yes	110	180	60	1.63 ± 0.05

as increasing the extruder temperature will soften the molten materials and decrease the diameter of the extruded filament, while decreasing the temperature will slow down the extrusion and increase the diameter. Successfully printed filaments diameter was in the range between 1.5 and 1.75 mm.

Mechanical Characterization of Filaments

Filaments used in FDM printers should have critical mechanical properties to be successfully printed. In this study, the Repka-Zhang test was adapted to measure the flexibility, brittleness, and stiffness of the extruded filaments.[20] Two different texture analysis methods were done using TA. XT Plus (Stable Micro Systems Ltd, Godalming, Surrey, UK) texture analyzer.

For the flexibility and brittleness analysis, a 3-point bend test was used, using a modified 3D printed sample holder probe with a 25 mm supporting gap, and a 3D printed blade attached to the cylindrical probe of the texture analyser. Extruded filaments were cut into 5 cm length and the diameter was measured using a digital caliper (Neiko, China) and placed on the sample holder (Table 2). Using the Return to Start mode in the Exponent software version 6,1,16,0 (Stable Micro Systems Ltd, Godalming, Surrey, UK) with the following parameters: Pre-test speed 1-mm/sec, Test speed 10 mm/sec, Post-test speed 20 mm/sec, and the blade moves with a target distance of 15 mm under the supported filament with a trigger force of 5 gm. Testing for each filament was repeated three times and the breaking distance and breaking stress were recorded and analyzed using the Exponent software.

For the stiffness analysis, the same test setting above was used except that the filaments were placed on solid flat metal, and the blade moves and penetrates the filaments with a speed of 1 mm/sec to a target distance of 0.6 mm. Again, each filament was tested three times and the breaking stress was recorded and analyzed using the Exponent software.

Tablet Design and 3D Printing

The 3D printed tablets were designed using Fusion 360 software v 2.0.10244 (Autodesk, San Rafael, USA) and exported as .stl file to the slicer software PrusaSlicer v 2.2.0 (Prusa Research, Prague, Czech Republic) then exported as .gcode file to be printed. Two cylindrical shape tablets were designed with the following dimensions (diameter, 8 mm; thickness, 3 mm) and (diameter, 10 mm; thickness, 3 mm) except F17 100% infill tablets where it was (diameter, 7 mm; thickness, 3 mm) to ensure low weight hence low dose. Filaments produced from the HME process were printed using a commercial FDM-3D printer (Prusa i3 MK3S, Prusa Research, Prague, Czech Republic) equipped with a 0.4 mm nozzle. The 8×3 tablets were printed with the following slicer setting: Layer height, 0.15 mm; printing speed, 50 mm/s; infill percentage 100%, two outer vertical shells, and rectilinear fill pattern. While the 10×3 tablets were printed with the following setting: Layer height, 0.15 mm; printing speed, 50 mm/s; infill percentage 50%, two outer vertical shells, no outer horizontal shells (without solid top and bottom layers), and grid fill pattern, except F16 and F17 where their 50% infill tablet dimensions were 8×3 (diameter, 8 mm; thickness, 3 mm). The printability of each formula with the printing temperature and bed temperature are shown in Table 2. To avoid adhesion of tablets to the printer bed and possible damage after removal, painting tape was sticked on the bed and printing was on this tape.

Preparation of Directly Compressed Tablet

A physical mixture of F14 was mixed in a mortar and pestle for 15 min, and 200 mg of the powder were weighed and compressed using a 10 mm single punch tablet machine (Manesty, UK), to compare the dissolution profile of the 3D printed tablet with the directly compressed tablet, and study

the effect of HME and FDM printing on the solubility and dissolution profile.

Saturated Solubility Study

The saturated solubility test was conducted in distilled water for the pure RXB, hot-melt extruded filaments, and 3D printed tablets to study the effect of hot-melt extrusion and FDM 3DP on the solubility enhancement of RXB. Excess amount of pure RXB powder, small pieces of extruded filaments, and 3D printed tablet of each formula was added to 10 ml distilled water in a sealed plain tube and kept in a shaker water bath for 72 hours at 25.0 ± 1.0°C to reach equilibrium.[19] Then, samples were centrifuged at 5000 rpm for 15 min and the supernatant was filtered through a 0.45 µm syringe filter. The filtrate was diluted with distilled water and analyzed by UV/VIS-spectrophotometer at 249 nm (Cary® 100, Varian Inc., USA) and the concentration was measured according to the calibration curve of RXB in water. The procedure was conducted in triplicate.

Determination of Drug Content

Drug content was determined for the 3D printed tablet by dissolving accurately weighted tablet in 100 mL methanol under magnetic stirring for 60 min, then sonication for 15 min. The solution was then filtered through a 0.45 µm syringe filter and 1-mL of the filtrate was transferred to a 10 mL volumetric flask and diluted with methanol. Dilution was done in triplicate and actual drug concentration was determined spectrophotometrically at λ = 250 nm, and compared to theoretical drug concentration, then percent drug content was calculated.

