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3D printing of pharmaceutical oral solid dosage forms by fused deposition: the enhancement of printability using plasticised HPMCAS

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ABSTRACT

3D printing (3DP) by fused deposition modelling (FDM) is one of the most extensively developed methods in additive manufacturing. Optimizing printability by improving feedability, nozzle extrusion, and layer deposition is crucial for manufacturing solid oral dosage forms with desirable properties. This work aimed to use HPMCAS (Affinisol™ HPMCAS 716) to prepare filaments for FDM-3DP using hot-melt extrusion (HME). It explored and demonstrated the effect of HME-filament composition and fabrication on printability by evaluating thermal, mechanical, and thermo-rheological properties. It also showed that the HME-Polymer filament composition used in FDM-3DP manufacture of oral solid dosage forms provides a tailored drug release profile. HME (HAAKE MiniLab) and FDM-3DP (MakerBot) were used to prepare HME-filaments and printed objects, respectively. Two diverse ways of improving the mechanical properties of HME-filaments were deduced by changing the formulation to enable feeding through the roller gears of the printer nozzle. These include plasticizing the polymer and adding an insoluble structuring agent (talc) into the formulation. Experimental feedability was predicted using texture analysis results, was a function of PEG concentration, and glass-transition temperature \(T_g\) values of HME-filaments. The effect of high HME screw speed (100 rpm) resulted in inhomogeneity of HME-filament, which resulted in inconsistency of the printer nozzle extrudate and printed layers. The variability of the glass-transition temperature \(T_g\) of the HME-filament supported by scanning electron microscopy (SEM) images of nozzle extrudates and the lateral wall of the printed tablet helped explain this result. The melt viscosity of HPMCAS formulations was investigated using a capillary rheometer. The high viscosity of unplasticized HPMCAS was concluded to be an additional restriction for nozzle extrusion. The plasticization of HPMCAS and the addition of talc into the formulation were shown to improve thickness consistency of printed layers (using homogeneous HME-filaments). A good correlation \((R^2=0.9546)\) between the solidification threshold (low-frequency oscillation test determined by parallel-plate rheometer) and \(T_g\) of HME-filaments was also established. Drug-loaded and placebo HPMCAS-based formulations were shown to be successfully printed, with the former providing tailored drug release profiles based on variation of internal geometry (infill).

**Keywords:** 3D printability, FDM, heat-fusion deposition, printability, filament, rheology, mechanical properties.
FDM-3DP: the improvement of printability utilizing HPMCAS-polymer
1. INTRODUCTION

Among other additive manufacturing methods, 3D printing (3DP) by fused deposition modelling (FDM) is one of the most commonly employed (Norman, Madurawe et al., 2017; Mathew, Pitzanti et al., 2020; Wallis, Al-Dulimi et al., 2020; Brambilla, Okafor-Muo et al., 2021; Katsiotis, Åhlén et al., 2021; Nashed, Lam et al., 2021; Patel, Khoder et al., 2021). FDM-3DP is highly anticipated to be the first 3DP technology deployed by pharmacies due to its relative user simplicity (Kipping, 2021). There is an increasing interest in the use of FDM-3DP for the manufacture of pharmaceutical oral dosage forms. This is driven by the ability of FDM-3DP to provide flexibility in dosage form design. Also, drug release from printed dosage forms can be modified using different polymers, other excipients and through alteration of design geometry and/or internal structure (Januskaite, Xu et al., 2020; Wang, Dumpa et al., 2020; Borandeh, van Bochove et al., 2021; Fanous, Bitar et al., 2021; Patel, Khoder et al., 2021). In the context of personalized medicine, patient-centricity, and targeted therapies, 3D permits the manufacture of dosage forms with tailored dose strengths and drug release profiles to be delivered to specific parts of the gastrointestinal tract to optimize medication outcomes (Scoutaris, Ross et al., 2018; Tan, Maniruzzaman et al., 2018; Palekar, Nukala et al., 2019; Cerda, Arifi et al., 2020; Dumpa, Butreddy et al., 2021). Compared to large-scale dosage form production, FDM-3DP follows a new paradigm (Rayna and Striukova, 2021). Unlike conventional manufacturing techniques, FDM-3DP permits on-demand tablet production with tailored dose and drug release patterns avoiding stock storage and material wastage (Khaled, Alexander et al., 2018; Park, Choi et al., 2018; Thakkar, Pillai et al., 2020; Gultekin, Tort et al., 2021; Krause, Müller et al., 2021). FDM-3DP also allows lifecycle management opportunities to prolong the intellectual ownership of innovative products in the period of exclusivity loss (FierceMarkets, 2021).

The method consists of: the design of the 3D structure of the dosage form using a computer-aided design (CAD) software, the conversion of the CAD file into a printer-readable file format (.stl), and the initiation of the printing process by uploading the stl-file into the printer software (Dumpa, Butreddy et al., 2021). The pre-compounded drug-loaded filament is fed into the printer nozzle by feeding gears equipped with rollers. In the heating zone of the printer nozzle, the filament is melted at a specific temperature (the temperature of the heating zone is a dependent variable) and then squeezed in the form of molten viscous liquid through a heated nozzle (nozzle extrusion process) to form a 3D object upon solidification by layer-to-layer deposition. The printing process occurs on the printer's build plate, whose temperature along
with that of the surrounding environment (equipment dependent) can be controlled to influence the layer-to-layer deposition temperature (Gibson, Rosen et al., 2010; Ilyes, Kovacs et al., 2019; Elbadawi, Muniz Castro et al., 2020; Ivone, Yang et al., 2021).

One of the main challenges of FDM-3DP is the lack of suitable pharmaceutical excipients (Govender, Ofosu Kissi et al., 2021; Tabriz, Scoutaris et al., 2021; Wang, Zhang et al., 2021). The manufacture of filaments by hot-melt extrusion (HME) significantly increases the possibilities of FDM-3DP (Shaqour, Samaro et al., 2020). HME allows the formulation of drug-loaded filaments with different physicochemical properties due to short (minutes) processing time within a wide temperature range and predetermined mechanical/mixing (characterized by torque). The HME processing temperature of thermoplastic materials should be set high enough to provide a melt viscosity lower than the maximum allowed (equipment-dependent) torque.

