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3D printed, personalized sustained release cortisol for patients with adrenal insufficiency

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A B S T R A C T

The standard of care for patients with Adrenal Insufficiency (AI) is suboptimal. Administration of hydrocortisone three times a day produces plasma cortisol fluctuations associated with negative health outcomes. Furthermore, there is a high inter-individual variability in cortisol need, necessitating a personalized approach. It is hypothesized that a personalized, sustained release formulation would enhance the pharmacotherapy by mimicking the physiological cortisol plasma concentration at a higher level. Therefore, a novel 24 h sustained release 3D printed (3DP) hydrocortisone formulation has been developed (M3DICORT) by coupling hot-melt extrusion with fused deposition modeling. A uniform drug distribution in the 3DP tablets is demonstrated by a content of 101.66 ± 1.60 % with an acceptance value of 4.01. Furthermore, tablets had a stable 24 h dissolution profile where the intra-batch standard deviation was ± 2.8 % and the inter-batch standard deviation was ± 6.8 %. Tablet height and hydrocortisone content were correlated (R^2 = 0.996), providing a tool for easy dose personalization. Tablets maintained critical quality attributes, such as dissolution profile (f2 > 60) and content uniformity after process transfer from a single-screw extruder to a twin-screw extruder. Impurities were observed in the final product which should be mitigated before clinical assessment. To our knowledge, M3DICORT is the first 3DP hydrocortisone formulation specifically developed for AI.

1. Introduction

The current cortisol replacement therapy for patients with adrenal insufficiency (AI) is suboptimal (Simon et al., 2010). The treatment goal is to mimic complex physiological cortisol plasma concentrations. This goal cannot be achieved by current registered hydrocortisone (HC) formulations due to their drug-release profile and fixed-dose character (Nowotny et al., 2021; Oprea et al., 2019). The standard of care (SOC) is 15–25 mg HC per day, in 2 to 3 divided dosages; in daily practice patients usually receive 10 mg in the morning, 5 mg at midday and 5 mg in the afternoon. The immediate release HC formulations lead to times of under- and overreplacement, associated with negative health outcomes (Debono and Ross, 2013). Furthermore, the SOC is not suitable for accurate dose adaptation based on individual needs while there is a high inter-individual variability in optimal HC dose, due to e.g. differences in absorption and metabolism (Oprea et al., 2019). Quality of life is also poor in patients with AI, which is associated with several factors such as supraphysiological and subphysiological cortisol levels and, for instance, beliefs and concerns around HC replacement therapy (Tiemensma et al., 2014; Andela et al., 2016; Neary and Nieman, 2010). A dual release (DR) HC formulation, Plenadren®, has been developed and marketed in an effort to optimize the treatment (Guarnotta et al., 2019). This formulation seems to be equally effective as the thrice daily formulation and is associated with improvement of metabolic parameters and cardiovascular risk when compared to conventional therapy (Guarnotta et al., 2019). Although this formulation mimics the physiological cortisol levels to a higher degree, it is still not satisfactory due to the lack of nocturnal HC release and the fixed dose character, restricting dose flexibility (Oprea et al., 2019). The DR formulation is not yet widely implemented in the Netherlands, possibly due to the economic burden, fixed dose character, lack of experience of prescribers and/or the moderate strength of the evidence of registration studies (Nowotny et al., 2021).

Taken the above into account, there is an unmet medical need for a sustained release HC formulation which covers daytime cortisol levels and can be dosed in a flexible manner. This will potentially lead to a

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better treatment control, improved drug-adherence and a better quality of life.

Three dimensional (3D) printing technology can be utilized as a compounding method which enables pharmacists to produce oral dosage forms with any desired dose and release profile (Vaz and Kumar, 2021). There are several 3DP techniques of which fused deposition modelling (FDM) is the most extensively researched in medicine (Ayyoubi et al., 2021; Seoane-Viaño et al., 2021; Abaci et al., 2021; Konta et al., 2017). In FDM, drug loaded polymeric filaments are fed into the printer where they are melted at a specific temperature (Fig. 1) (Ayyoubi et al., 2021; Cerda et al., 2020). The molten material is then deposited in a layer-by-layer manner onto the platform until the final product is created. Prior to printing, the desired shape is designed with computer-aided design software, creating an.stl file (Cailleaux et al., 2021). This file is subsequently transformed into a sliced model by 3D printing software, which can be read by the printer.

Drug loaded filaments can be produced by hot melt extrusion and/or passive diffusion, where a commercially available filament is impregnated with the active pharmaceutical substance. Earlier research shows that a higher drug load can be achieved using hot melt extrusion rather than passive diffusion (Ayyoubi et al., 2021).