***In-vitro* Drug Release Studies**

In-Vitro Drug Release was studied using dissolution testing apparatus type II (Faithful, China). 3D printed tablets were accurately weighed and placed in a dissolution jar containing 900 ml acetate buffer pH 4.5 + 0.4 % sodium dodecyl sulfate (SDS) and paddles were rotated at speed of 75 rpm at 37 ± 0.5°C. Five ml aliquots were manually collected using 5 mL syringes at (10, 15, 20, 30, 45, 60, 90, and 180 min) time intervals and filtered through a 0.45-µm syringe filter. fresh dissolution media were replaced in the dissolution jar in 5 ml after each sampling. The amount of RXB in each sample was analyzed spectrophotometrically at λ = 249 nm using Cary 100 UV/VIS spectrophotometer). For comparison study, pure RXB, the extruded filament of selected formulas, and compressed tablet of F 14 were also analyzed for *In-vitro* drug release in the same buffer above. Pure RXB, extruded filament of (F14, F15, F16), and F 14 compressed tablet, all containing an equivalent amount of 20 mg drug, and an amount of F 17 extruded filament equivalent to 2.5 mg drug, were filled in hard gelatin capsules. Extruded filaments of the selected formulas were cut into small pieces (around 2 mm) and filled into the capsule. Dissolution of the capsules was performed in the same apparatus above with the same conditions but the paddle was replaced with basket and the capsules were placed into the baskets.

Tablet Characterization

Assessment of Tablet Dimensions

A digital caliper (Neiko, China) was used to determine the diameters and thicknesses of the tablets.

Hardness

The crushing strength of three tablets from each selected formula was measured using a YD-1 tablet hardness tester (Huanghua Faithful Instrument Co., China), whereby an increasing force was applied to the tablet until it was fractured or deformed.

Friability

The friability of the 3D printed tablets of selected formulas was measured using an Erweka Friability Tester TA3R (Erweka GmbH, Heusenstamm, Germany). Twenty tablets from each selected formula were weighed and placed in the drum and rotated at 25 rpm for 4 minutes then tablets were reweighed and the differences in weight were calculated and displayed as a percentage.

Differential Scanning Calorimetry (DSC)

Thermodynamic properties of pure RXB, 3D printed tablets of selected formulas (F14, F15, F16, F17), F14 extruded filament, and F14 placebo extruded filament was analyzed using DSC 60 (Shimadzu, Japan), the samples (5–6 mg) were put in an aluminum pan, and heating rate of 10°C/min was set between 25°C and 300°C under a purge of dry nitrogen. The calibration of DSC temperature and enthalpy scale was determined by Indium/Zinc standards, while the reference was determined by an empty aluminum pan.

X-Ray Powder Diffraction (XRPD)

The physical state of pure RXB and 3D printed tablets of selected formulas (F14, F15, F16, F17) was measured by Haoyuan DX-2700BH X-ray diffractometer (Dandong, China) with a monochromatic Cu-Ka radiation source. The diffractometer was operated with a copper anode tube at the generator voltage and the current of 40 kV and 30 mA, respectively. The 2θ scanning was used from 10° to 80° at the rate of 2°/min.

RESULTS AND DISCUSSION

Filament Preparation and Characterization

For successful FDM 3D printing, filaments should have optimum mechanical properties, flexibility, and melt viscosity.[21] Generally, most of the pharmaceutical grade polymers lack these properties and HME will produce filaments that are either brittle which breaks in the motor gear and preventing the forward movement of the filament toward the nozzle, or soft filaments that can't be pushed by the motor gear due to pliability of the filament resulting in squeezed filaments out of the driving gear, thus printing failure.[12] So, plasticizers and other additives are usually used to enhance the mechanical properties of the extruded filament and enable 3D printing. In this study, the Repka-Zhang test was adapted to measure the flexibility, brittleness, and stiffness using a

texture analyser, where 3 point bend test was used to record the breaking distance and breaking force. The flexibility of filaments was related to the breaking distance, where greater breaking distance indicates better flexibility, while the peak breaking force represents the brittleness, where the greater force required to bend or break the filament indicates more brittle filament. The stiffness of the filament is another critical parameter for successful 3D printing, and since it's defined as the load required to achieve certain deformation, the penetration of the blade into the filament was considered the deformation in this test, and since the force required for this penetration is directly proportional to stiffness, thus the penetration force was considered to represent the stiffness. Since PLA filament is considered the most suitable and widespread commercially available filament and designed specifically for FDM printers, it was selected as a reference in this study, to compare it's result with the extruded filaments.

The main focus of this research was to develop a suitable formula that produces appropriate filament with sufficient mechanical properties and accepted diameter to be suitable for FDM printing and produce tablets with an immediate-release profile upon dissolution. Thus, different ratios of plasticizer and additives were used and their effect on the mechanical properties and dissolution profile was firstly studied, then further characterization of selected formulas was done.