FDM-3DP is a multistage process. To enable the successful printing of dosage forms (printability), the properties of fed HME-filaments should meet print requirements (Bandari, Nyavanandi et al., 2021; Henry, Samaro et al., 2021). Printability is a new term, and it has been defined differently across various publications, with the stated examples having some relevance to our current work. Recently, printability has been defined as the ability of HME-filaments to possess specific mechanical and rheological properties, which include: to withstand the mechanical impact of the printer feeding gear; to be extruded (in the molten state) through the nozzle; to provide an acceptable layer deposition and adhesion (Elbadawi, Muniz Castro et al., 2020; Xu, Li et al., 2020; Govender, Ofosu Kissi et al., 2021; Tabriz, Scoutaris et al., 2021). In other work, printability was defined using dimensional deviation and calculated as the ratio between the achieved dimension of the printed object and its target dimension (Azam, Zhang et al., 2018).

The mechanical properties of HME-filaments are composition- (both qualitative and quantitative) and HME-processing dependent. In some cases, functional polymers (e.g., hypromellose acetate succinate) can provide desirable drug release from HME-filaments but cannot be directly used for printing because they do not meet printability requirements. Nevertheless, polymers with high $T_g$ ($T_g > 100\,^\circ C$) can be used to prepare HME-filaments that can be applied for FDM-3DP after compounding with plasticizers which reduce their glass transition temperature (Pereira, Figueiredo et al., 2020).
The ability of molten material to be pushed forward through the printer nozzle depends on its composition and rheological properties at the applied temperature (Ilyes, Kovacs et al., 2019; Samaro, Janssens et al., 2020). The applied temperature, in this case, is a function of the set printing temperature and the environmental temperature, which results in the true temperature of the nozzle tip and the material upon extrusion from the nozzle (Henry, Samaro et al., 2021). Compared to HME, the printer extrusion unit has a much simpler mechanical system for flow, with the nozzle tip outlet having a smaller diameter. Therefore, a comparatively higher temperature should be applied to achieve a lower viscosity to squeeze the molten material through the printer nozzle. Most printers have a narrow temperature range or a single applied printing temperature, making the processing temperature a significant limiting factor in choosing materials (Shaqour, Samaro et al., 2020).

The choice of a suitable plasticiser, its amount, and homogeneous distribution within the HME-filament are crucial for a homogeneous structure, physicochemical and mechanical properties of the HME-filament and consequently, reproducible rheology of the molten material within the printer nozzle, extrusion through the printer nozzle, printing accuracy (theoretical vs. printed dimensions of the object) and properties of the printed object (Pereira, Figueiredo et al., 2020). The examples of polymer plasticisation and appropriate homogenization can be found in the literature. Co-dissolving the plasticiser and polymer in an acceptable solvent, followed by forming a polymer-plasticiser film by solvent evaporation and the use of ground film to prepare the HME-filament (Elbadawi, Gustafsson et al., 2020) is one approach. The second is more practical and widely accepted, involving direct polymer and plasticiser compounding and processing (Fanous, Gold et al., 2020; Katopodis, Kapourani et al., 2020). The use of the second approach may be more time- and resource-consuming at development stage but much easier to scale making it more attractive for mass production.

HPMCAS (Affinisol™ HPMCAS 716 or AQQAT® AS-L) is a commonly used functional polymer in the formulation of oral solid dosage forms. Due to its chemical nature (acetyl and succinoyl functional group content dependent), it has a pH-dependent solubility (soluble at pH higher than 5.5) and can be used for pH targeted drug release (Colorcon, 2016; Giri, Poudel et al., 2020). Pure HPMCAS cannot be used in FDM-3DP because the resultant HME-filaments are too brittle to be fed through the printer roller gears. Brittleness is a widespread problem for the range of existing HME polymers used for FDM-3DP and similar challenges have been reported for Soluplus®, Kollidon® VA64, and Eudragit® EPO (Gottschalk, Bogdahn et al.,...
Thus, optimizing HPMCAS HME-filament properties by plasticisation would be a logical approach to improve its printability; this is an example of a formulation approach for brittle polymers.

HPMCAS is intended for delayed and sustained release (Colorcon, 2016; Goyanes, Fernandez-Ferreiro et al., 2018; Pereira, Figueiredo et al., 2020; Nashed, Lam et al., 2021). In the printed tablet the drug is situated in the polymer matrix of printed filament. Drug release from the matrix is a function of dissolution of the polymeric matrix, matrix erosion, drug dissolution from the matrix, dissolution media diffusion into the matrix and drug diffusion through the matrix into the dissolution media (Borandeh, van Bochove et al., 2021; Nashed, Lam et al., 2021; Patel, Khoder et al., 2021; Shi, Salvage et al., 2021). Drug release from delayed release tablets is also dependent on the polymer matrix composition (incl. soluble or insoluble plasticiser), drug loading and the internal structure of the formulations (Goyanes, Fina et al., 2017). The internal structure of a 3DP tablet formulation (e.g., infill percentages) has a profound influence on drug release (Thakkar, Pillai et al., 2020; Dos Santos, Deon et al., 2021; Müller, Krause et al., 2021; Obeid, Madzarevic et al., 2021; Sharma, Shaik et al., 2021). Moreover, it has been shown that if low-density tablets (varying the infill density) can be printed then gastroretentive tablets can be manufactured (Dumpa, Bandari et al., 2020; Pitzanti, Mathew et al., 2021). Moreover, the surface area to volume ratio has a profound influence on the mean dissolution time and drug release profile (Windolf, Chamberlain et al., 2021; Lapidus and Lordi, 1968; Chen, Desai et al., 2016).

The aim of this work was to use HPMCAS polymer (Affinisol™ HPMCAS 716) to prepare HME-filaments intended for FDM-3DP. The study targeted exploring and demonstrating the effect of HME-filament composition and process conditions on printability using thermal, mechanical, and thermo-rheological properties. In addition, the work aimed to evaluate the ability of the chosen polymer to produce an oral solid dosage form with a tailored drug release profile.
2. MATERIALS AND METHODS

2.1. Materials

Hypromellose acetate succinate (HPMCAS; Affinisol™ HPMCAS 716) was a generous gift from DOW Chemical Company (USA). Polyethylene glycol (PEG 600), dibutyl sebacate (DBS), and triethyl citrate (TEC) were purchased from Sigma Aldrich (UK) and used as plasticisers to improve the mechanical properties. Talc powder, purchased from Alfa Aesar/Thermo Fisher Scientific (USA), was employed as a thermostable filler. Hydrochlorothiazide (HTZ), employed as the model drug, was purchased from Sigma Aldrich (UK). Other chemicals used to prepare the dissolution media were of Pharmacopoeia grade and used as received.