Soluplus and Kollidon VA64 have been widely used in the preparation of solid dispersions through HME for the enhancement of solubility and dissolution of poorly water-soluble drugs.[22-24] However, HME of these polymers on their own will result in brittle filaments that are not suitable for FDM printers.[25,26] Plasticizers have been widely used in HME to enhance the mechanical properties of the filaments and decrease the extrusion temperature since it increases the flexibility of the filament and reduces the glass transition temperature of the polymers.[27,28] Low molecular weight polyethylene glycols PEG 400 and PEG 4000 were used as a primary plasticizer in this study, while mannitol and Poloxamer 407 were added as a secondary plasticizer in some formulas. PEO 100 K has been used to increase the flexibility and improve the mechanical properties of the filament as reported in previous works.[25,29] PVP K30 and PVP K12 are thermoplastic hydrophilic polymers that have been used in solubility enhancement and formulation of solid dispersion but have the same problem as Soluplus and Kollidon VA64 that they form a brittle filament upon extrusion alone and need plasticizers to make it suitable for FDM printing, thus here used as a secondary polymer to study their effect on solubility and mechanical properties of the resulted filaments.[30,31] Croscarmellose sodium and Sodium Starch Glycolate were used as a super-disintegrant.

Results of the Repka-Zhang test are shown in Figure 1. F1 filament has failed to print because of the high flexibility and low stiffness, compared to PLA filament, F1 is 54% lower in stiffness than PLA, and this softness resulted in a filament that's unable to be pushed by the feeding gear, thus printing failure. This flexibility is attributed to the plasticization effect of PEG 4000 combined with mannitol. On the other hand, F2 has failed to print due to brittleness, although the stiffness was acceptable, but the breaking force and breaking distance were lower than PLA in 91% and 88% respectively. This resulted in filament fracture at the feeding gear and printing failure. High filament brittleness may be attributed to the high concentration of Kollidon VA64 and PVP K12, which need further plasticization to make it more flexible. Increasing the % of PEO in F3, F4, and F5 resulted in increased flexibility and enhanced printability but at the expense of drug dissolution, since PEO has been used as a controlled release excipient.[32] Replacing Soluplus in F5 instead of Kollidon VA64 in F4 resulted in increased flexibility, brittleness, and stiffness which indicate the superiority of Soluplus over Kollidon VA64 in producing printable filaments with sufficient mechanical properties. Although removing PEO from the formulas F6, F7, F8, and F9 resulted in printable filaments, but the filament diameter was difficult to control as a slight increase or decrease in extrusion temperature results in filament diameter variation which causes inconsistency in printing and weight variation in printed tablets as has been previously reported.[33] Adjusting the percentage of plasticizers to 5% of PEG 400 and PEG 4000 was found to produce printable filaments with sufficient mechanical properties. Adding 5% Poloxamer 407 in F9 resulted in reducing extrusion temperature to 90°C due to its plasticization effect but the flexibility and stiffness were reduced resulted in frequent filament fracture at the feeding gear. Mannitol was used as a secondary plasticizer in F10 and F11. Increasing the percentage of Mannitol from 5% in F10 to 10% in F11 results in reducing extrusion temperature by 10°C and increasing the flexibility (breaking distance) by 56% compared to F10 owing to the pore-forming capability and its ability to work as a channeling agent in 3D printed formulations.[31,34]

Based on the dissolution profile, F14 3D printed tablet with 50% infill showed the fastest release, while F15 3D printed

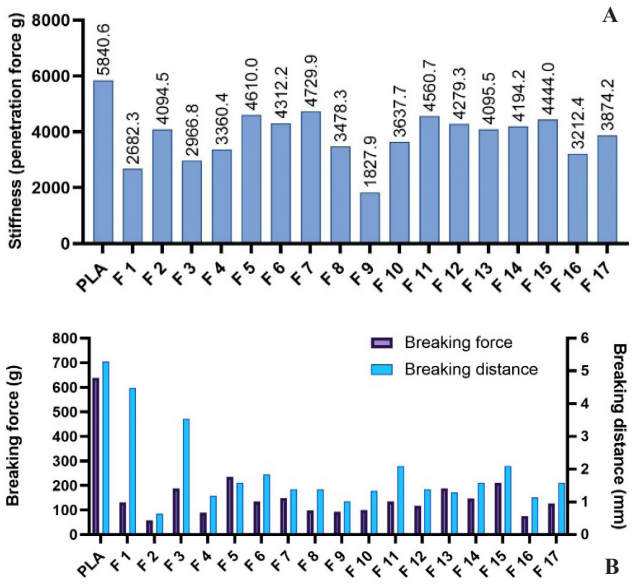


Figure 1: (A) Repka-Zhang test results of the breaking force and breaking distance, and (B) stiffness test results (penetration force) of extruded filaments.

tablet with 100% infill showed the fastest release and was selected for further characterization. Increasing the percentage of RXB to 20% in F16 required a slight increase in extrusion temperature to 115°C and resulted in reducing the flexibility and brittleness of the filament due to an increase in the concentration of non-thermoplastic component and decrease in the concentration of thermoplastic polymers, which reduces the mechanical properties of the extruded filament. On the other hand, reducing the percentage of RXB to 2.5% in F17 resulted in a slight decrease in stiffness compared to F14 and F15.

In this study, filaments were printable if they have adequate flexibility (breaking distance > 1.016 mm), brittleness (breaking force > 93.2 gm), and stiffness (penetration force > 1827.9 gm). Although these tests can give an idea about the mechanical properties of the extruded filaments and hence the printability, it's still not conclusive because there is more than one factor that needs to be taken into account e.g. different FDM printer models may have different mechanical requirements, and the ability to adjust the force of the feeding gear may render some filaments into printable one.[20]

3D Printing of Tablets

Cylindrical shape tablets with two different diameters and infill percentages were successfully printed via an FDM printer. For the 50% infill tablets, the outer top and bottom layers were removed during the slicing of the 3D design, and the two outer vertical shells were 0.8 mm in thickness, to ensure enough tablet strength. This design with a low infill percentage allows the rapid dissolution of tablets compared to the 100% infill tablets, because of the higher surface area to volume ratio and high porosity, which allows dissolution media penetration and tablet disintegration faster than the compact design of 100% infill tablets which does not disintegrate and dissolve by erosion only, as reported by Solanki *et al*.[12]

The printing temperature was ranging from 180°C to 220°C depending on the melt flow of the filaments.[33]Printing temperature was significantly higher than extrusion temperature because of the shorter time required for the filament to pass through the nozzle, and lowering the printing temperature will cause frequent nozzle clogging due to the high viscosity of the filaments.[35]

Saturation Solubility Study

Poor aqueous solubility of drugs due to their crystallinity can be improved by the conversion to the amorphous form, which will disorganize the long-range order molecular structure of crystalline, resulting in thermodynamically unstable compound but with higher solubility and dissolution rate because of their high internal energy.[36] Drug incorporation into the polymeric matrix is considered an option to solve this instability and the resulting mixture is called amorphous solid dispersion.[37] HME is one of the most convenient techniques used for the formulation of amorphous solid dispersion, where a uniform shape and density product composed of different polymers and the active drug is produced through the application of heat, kneading, and pressure without the use of toxic solvents.[38] Hydrophilic polymers such as Soluplus, Kollidon® VA 64, PVP, PEG, and PEO have been successfully used in HME to enhance the solubility and hence bioavailability of poorly water-soluble drugs.[39] Results of saturation solubility determination are shown in Figure 2 A. The solubility of pure RXB was found to be 6.59 µg/mL which is considered practically insoluble in water. All the formulas which are successfully printed (F3-F17) significantly increased the solubility ($p < 0.05$) compared to the pure RXB. Formulas containing a high concentration of PEO (F3, F4, F5) were not effective in increasing the solubility compared to other formulas. The incorporation of Soluplus was found to produce a significant improvement in solubility especially with high concentration as found in F6 where the solubility of 3D printed tablets increased by more than 21 folds. Reducing the concentration of RXB to 2.5% in F17 slightly decreased the efficacy of solubility enhancement compared to other formulas containing the same constituents with 10% RXB, while increasing the concentration of RXB to 20% has the same average of solubility increment compared to other formulas with 10% RXB.

It is worth to be noted that the solubility of RXB in 3D printed tablets of all formulas was higher than that in hot-melt extruded filaments, this may be attributed to the difference in extrusion temperature, where the printing temperature was higher than the extrusion temperature by at least 65°C, and this may result in a superior amorphous dispersion over the extruded filaments.[40]

Determination of Drug Content

The chemical integrity of RXB in the 3D printed tablets was analyzed using a UV–vis spectrophotometer. Drug content

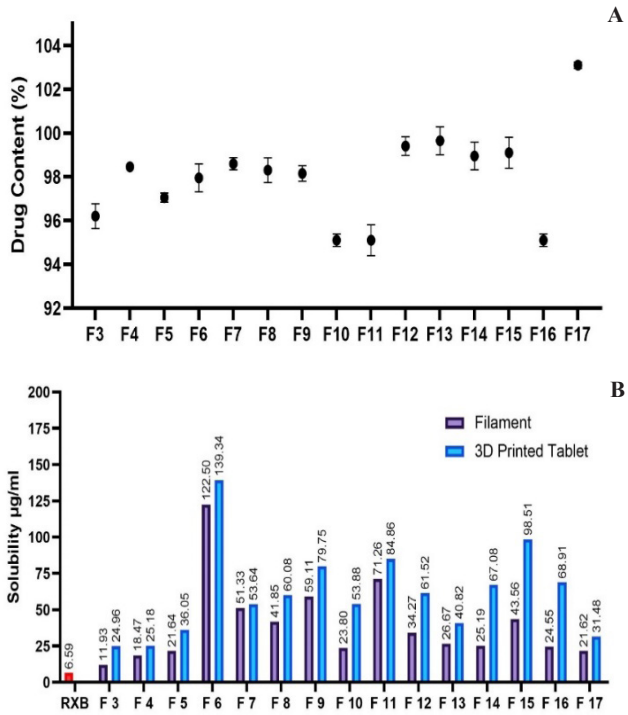


Figure 2: (A) Saturation solubility study results (mean, n=3) of pure RXB, extruded filaments, and 3D printed tablets. (B) Drug content of 3D printed formulas (mean ± SD, n=3),

was in the range of 95.1% to 103.1% as shown in Figure 2 B indicating no significant drug loss occurred during HME and 3D printing since extrusion and printing temperature were lower than the melting point of RXB which is 232°C.[16]

In-vitro Drug Release Studies

The main aim of this study is to enhance the solubility and dissolution of RXV through the formation of amorphous solid dispersion via different polymers and select the best polymeric blend that produces printable filaments with an immediate release profile. Previous studies demonstrated that lowering the infill percentage of the 3D printed tablets will improve the dissolution compared to the 100 % solid infill, especially when removing the top and bottom layers since the dissolution media will penetrate the porous structure of the tablet more easily and the fact that the dissolution of solid dispersion and crystals are directly linked to the surface area/mass ratio.[12,41-44] Therefore tablets with two infill percentages 50% and 100% were printed and their effect on dissolution profile were studied.