2.2. Preparation of filaments using Hot Melt Extrusion (HME)

Various compositions of individual raw materials (Table 1) were accurately weighed and mixed with a mortar and pestle. Formulations F1, F2, and F4 had ratios of HPMCAS, and PEG as follows, 90:10, 85:15, and 80:20, respectively. Formulation F3 maintained an identical ratio of HPMCAS and PEG to formulation F2 (85:15) but included the 5% (w/w) of HTZ (based on the total weight). In formulation F5, the proportion of HPMCAS and PEG was identical to F4 (80:20) but included 20% (w/w) of Talc (based on the total weight). The resultant physical mixture of each formulation was fed manually into a co-rotating twin-screw HAAKE MiniLab extruder (Thermo Electron Corporation, Germany). Mixtures were extruded at 165°C with a screw speed of 30 or 100 rpm through a 1.5 mm die. The viscous extrudates were cooled via haul-off on a small conveyor belt (Ningbo Yinzhou Longway Tech Co., Ltd., China) at room temperature. Solid rod-like filaments were collected and stored in air-tight bags in a vacuum desiccator.

2.3. 3D printing using heat-fusion deposition (HFD) modelling

Tablets were designed using TinkerCad 2018 (Autodesk Inc., USA), and the template was exported as a stereolithography file (.stl) into the printer software (MakerBot Print ver. 2.8.1, MakerBot Inc., USA). The dimensions of tablets were: 4 mm thickness and diameter of 10 mm. A 3D printer (MakerBot Replicator 2X desktop 3D printer, USA) equipped with an extrusion nozzle of 0.4 mm diameter was used to print tablets using the pre-fabricated HME extrudates. A printing temperature of 170°C and a heated platform of 50°C were used in all printing processes. Other printer settings used include speed while extruding (20 mm/s), speed while travelling (20 mm/s), infill percentage (30, 65, or 100 %), number of shells (two), layer height
layer-to-layer deposition temperature during FDM-3DP was determined by analysing the thermal videos captured in Vernier Thermal Analysis™ Plus App (Vernier Software & Technology, USA), taken using FLIRONE® PRO LT smartphone accessory thermal imaging camera (third generation; FLIR, USA). The minimum observation distance between the surface of the tablet and the camera lens was set at approximately 15 cm to ensure focus. The temperature measured by the FLIR camera was confirmed by external validation, with a difference of ±1°C obtained between the data of an analogue thermometer and the IR-camera in the temperature range between 50 and 90°C.

2.4. Thermogravimetric analysis (TGA)

The thermal stability of each component and their physical mixtures were examined using Thermal Advantage Q50 TGA (TA Instruments, USA). The results were further analysed using a Universal Analysis Software version 4.5A (TA Instruments, USA). A decomposition temperature was determined for each sample when significant weight loss occurred (5% by mass). For analysis, samples (5-10 mg) were heated in an open aluminium pan at a heating rate of 10°C/min from room temperature to 400°C. Nitrogen was used as a purge gas at a flow rate of 40 mL/min for all TGA experiments. The weight remaining (%) was plotted as a function of temperature (°C).

2.5. Differential scanning calorimetry (DSC) and temperature modulated DSC (TM-DSC)

DSC was used to deduce the thermal properties of the materials. Thermal experiments were conducted on a Q20 DSC (TA Instruments, USA) and Universal Analysis Software version 4.5A was used for the determination of thermal events. Samples (5 – 10 mg) were accurately weighed into aluminium DSC-pans and crimped with an aluminium pan lid. Nitrogen was used as a purge gas for all experiments at a flow rate of 50 mL/min to retain an inert atmosphere. Indium was used to calibrate the machine for cell constant and enthalpy. Preliminary DSC studies were conducted on pure excipients, physical mixtures, and extrudates. A heating rate of 10°C/min was used for all experiments. For pure HMPCAS, physical mixtures and extrudates at plasticiser concentrations of 10, 15, and 20% w/w with or without talc, the crimped pan was subjected to a heat-cool-heat cycle by heating from -40°C to 180°C, then cooling to -40°C before heating back up to 220°C. The plasticisers (PEG 600, DBS, and TEC) were heated from -40°C to 50°C. All samples were analysed in triplicate.
A temperature modulated DSC heat-cool-heat cycle was also performed on extrudates using
DSC 214 Polyma (Netzsch, Germany) within a heating range of -60°C to 200 or 250°C. All
experiments were conducted with a sample mass of 5–10 mg in crimped aluminium DSC-pans.
A heating rate of 5°C/min, a modulation period of 60 s, and a modulation amplitude of 0.796°C
were applied. The glass transition temperature was determined using Proteus thermal analysis
software ver. 8.0 (Netzsch, Germany). All experiments were performed in triplicate.

2.6. Determination of drug solubility in the polymer in accordance with Gordon-Taylor
equation
For the determination of HTZ solubility, the Gordon-Taylor equation was employed (An, He
et al., 1997) to calculate the theoretical $T_g$ of formulation F3 ($T_{g\ F3}$):

$$T_{g\ F3} = \frac{w_1 T_{g\ 1} + K w_2 T_{g\ 2}}{w_1 + K w_2}$$

where: $w_1$ and $T_{g\ 1}$ are weight fraction and $T_g$ of HPMCAS mixture with 15% (w/w) PEG (F2),
respectively; $w_2$ and $T_{g\ 2}$ are weight fraction and $T_g$ of pure HTZ, respectively; K is a constant
parameter; and $\Delta C_{p\ 1}$ and $\Delta C_{p\ 2}$ are the change in heat capacity associated with $T_g$ (TM-DSC
determined) for formulation F2 and pure HTZ, respectively.