Pure RXB powder showed a relatively low dissolution of about 61% of the dose dissolved after 180 minutes in acetate buffer pH 4.5 + 0.4 % SDS (Figure 3 A). For the 50% infill tablets, there was a significant improvement in the dissolution rate compared to the pure drug. Although all the formulas showed improvement in solubility, but the change in polymeric combination affects the dissolution rate depending on the dissolution profile of each polymer. Incorporation of a high percentage (>40%) of PEO in formulas F3, F4, and F5 enhanced the mechanical properties of the extruded filaments but on the expenses of dissolution rate as PEO has been used in prolonged-release tablets especially for high molecular weight grades.[45] Replacement of Soluplus instead of Kollidon VA64 in F5 resulted in a slower dissolution of 79% after 180 min, because Soluplus can form gelling in dissolution media thereby slowed the dissolution rate of the tablets.[46,47] Increasing the percentage of Soluplus to 75% and removing PEO in F6 greatly enhanced the solubility up to 21 folds more than the pure RXB but the dissolution rate was not the fastest, again because of the gelling ability of Soluplus that slowed the release rate. PVP K30 was used in F8 instead of Kollidon VA64 in F7 to study its effect on dissolution and the result was the produced filament of F8 was more brittle and easily break while both formulas have similar dissolution profile with similarity factor f2=82.94. Addition of Poloxamer 407 which is a hydrophilic surfactant in F9 resulted in relatively slow dissolution compared to F14 which contains PEO instead of Poloxamer 407 with the same concentration (5%) where f2=37.76. This might be explained by the formation of a gel layer around the tablet that slowed down the release as described in previous literature, in addition to the effect of Soluplus as described earlier.[28] Mannitol has been used previously as a secondary plasticizer and pore-forming agent in FDM 3D printed tablets.[31] The incorporation of 5% and 10% mannitol in F10 and F11 respectively didn't give the fastest release and there was no significant difference between the two formulas with f2=71.66, but F11 filament was more flexible than F10 as described earlier (Figure 3 B). In F12 and F13, the effect of increasing the concentration of super disintegrant

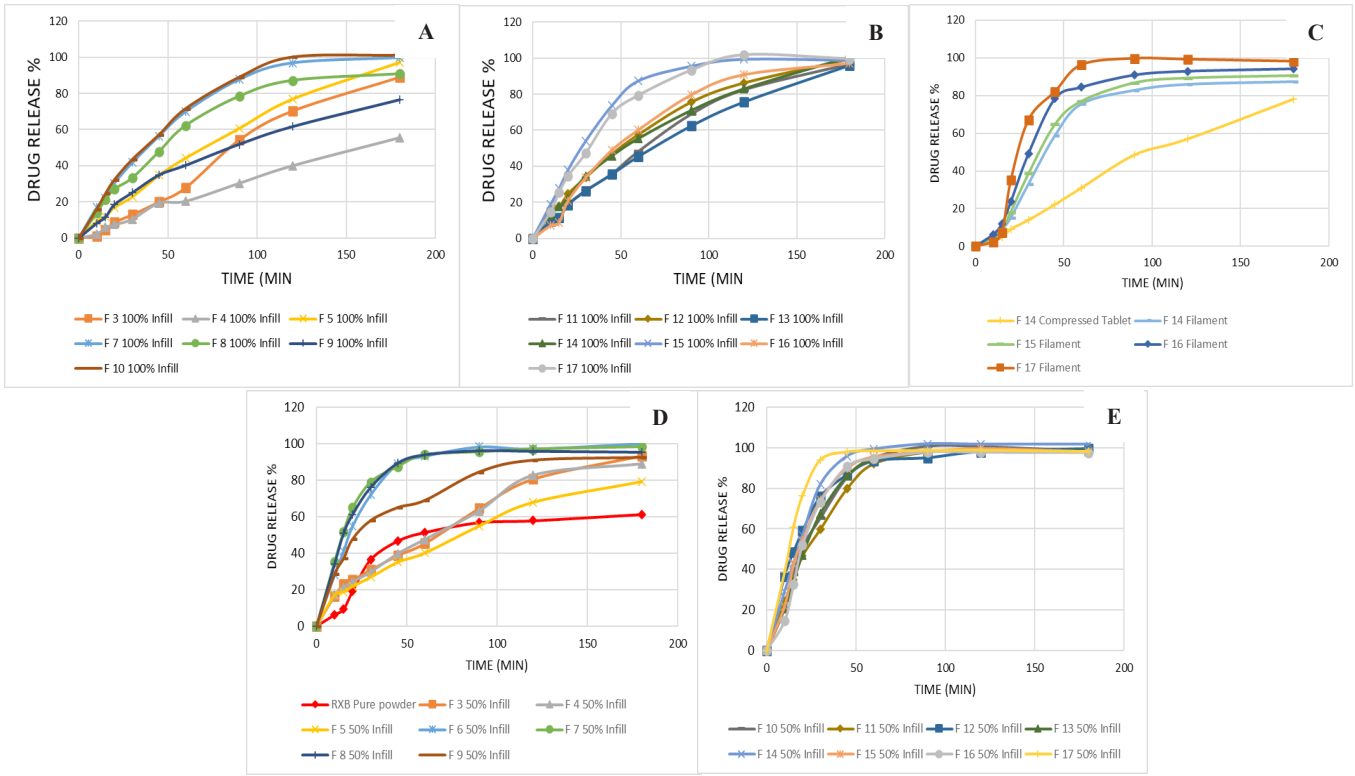


Figure 3 (A, B): *In-vitro* Drug dissolution of Pure RXB powder and 50% infill 3D printed tablets in acetate buffer pH 4.5 + 0.4 % SDS at 37°C. **(C, D)** *In-vitro* Drug dissolution of 100% infill 3D printed tablets in acetate buffer pH 4.5 + 0.4 % SDS at 37°C. **(E)** *In-vitro* Drug dissolution of F14 Compressed tablet and filaments of (F14, F15, F16, F17) in acetate buffer pH 4.5 + 0.4 % SDS at 37°C

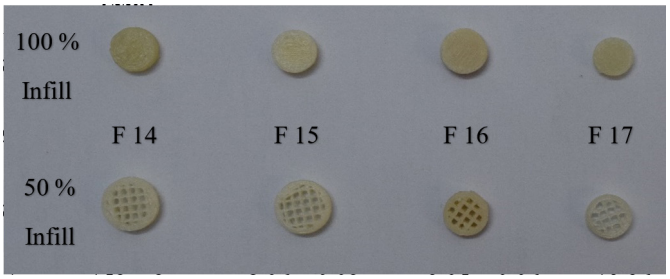
sodium starch glycolate from 5% to 10%, respectively was studied, while maintaining the concentration of PEO at 10%, no significant difference between the two formulas was seen with f2=53.99, and the release was not the fastest maybe because of the reduced concentration of Kollidon VA64 which gives an immediate release action. F14 tablets with 50% infill gave the fastest release profile with more than 95% of the drug released in 45 min, and it was selected for further characterization. Increasing the concentration of Kollidon VA64 by 5% on the expenses of Soluplus in F15 compared to F14, results in no significant difference in the dissolution of 50% infill tablets with f2=66.5, while F15 tablets with 100% infill gave the fastest release with complete dissolution after 90 min due to the superior immediate release action of Kollidon VA64 compared to Soluplus, and this formula also was selected for further characterization. The effect of increasing the concentration of RXB to 20% was studied in F16 and there was a slight decrease in dissolution rate compared to F14 where 90% of the drug was released in 45 min and f2=56.78, and this was in concordance with other studies where increasing the concentration of the drug results in slowed dissolution rate.[12] On the other hand, reducing the concentration of RXB to 2.5% in F17 results in further improved dissolution rate compared to F14 where 94% of the drug released after 30 min and f2=50.27. F16 and F17 was also selected for further characterization.

Regarding the 100% infill tablets, almost all the factors that affect the dissolution of 50% infill tablets above was the same on the 100% infill tablets but the dissolution was slower and complete release of the drug was observed from 90 min to more than 180 min (Figure 3 C), because of the solid structure of the tablets that's consist of a high percentage of extruded polymers which doesn't disintegrate and the dissolution occurs mainly by erosion and diffusion mechanisms.[11,12]haloperidol, for rapid release by fused deposition modeling. Filaments for 3D printing were prepared by hot melt extrusion at 150°C with 10% and 20% w/w of haloperidol using Kollidon® VA64, Kollicoat® IR, Affinsiol™15 cP, and HPMCAS either individually or as binary blends (Kollidon® VA64 + Affinisol™ 15 cP, 1:1; Kollidon® VA64 + HPMCAS, 1:1 F15 tablet with 100% infill showed the fastest release profile with 95% of the drug released in 90 min. F17 also showed fast release relative to other formulas because of the low concentration of RXB (2.5%) where more than 93% of the drug was released in 90 min with f2=68.05 compared to F15 (Figure 3 D). For comparison and to study the effect of FDM 3D printing on the release profile, the dissolution of F14 compressed tablet and filaments of F14, F15, F16, and F17 was also studied as shown in (Figure 3 E). F14 compressed tablet showed slowed dissolution where 78% of the drug was released in 180 min, and this may be attributed to the crystalline structure of RXB with limited solubility compared to the amorphous form produced during the HME and FDM 3D printing which enhanced the solubility and dissolution rate. Similarity factor f2 between dissolution curve of F14 compressed tablet and RXB pure powder, F14 50% infill tablet, 100% infill tablet and F14 filament was 42.3, 15.21, 35.61, and 30.74, respectively. Dissolution of F14, F15, F16, and F17 filaments was relatively faster than their 3D printed tablets with 100% infill counterpart while they were slower than the 50% infill tablets and this is related to the surface area/mass ratio where they were in the following order 50% infill tablets > filament> 100% infill tablet. All the filaments showed an enhanced dissolution rate compared to the pure RXB powder with similarity factor f2= 38.23, 35.64, 31, and 25.67 for the F14, F15, F16, and F17 filaments, respectively.