2.7. Rheological Studies
Melt viscosity analysis was performed using a twin-bore benchtop capillary rheometer (Rosand
RH2000; Malvern, UK) at 170°C (printing temperature) for all tests. Physical mixtures of
HPMCAS with plasticiser at content of at 10, 15, and 20% w/w with or without talc were
analysed. Both Bagley and Weißenberg-Rabinowitsch correction factors were used (Schramm,
2000). Bagley correction was performed through simultaneous measurements on both long
(16 mm, on the left side) and short (“zero”, on the right side) dies by determining the inlet
pressure drop at the die (diameter of 1 mm), and hence absolute viscosity. The capillary
rheometer was preheated before loading with the sample. Each barrel was loaded with 30 g of
sample and manually compressed to remove air gaps before compressing with the pistons.
After heating the sample, both barrels were compressed at a speed of 20 mm/min until
extrudates were produced from both dies before running the test. The tests were run in 5 stages
with shear rates of 10, 15, 20, 30, and 50 s⁻¹. An equilibrium pressure reading was obtained for
an average of four samples at each shear rate. Results were plotted as viscosity versus shear rate.

In addition, rheology studies were performed through oscillatory analysis using an AR2000 rheometer (TA Instruments, USA). A parallel plate with crosshatch surface and diameter of 20 mm was utilized for testing at a 1000 µm sample gap. Extrudates were placed on the rheometer lower stationary plate, melted at higher temperatures, and allowed to equilibrate for two minutes in the pre-conditioning step. A continuous flow ramp was performed on all formulations from shear rate 1 to 100 s⁻¹ at 70 and 90°C.

A temperature sweep analysis was undertaken within the range of 170 to 100°C using AR2000 rheometer (TA Instruments, USA) to determine storage ($G'$) and loss modulus ($G''$). The phase angle ($\delta$, [degrees]) was determined using the following equation (Grillet, Wyatt et al., 2012):

$$\delta = \arctan \delta$$

$$\tan \delta = \frac{G''}{G'}$$

An angular frequency of 0.16 Hz and constant strain ($2.5 \times 10^{-5}$) were applied for all formulations. The output data was generated by TA rheology analysis software (TA Instruments, USA). All experiments were performed in triplicate.

2.8. Filament’s flexibility determination by Texture Analysis

Texture analysis was used to determine the flexibility of the filament, which influences its feedability through the driving gears into the printer nozzle. The filament’s flexibility was determined by compression testing using a TA.XTplus Texture Analyser (Stable Micro Systems, UK). The extruded filament samples with the required diameter were cut into 50 mm segments and fixed vertically with clamps. A compression speed of 3 mm/sec was used to compress the filaments axially through a distance of 20 mm, with a trigger force of 0.05 N. All tests were performed in triplicate. (Xu, Li et al., 2020)

2.9. Scanning Electron Microscopy (SEM) and Particle Size Distribution Analysis

SEM pictures were captured (SEM microscope model TM3030; Hitachi High-Tech Corp., Japan) under vacuum at 15 kV to obtain information about printed tablet and talc powder morphology on a microscopic level.
Particle size distribution of talc was determined by powder dispersion in deionized water, followed by dynamic light scattering measurements, which were analysed with inbuilt software (ver. 3.62) (Mastersizer 3000; Malvern Instruments, UK). Analysis was performed in triplicate.

2.10. Assessment of printed tablet and filament dimensions

Tablet dimensions were measured to compare the printed tablet dimensions to the designed prototype. The diameter and thickness of tablets printed with each filament and the diameter of the filaments used for printing were measured using a digital calliper (Duratool, UK) with a resolution of 0.01 mm. The diameter of the filaments was measured at a frequency of 2 cm along its length.

2.11. Dissolution test

HTZ release from the 3D-printed tablets were determined under sink conditions for 2 hours at pH 1.2 and for 10 hours at pH 6.8. In brief, 750 ml of 0.1 N HCl solution (pH 1.2) was used during the first 2h, and 250 ml of preheated (37°C) 0.2 M Na3PO4 solution was added to achieve the resultant pH 6.8. The dissolution test was carried out using USP Apparatus II (VK 7000; VanKel Industries Inc, USA) at 37°C and a paddle speed of 50 rpm. During the dissolution test, the absorbance of HTZ was measured (every 60 s) at a wavelength $\lambda_{\text{max}}$ of 272 nm using in-situ fibre-optic UV-probes, equipped with 10 mm pathlength tips and connected to a Rainbow® µDISS Profiler™ (Pion Inc., MA, USA). The HTZ concentration was instantly measured in each vessel using the equations deduced from the calibration curves at pH 1.2 (C=A•25.84-0.143; $R^2=0.9996$) and pH 6.8 (C=A•18.32-0.085; $R^2=0.9997$). Drug release from each formulation was measured in triplicate.

2.12. Statistical Analysis

The variation between DSC and TM-DSC results, texture analysis data, tablet properties, and solidification results were statistically analysed using one-way analysis of variance (ANOVA) with a post-hoc test (Tukey-Kramer’s test) for individual differences (GraphPad Prism ver. 8; GraphPad Software Inc., USA). The software provides a significance value (P-value) for each comparison based on the confidence interval set at 95%; this means that a ‘P’ value less than 0.05 signifies a significant difference between the two data sets.
3. RESULTS AND DISCUSSION

3.1. Plasticisation of HPMCAS polymer and thermal analysis of polymer compositions

The degradation temperature ($T_d$) deduced from TGA analysis was used to evaluate the thermal stability of materials during HME and FDM-3DP processes. Based on the $T_d$, HPMCAS was thermally stable up to $253\pm3^\circ C$ (Av.±S.D.; Figure 1A). The HPMCAS-polymer was plasticised to improve its processability for FDM-3DP. As such, common plasticisers (TEG, TEC, and DBS) were examined. The $T_d$ results showed that PEG had higher thermal stability compared to TEC and DBS: $PEG (245\pm6^\circ C) > DBS (175\pm2^\circ C) > TEC (149\pm5^\circ C)$. Subsequently, analysis performed on physical mixtures of HPMCAS with each plasticiser at 10% (w/w) concentration confirmed that blends containing PEG had higher thermal stability compared to blends with DBS and TEC: $PEG (263\pm3^\circ C) > DBS (210\pm6^\circ C) > TEC (178 \pm 7^\circ C)$. Further analysis was performed using PEG formulations because of their higher thermal stability. Talc was included in the filament formulation and its $T_d$ was re-evaluated. Talc is an inorganic crystalline silicate mineral; thus, it did not show any $T_d$ in the investigated temperature range, confirming its thermal stability during HME and FDM-3DP processing (Pereira, Figueiredo et al., 2020). HTZ showed a high $T_d (303\pm1^\circ C)$, suggesting no additional limitations were posed by the thermal stability of the model drug.