Tablet Characterization

The average weight, thickness, and diameter are shown in (Table 3). Tablet hardness was ranging from 10.26 Kg to 14.22 Kg for the 100% infill tablets and from 3.06 Kg to 4.59 Kg for the 50% infill tablets as shown in (Table 3). Tablets with

Table 3: Tablets weight, dimensions, hardness and friability (mean ± SD) of F14, F15, F16, and F17.



Formula	*Infill %*	*Tablet weight (Mg)*	*Diameter (Mm)*	*Thickness (Mm)*	*Hardness (Kg)*	*Friability %*
F 14	50%	122.6 ± 1.2	10.07 ± 0.03	3.05 ± 0.04	4.58 ± 0.12	0.36%
	100%	130 ± 2.6	8.07 ± 0.02	3.07 ± 0.06	10.26 ± 0.84	0.12%
F 15	50%	117 ± 1	10.13 ± 0.06	2.96 ± 0.04	3.16 ± 0.54	1.16%
	100%	152 ± 2	8.06 ± 0.02	3.05 ± 0.06	13.96 ± 0.5	0.66%
F 16	50%	63 ± 1	8.06 ± 0.05	3.02 ± 0.04	3.56 ± 0.27	0.55%
	100%	120.6 ± 2.3	8.04 ± 0.06	3.04 ± 0.02	11.87 ± 0.64	0.32%
F 17	50%	86.6 ± 1.2	8.13 ± 0.06	3.02 ± 0.03	3.05 ± 0.06	0.98%
	100%	110.6 ± 0.6	7.08 ± 0.03	3.07 ± 0.03	14.22 ± 0.36	0.11%

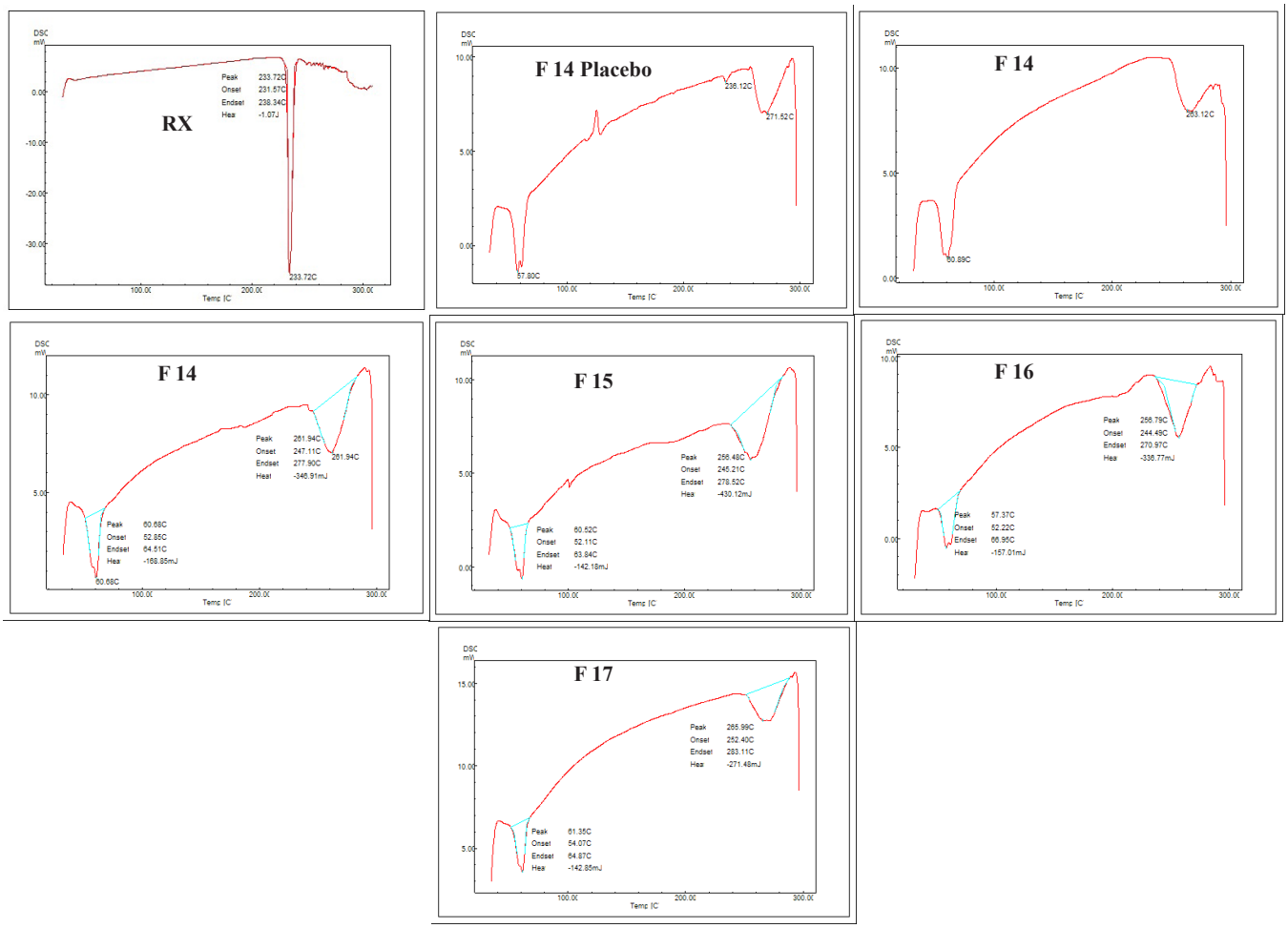


Figure 4: DSC thermograms of pure RXB, F14 placebo filament, F14 Filament, and 3D printed tablets of (F14, F15, F16, F17)

100% infill are hard and sometimes fail to break but they deform during the compaction because of their rigid structure formed after solidification of the melted polymers.[48] These values demonstrate the superiority of FDM 3D printing in the formulation of mechanically strong tablets over other 3D printing technologies such as extrusion-based and powder-based 3D printing.[49,50] Friability of selected formulas were below 1% except for 50% infill tablets of F15 which was 1.16% (Table 3) and this may be attributed to the porous structure of the tablets and sometimes the difference in extruded filaments diameter results in erratic melt deposition and the subsequent layers are not deposited on each other firmly which results in friable structure.

Differential Scanning Calorimetry (DSC)

The DSC thermogram of pure RXB, F14 Placebo filament, F14 filament, and 3D printed tablets of F14, F15, F16, and F17 are shown in (Figure 4). The DSC curve of pure RXB shows a sharp endothermic peak at 233°C corresponding to its melting point and reveals the crystallinity nature of the drug.[16] DSC curves of extruded filament and 3D printed tablets show two endothermic peaks, the first one at around 60°C which correspond to the melting of Soluplus, the main constituent of the formulas since it has a glass transition temperature (T_g) value at 72°C, but due to the plasticization effect of PEG 400 and PEG 4000, T_g is lowered to around 60°C.[51] The second peak is ranging from 256°C to 271°C which may be attributed to the degradation of Soluplus since it has a degradation temperature (T_d) at around 278°C.[16] The absence of RXB endothermic peak at 233°C from the extruded filament and all the 3D printed tablets indicate the conversion of crystalline RXB into its amorphous state and this was confirmed also in XRPD patterns. To ensure that the second peak (256°C to 271°C) is not related to RXB, F14 placebo formula was prepared by removing the RXB from the F14 component and the other constituents remain the same then extruded and DSC of the resulting filament was done and shows the same two endothermic peaks as the formulas containing RXB, which confirms that the second peak is not related to RXB.

X-Ray Powder Diffraction (XRPD)

The XRD diffractogram of pure RXB and 3D printed tablets of selected formulas (F14, F15, F16, F17) are shown in (Figure 5). Analysis of powder diffraction patterns of pure RXB shows characteristic high-intensity peaks at 2θ = 16.4°, 19.4°, 19.8°, 22.4°, 25.6°, and 26.6° that are typical of crystalline RXB.[14] The absence of the characteristic peaks of RXB from the diffraction pattern of all selected 3D printed tablets confirms

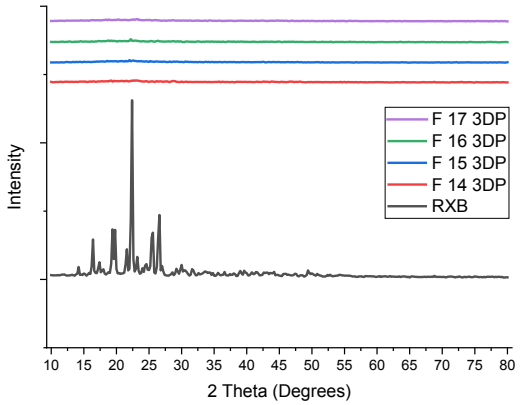


Figure 5: XRPD patterns of pure RXB and 3D printed tablets of F14, F15, F16, and F17.

the conversion of crystalline RXB into its amorphous state during the thermal process of HME and FDM 3D printing.

CONCLUSION

Formulation of Rivaroxaban immediate-release tablets was successfully done through the coupling of hot melt extrusion and fused deposition modeling 3D printing. Polymers selection and plasticizers ratios were crucial for the formulation of filaments with appropriate mechanical properties to be suitable for FDM printing. Improved solubility and dissolution of Rivaroxaban were achieved by the formation of amorphous solid dispersion during HME and FDM 3D printing. Infill percentage was found to significantly affect the dissolution rate where the 50% infill tablets were dissolved faster than the 100% infill tablets.

The combination of HME and FDM 3D printing is considered a potential tool to formulate personalized dosage forms with the required dose and release profile, yet further investigation and development of polymers specifically designed for this technique are mandatory to avoid the common drawbacks to make the process more producible.

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