DSC was used to examine the thermal properties of excipients, focusing on glass transition temperature ($T_g$) and melting temperature ($T_m$). Based on the DSC thermograms (Figure 1B), the $T_g$ of HPMCAS was $122.2\pm0.6^\circ C$, the $T_m$ of PEG was $18.4\pm0.4^\circ C$, and the $T_m$ of HTZ was $271.7\pm0.3^\circ C$, during a single heat cycle. After rapid cooling cycle, the $T_g$ of HTZ was observed in the second heat cycle at $103.1\pm0.8^\circ C$.

The inclusion of PEG into HPMCAS was to decrease the $T_g$ of the polymer-plasticiser mixture, increase the plasticity of the HME-filament, and decrease blend viscosity. To evaluate the effect of varying PEG concentration on the $T_g$ of HPMCAS, HME was used to homogenously disperse PEG within the polymeric matrix at a screw speed of 30 rpm and an extrusion temperature of $165^\circ C$. The obtained TM-DSC thermograms showed a corresponding significant decrease in the $T_g$ of HPMCAS ($105.4\pm1.0^\circ C$) with increasing PEG concentration from 10-15-20% w/w resulting in glass transition values of: $53.8\pm0.4^\circ C > 40.9\pm0.5^\circ C > 33.7\pm1.6^\circ C$, respectively (Figure 1C). Furthermore, the results showed that the addition of talc (F5) had no significant impact on $T_g$ when compared to the formulation without HTZ (F4): $35.2\pm1.2^\circ C$ vs. $33.7\pm1.6^\circ C$, respectively. However, the inclusion of HTZ (F3 vs. F2) resulted
in a significant increase in $T_g$ (48.0±0.5°C vs. 40.9±0.5°C, respectively) due to the relatively high $T_g$ of HTZ and HTZ solubility in the formulation. The TM-DSC results of formulation F3 (experimentally measured) were similar to the theoretically calculated $T_g$ values (48.0 vs. 47.9°C) obtained using the Gordon-Taylor equation. This result confirmed the complete dissolution of HTZ within the HPMCAS-polymer (F3), explaining the increase in $T_g$ observed compared to formulations without HTZ (F3 vs. F2).

3.2. Filament fabrication by HME and its utilization for FDM-3DP

Formulations were prepared by HME at screw speeds of 100 and 30 rpm while all other conditions were kept constant, including a processing temperature of 165°C. Formulation F1 containing 10% (w/w) PEG-processed at 100 rpm produced $T_g$ values with high levels of variability across the extrudate length (up to ±12°C), suggesting the high screw speed applied did not provide homogeneous PEG distribution. On the other hand, at 30 rpm (longer residence time), the variability (using SD as a measure of the $T_g$) F1, F2 and F4 (with higher PEG-plastici
er content of 10, 14, and 20% w/w) were ±0.4, ±0.5, and ±1.1°C, respectively, suggesting the more homogeneous distribution of PEG within the extrudate.

Formulation F1 (100 rpm) and F2 (30 rpm) were used to examine the effect of HME-filament homogeneity on quality of printer nozzle extrudates and subsequently printed tablets. The high levels of PEG variability (demonstrated by variation of $T_g$ across length of extrudate) within F1 (100 rpm) resulted in an irregular shape and structure of nozzle extrudate and thus printed tablet (Figure 2). Conversely, formulation F2, produced a uniform nozzle extrudate and printed tablet. Visual observation of the printed structure prepared using the HME-filament (F1; 100 rpm) confirmed inconsistent flow (Figure 2) caused by the heterogeneity of the molten blend due to the presence of over- and under-plasticised PEG regions.

On the other hand, when using filaments (F2; 15% of PEG), the extrudates egressed from the printer nozzle (diameter of 0.4 mm) and had reproducible dimensions (0.41±0.01 mm), producing printed tablets with dimensions to the designed prototype (Figure 2). This result shows the importance of filament homogeneity on melt flow consistency during printing and thus printability in terms of printed tablet structure, shape, and dimension.

The heterogeneity of HME-filaments was successfully resolved by decreasing the screw speed from 100 to 30 rpm, thus increasing the residence time for mixing. The increased residence
time generated more homogeneous samples, which were confirmed by the presence of a low
standard deviation across $T_g$ values and more consistent (acceptable for FDM-3DP) HME-
filaments dimensions (1.65±0.05 mm). Homogeneous HME-filaments were prepared for F1, 
F2, and F3 at 30 rpm, which allowed tablets to be successfully printed by FDM-3DP (Figure
3; Table 2). However, formulation F4 could not be consistently fed into the printer nozzle as it coiled up within the roller gears, suggesting over-plasticisation and insufficient stiffness of the HME-filament.

The SEM images enabled visualisation of the impact of formulation composition on the quality of printed layers. F1 and F2 showed excellent layer-to-layer deposition (Figure 3). Formulation F2 had irregular layer structure, which demonstrated the effect of higher PEG-plasticisation on the structure of printed tablets. Inconsistency within printed layer structure suggested the presence of a prolonged fluid state during layered deposition and solidification. Thus, increasing the PEG concentration from 10 to 15 %w/w resulted in an inability to maintain tablet layer quality. It was impossible to observe the effect of higher plasticisation (F4: PEG 20%, w/w) on the structure of printed layers because the HME-filaments (F4) were too flexible to be fed by the printer roller gears into the printer nozzle, thereby suggesting excessive plasticisation. Moreover, considering the effect of increased PEG concentration from 10 to 15% (w/w) and the appearance of inhomogeneous F1 formulations with over-plasticised regions, 20% PEG concentration would result a decrease quality, indicted by increased thickness variability and structural inconsistency. While PEG-plasticiser concentrations of 10 and 15% (w/w) enabled the fabrication and printability of HME-filament by plasticising the HPMCAS-polymer (overcoming its brittleness), a PEG concentration of 20% (w/w) prevented filament feeding.

To improve the stiffness of the F4 HME-filament, talc (Kibbe, 2006), was introduced into the F4 composition to produce the F5 HME-filament (Figure 1 A and B). In formulation F5, the HPMCAS-PEG proportion of F4 (80 and 20% w/w, respectively) was maintained, and talc was introduced at a concentration of 20 %w/w (Table 1). The inclusion of talc did not influence the $T_g$ of the formulation (F4 vs. F5; (Figure 1 C) but made it printable: the filaments were successfully fed, extruded through the printer nozzle, and layered on the build plate (Figure 3, Table 2). Talc increased the HME-filament’s stiffness which supported feeding by the printer roller gears and extrusion through the printer nozzle. Visual comparison of the SEM images of formulations F2 and F5 printed tablets showed better reproducibility of the layer height in
formulation F5. However, the formulation F5 tablet showed greater layer surface roughness relative to formulation F2. The improved layer height reproducibility (F5 vs. F2) suggests that even at a higher level of plasticisation (20 vs. 15% w/w PEG, respectively), the inclusion of talc positively influenced the rheological properties of the nozzle extrudate. This suggests that during the deposition of new layers, the extrudate with talc (F5) had a more viscous structure resulting in less layer deformation during solidification. The usage of talc in FDM 3D printing has been previously reported as an inert additive for the improvement of the flow of the printer nozzle extrudate, regulating the filament diameter, and helping achieve successful 3D printing (Okwuosa, Stefaniak et al., 2016; Sadia, Sosnicka et al., 2016; Okwuosa, Pereira et al., 2017; Choudhury, Murty et al., 2021).

The incorporation of HTZ at a concentration of 5% (F3) increased the reproducibility of the layer height (Figure 1 C) compared to the F2 formulation, indicating the influence of HTZ on the rheological properties of the formulation with the formation of a more solid structure (F3) during layer-to-layer deposition. The influence of HTZ on the rheological properties of the formulation could be further explained through an elevated T_g value obtained for F3 relative to F2 (48.0±0.5°C vs. 40.9±0.5°C, respectively; Figure 1 C), driven by the high T_g of HTZ (103.1±0.8°C; Figure 1 B).

No significant difference was observed between printed tablet apparent volume for F1, F2, and F5, but a significant difference was observed in weight and apparent density (Table 2). Comparing formulation F1 and F2, the different densities can be explained by the different melt flow properties; a higher level of plasticisation resulting in higher melt flow (Henry, Samaro et al., 2021). For F1 and F2 relative to F5, differences can be explained by the high true density of talc (Kibbe, 2006). As expected, a decrease in infill percentage (design-dependent printing parameter) from 100 to 65 to 30%, exemplified by formulation F3, resulted in a significant reduction in the printed tablet weight and apparent density from 0.93±0.02 to 0.82±0.02 to 0.70±0.01 mg/mm^3, respectively (Table 2).

3.3. Mechanical properties of HME-filaments: force-displacement profiles
Filament flexibility and stiffness impact feeding potential and thus printability. The roller gears could not continuously feed HME-filaments of pure HPMCAS into the printer nozzle due to its brittle nature. Conversely, HME-filaments containing 10 and 15% (w/w) of PEG (F1 and F2) were shown to be applicable for FDM-3DP due to continuous feeding by the roller gears
into the printer nozzle. However, the formulation containing 20\% (w/w) PEG (F4) was too flexibility (too ductile), resulting in it coiling up within the roller gears. The inclusion of talc (F5 vs. F4) improved the stiffness of the HME-filament, making it feedable by the roller gears. These practical results were compared with the compression tests results, which could be used as a pre-screening tool for the determination of FDM-3DP processability. The compression test determined the force-displacement profiles of HME-filaments to examine the relationship between the feeding ability and mechanical properties of HME-filaments (Ilyes, Kovacs et al., 2019; Xu, Li et al., 2020).

Deformation (flexibility) of HME-filament is reflected in breaking force (“breaking point”), while the stiffness of the filament is reflected by bending force (Bf; “bending point” on the graph) (Xu, Li et al., 2020). Pure HPMCAS HME-filaments demonstrated relatively high Bf at 35.6±1.8 N and breaking force of 17±0.5 N after approximately 16 mm (Figure 4). The plasticisation of HPMCAS with 10, 15, and 20\% (w/w) PEG resulted in a decrease in Bf to 9.3±0.5, 7.5±0.2, and 2.7±0.7 N, for F1, F2, and F4, respectively. The Bf results obtained correlated well (R²=0.984) with the corresponding Tg values (Figure 5). The low Bf of F4 HME-filament resulted in highly ductile behaviour with an inadequate level of stiffness, resulting in an inability to feed these filaments through the roller gears. The HME-filament containing 15\% (w/w) PEG and 5\% (w/w) HTZ (F3) generated a Bf of 10.6±1.6 N, which was a significantly greater than the bending force of the formulation without HTZ (F2). A similar observation occurred for the HME-filament with 20\% (w/w) PEG containing talc (F5). Formulation F5 (including talc) demonstrated a Bf of 10.8±1.6 N, which was significantly greater that the formulation devoid of talc (F4). The increase in Bf through the addition of HTZ can be explained by the increased Tg of F3 compared to F2, which occurred due to the high Tg of HTZ (Figure 1 C). However, the increase in Bf by the addition of talc can be explained by the structuring of talc particles within the HME-filament (Supplement) at the given particle size distribution (D_{10} 3.15 µm, D_{50} 11.7 µm, D_{90} 38.2 µm). In contrast to other force-displacement profiles, F5 showed small incomplete breaking steps (Figure 4) related to microstructural cracks caused by talc particles within the structure. In contrast to the force-displacement profile of pure HPMCAS-polymer, the rest of the profiles did not show any breaking point under test conditions.
3.4. Rheology studies of molten material to understand its behaviour during FDM-3DP

HME and FDM-3DP are non-ambient processes involving polymeric melt flow through the extruder die and printer nozzle tip. In contrast with FDM-3DP, the melt flow during HME is facilitated by the action of rotating screws; thus, extruders can work with more viscous materials (Zecevic and Wagner, 2013). While hot-melt extruders can be operated within a wide temperature range, the printer nozzle heating zone is usually operated at a much narrower range. In addition, FDM-3DP utilizes HME-filaments with a diameter of approximately 1.75±0.05 mm, which must be imparted by extruder die and the haul-off conveyor belt. The FDM-3D printer nozzle has a diameter of 0.4 mm, thereby imposing additional requirements for viscosity reduction (Henry, Samaro et al., 2021). This information shows that the viscosity-temperature-dependent operating space of FDM-3DP should be more constrained than for HME. For both processes, the rheological properties of the molten material are very important to enable extrusion through the extruder die or printer nozzle. Thus, a capillary rheometer was chosen to characterize the melt flow behaviour of materials through viscosity measurements at a range of shear conditions and process-relevant temperatures (Jones, Margetson et al., 2015).

Capillary rheometry was performed at 170°C, the temperature of the printer nozzle heating zone, which was very close to the HME temperature (165°C). Therefore, the viscosity profiles obtained for each formulation through capillary rheology (Figure 6 A) reflected the behaviour of the formulation during extrusion from the printer nozzle. These profiles displayed a gradual decrease in the melt viscosity of HPMCAS with increasing plasticiser concentrations (10, 15, and 20% w/w of PEG, respectively for F1, F2, and F4), thus facilitating polymer extrusion through the printer nozzle. The inclusion of talc increased the viscosity of F5 compared to formulation F4, and F5 had a similar viscosity profile to F1. The high viscosity of HPMCAS relative to plasticised formulations suggests that nozzle extrusion of unplasticised polymer can present a significant challenge during feeding into the printer nozzle and possibly excluding direct extrusion (Mendibil, Tena et al., 2021; Zheng, Deng et al., 2021).

Rheological measurements at a low (close to zero) shear rate provides information about the material behaviour during layer-to-layer deposition. Layer-to-layer deposition occurs at low shear rates; therefore, rotational rheology (parallel plate rheometer) was better suited for melt rheological measurements at low strain value (Aho, Boetker et al., 2015). Thermal imaging by an infra-red camera allowed the determination of the temperature range during layer-to-layer
deposition (between 70 and 90°C); thus, the rotational rheometry analysis of melt viscosity was performed at 70 and 90°C.

The viscosity profile of pure HPMCAS polymer could not be obtained using parallel-plate rotational rheology at temperatures of interest (70 and 90°C) due to its high T_g (122°C) and viscosity. The results obtained at 90°C showed a decrease in melt viscosity with increasing PEG concentrations (Figure 6 B); however, no significant difference was observed between formulation F1 and F2 (10 and 15% (w/w) PEG, respectively). Moreover, the viscosity of the talc-containing formulation (F5) was higher than the formulation without talc (F4), which correlated with observation of layer thickness reproducibility (F5 vs. F2; Figure 3). Generally, the results at 70°C showed a decrease in melt viscosity with increasing PEG concentration (Figure 6 C); however, no significant difference was observed between the formulation with and without talc (F5 vs. F4).

The viscosity of the formulation at a low shear rate and its solidification temperature can provide an understanding of the possible extent of deformation that could occur during layer-to-layer deposition. The extent of deformation defines printability in relation to layer thickness and shape regularity, and subsequently, the quality of the final printed product. Thus, the solidification behaviour (phase angle) of formulations at certain conditions was considered important for successful printing (Vancauwenberghe, Katalagarianakis et al., 2017; Azam, Zhang et al., 2018). A phase angle (delta, degrees) value greater than 45° indicates liquid-like behaviour, less than 45° indicates solid-like properties, and equal to 45° indicates the solidification threshold.

The solidification temperature was found to decrease (144 > 130 > 115°C) with increasing PEG concentrations: 10 > 15 > 20% w/w (F1, F2 and F4, respectively; Figure 7). F1 had a higher solidification temperature and viscosity than F2 at low shear rates (Figure 6), resulting in the deterioration of layer shape and shape regularity observed in F2 (Figure 3). The lower the solidification temperature, the longer the time required to solidify. The addition of talc (F5) was found to increase the solidification temperature (119°C) compared to formulations devoid of talc (F4; 115°C). The rapid solidification after extrusion from the nozzle of the talc-containing formulation has been previously reported in the literature (Okwuosa, Stefaniak et al., 2016; Okwuosa, Soares et al., 2018). The rapid solidification can be attributed to the
suspension of talc within the molten formulation, thereby generating a flocculated system that has a higher viscosity (Abbott, 2018).

The addition of HTZ (F3) was also observed to slightly increase the solidification temperature (134°C) compared to formulation without HTZ (F2; 130°C), which could be related to the high T_g of HTZ (103.1°C). The high correlation coefficient (R^2=0.9546) between the T_g values of HME-filaments containing PEG and HTZ and their solidification thresholds supported this hypothesis (Figure 8). Moreover, the standard deviation of the printed tablet diameter followed a same trend, with the standard deviation decreasing from 0.05 mm for F2 to 0.03 mm for F3 and F1 (Table 2) as the solidification threshold temperature increases from 130°C to 134°C and 144°C (Figure 7), respectively. Employing different mechanisms, such as the use of talc and HTZ, were found to increase solidification temperature and thus improve printability in terms of layer height and printed tablet diameter reproducibility.

3.5. In vitro dissolution study

The number of preclinical and clinical studies involving the use of FDM-3DP dosage forms is increasingly demonstrating a huge step towards implementing personalized medicines produced using this technology (Seoane-Viano, Trenfield et al., 2021).

Within this study, the effect of the print design (the infill percentage) on the release profile of the model drug HTZ (formulation F3) was demonstrated. Thus, attempts were made to achieve tailored dissolution profiles from printed tablets with various infill percentages (30, 65, and 100%; Table 2) placed in sinkers. A delayed release of HTZ was observed due to the use of an enteric polymer (HPMCAS), where HTZ was not released (not more than 10% in accordance with pharmacopeia criteria for delayed release formulations) in simulated stomach conditions (pH 1.2) but completely released at simulated large intestine environments, pH 6.8 (Figure 9) (Goyanes, Fina et al., 2017). A higher infill percentage resulted in a slower release of HTZ, and the time required for 85% of the drug to be released (DR_{85%}) varied with the infill percentage. The results obtained from the dissolution profiles showed that DR_{85%} was achieved at 234 min (3.9 h), 262 min (4.4 h), and 298 min (5 h) for 30, 65, and 100% infills, respectively. Thus, this set of printed tablets with different infill percentages and infill-dependent dissolution profiles demonstrated the possibility of tailoring drug release profiles through the design of the internal tablet structure.
4. CONCLUSION

HPMCAS (Affinisol™ HPMCAS 716) is a difficult to print pharmaceutical polymer. In this study we compounded HPMCAS with a suitable plasticiser-PEG 600 and included a model drug (HTZ) and rheological modifier (talc) within HME-filaments. The thermal, mechanical, and thermo-rheological properties of formulations were used to define the FDM-3DP process and printed object properties. The effect of HME conditions (30 vs. 100 rpm) on the HME-extrudate homogeneity and its influence on the printer nozzle extruded filament properties has been demonstrated. Three different approaches to improve printability, specifically, plasticisation using PEG, hardening by high Tg drug substance, and the use of a thermostable filler (talc) were explored and their applicability to improve printed object properties was demonstrated. The ability of infill density to tailor drug release from the printed oral solid dosage was also demonstrated.
CRediT author statement for revised submission of manuscript:


Declaration of Competing Interest

The authors declare no conflict of interest.

REFERENCES


Tables

Table 1. Compositions of used formulations.

<table>
<thead>
<tr>
<th>Composition</th>
<th>Formulations, % (w/w)</th>
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<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>HPMCAS</td>
<td>90</td>
</tr>
<tr>
<td>PEG</td>
<td>10</td>
</tr>
<tr>
<td>HTZ</td>
<td>-</td>
</tr>
<tr>
<td>Talc</td>
<td>-</td>
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\(^{a}\) – the concentration calculated based on the HPMCAS and PEG input only, other components (like HTZ or Talc) were not considered.

Table 2. Dimensions, thickness, volume, weight, and apparent density of tablets\(^{a}\) printed using HME-prepared filaments (screw speed of 30 rpm at 165\(^{\circ}\)C)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Infill</th>
<th>Diameter(^{b}) (mm)</th>
<th>Thickness(^{b}) (mm)</th>
<th>Apparent volume (mm(^3))</th>
<th>Weight (mg)</th>
<th>Apparent density (mg/mm(^3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>100</td>
<td>9.96 ± 0.03</td>
<td>3.96 ± 0.02</td>
<td>308.45 ± 3.21</td>
<td>279.1 ± 5.59</td>
<td>0.88 ± 0.06</td>
</tr>
<tr>
<td>F2</td>
<td>100</td>
<td>9.94 ± 0.05</td>
<td>3.98 ± 0.02</td>
<td>308.72 ± 2.60</td>
<td>291.14 ± 8.49</td>
<td>0.94 ± 0.03</td>
</tr>
<tr>
<td>F5</td>
<td>100</td>
<td>10.04 ± 0.04</td>
<td>3.92 ± 0.02</td>
<td>309.74 ± 2.17</td>
<td>305.96 ± 1.30</td>
<td>0.99 ± 0.01</td>
</tr>
<tr>
<td>F3</td>
<td>100</td>
<td>10.03 ± 0.03</td>
<td>4.03 ± 0.04</td>
<td>317.98 ± 4.00</td>
<td>295.52 ± 4.29</td>
<td>0.93 ± 0.02</td>
</tr>
<tr>
<td>F3</td>
<td>65</td>
<td>10.02 ± 0.03</td>
<td>4.00 ± 0.01</td>
<td>315.45 ± 2.86</td>
<td>258.96 ± 5.37</td>
<td>0.82 ± 0.02</td>
</tr>
<tr>
<td>F3</td>
<td>30</td>
<td>9.98 ± 0.04</td>
<td>4.03 ± 0.01</td>
<td>314.50 ± 2.35</td>
<td>221.18 ± 2.60</td>
<td>0.70 ± 0.01</td>
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</table>

\(^{a}\) Av.±S.D. (n=3)

\(^{b}\) target dimensions for the diameter and thickness were 10.00 and 4.00 mm, respectively
Figure 1. A) TGA thermograms of HPMCAS, PEG, Talc, HTZ and physical mixtures of HPMCAS with PEG (10 %w/w), HPMCAS with PEG (10 %w/w) and Talc (a heating rate of 10°C/min; Av. ±S.D., n=3); B) DSC thermograms of HPMCAS, PEG, talc, and HTZ (a heating rate of 10°C/min; Av.±S.D., n=3); C) TM-DSC thermograms (second heat cycle) for HPMCAS-PEG formulations (F1, F2, and F4) at PEG concentrations of 10, 15, 20 % (w/w), formulation with PEG and Talc (F5), and formulation with PEG and HTZ (heating rate of 5°C/min; Av. ±SD, n=3).
Figure 2. SEM images demonstrating the effect of inhomogeneous (F1; 10% PEG) and homogeneous (F2; 15% PEG) mixing with HPMCAS on the structure of: A) printer nozzle extrudate; B) the lateral wall of the printed tablet (the bar in each SEM image relates to 2 mm).
<table>
<thead>
<tr>
<th>Lateral view of layers</th>
<th>Top view of printed tablets</th>
<th>General view of printed tablets</th>
</tr>
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<tbody>
<tr>
<td>PEG 10% (F1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG 15% (F2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG 15%, +5% HTZ (F3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG 20%, + Talc (F5)</td>
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**Figure 3.** SEM images showing the surface morphology of the printed tablets from the lateral and top view, as well as photographic images of the FDM-3D printed tablets printed using HME-filaments (screw speed 30 rpm at 165°C).
**Figure 4.** Force-displacement profiles of HME-filaments (screw speed of 30 rpm at 165°C) of HPMCAS and formulations F1, F2, F3, F4 and F5; (Av.±S.D.; n=3).

**Figure 5.** The correlation between $T_g$s and bending force of HME-filaments.
Figure 6. Viscosity profiles of HPMCAS and HPMCAS formulations F1, F2, F4 (with 10, 15, and 20% (w/w) PEG) and F5 (with 20% w/w PEG and addition of talc) were obtained through: capillary rheometry at 170°C (A); rotational rheometry at 90°C (B) and 70°C (C) as a function of shear rate (s⁻¹); (Av.±S.D.; n=3).
Figure 7. Rheological curves obtained by parallel-plate rotational rheology and plotted as phase angle (delta, degrees) values vs. temperature (°C) for HPMCAS formulations F1, F2, and F4 (with 10, 15, and 20 % w/w PEG), F3 (with 15 and 5% w/w PEG and HTZ, respectively) and F5 (with 20 and 20% w/w PEG and talc, respectively); (Av.±S.D.; n=3).

Figure 8. The correlation between $T_g$s and solidification threshold temperature of HME-filaments.
Figure 9. The in-vitro dissolution profile of printed tablets (F3) with different infill percentages 30, 65, and 100% (Av.±S.D.; n=3).