In hot melt extrusion, powder mixtures, consisting of raw material, can be fed to the extruder where the mixture melts due to exposure to high temperatures generated by the heating elements (Fig. 1). The molten material is subsequently pushed towards the die due to the pressure formed by the screw. The molten material hardens after exposure to the colder air temperature, with aid of a fan. No commercial drug loaded filaments are available currently.

The primary aim of this study is to formulate a sustained release HC formulation using HME, with a single screw extruder, coupled with FDM 3D printing. Secondary aims are (Simon et al., 2010) to demonstrate that dose adaption is straightforward with this technique, (Nowotny et al., 2021) to test the final formulation against European Pharmacopeia (Ph. Eur.) requirements and (Oprea et al., 2019) to demonstrate that the proof of concept formulation maintains the same quality when scaling-up, using a twin-screw extruder.

To our knowledge, this will be the first 3D printed HC formulation specifically developed for patients with adrenal insufficiency.

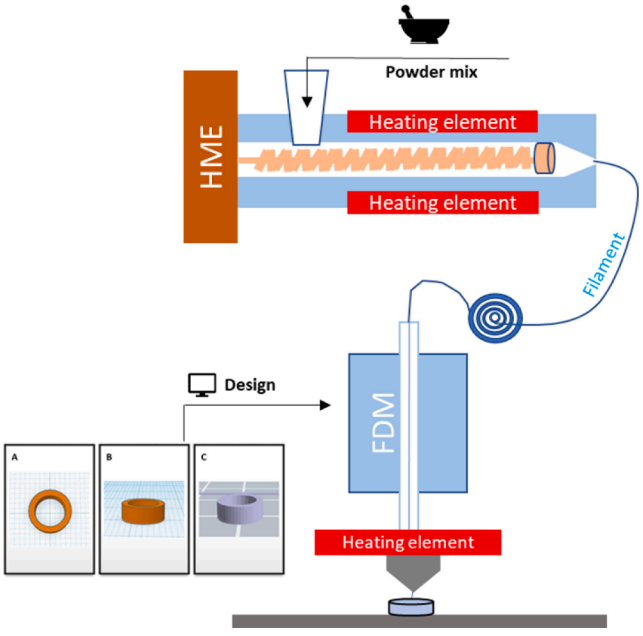

Fig. 1. Hot melt extrusion coupled with fused deposition modelling 3D printing.

2. Materials and methods

2.1. Materials

HC micronisate was purchased from Duchefa Farma B.V. (Haarlem, The Netherlands), magnesium stearate (MgS) and polyethylene glycol 4000 (PEG) were purchased from Spruyt Hillen (IJsselstijn, the Netherlands). Klucel hydroxypropyl cellulose (HPC) grade EF and Aqualon© ethylcellulose (EC) were kindly donated by Ashland (Delaware, United States). Eudragit RL (RL) was kindly donated by Evonik Healthcare (Essen, Germany). Kollidon VA 64 (KVA) was kindly donated by BASF (Ludwigshafen, Germany). Polyethylene oxide (PEO) N750 was kindly donated by Colorcon (Pennsylvania, USA) Plenadren® 5 mg (Takeda, Leverkusen, Germany) was included as a commercialized formulation for comparison purposes. Plenadren® 5 mg tablets are composed of hypromellose, microcrystalline cellulose, pregelatinised starch, colloidal anhydrous silica and MgS and a coating containing macrogol, polyvinyl alcohol, talc, titanium dioxide and iron oxide (Summmary of product characteristics Plenadren 5 mg and 20 mg modified-release tablets [Internet], 2022). Analytical reagents were used without further purification.

2.2. Methods

2.2.1. Hot melt extrusion

Four formulations were developed (Tables 1 and 2). Formulation 1 (F1) and 2 (F2) and 3 (F3) were used in preformulation experiments. F1 and F3 were used to assess if production at lower processing temperatures was possible. F2 was used to assess tablet-height and HC content correlation, to demonstrate easy dose adaptation. Formulation 4 (F4) was developed as the final product and tested against compendial standards (n = 3 batches). Mixtures of HC, EC, PEG, MgS, KVA and HPC (Table 1) and HC, PEO, HPC, MgS and RL (Table 2) were extruded at 30 RPM with a Noztek touch single-screw extruder (Shoreham, UK) designed with two heating zones. Raw materials were mixed by ball milling (IKA Ultra-Turrax® Tube Drive Disperser) at 4000 rpm for 10 min after which the mixture was sieved through a 1.6 mm screen prior to extrusion at barrel temperatures of 110 °C and 150 °C.

2.2.2. Translation of proof of concept formulation F4 from single-screw extruder to a twin-screw extruder

F4 (n = 3 batches) was also extruded in a twin-screw extruder for comparison purposes. The powder mix was extruded using a co-rotating twin-screw extruder with 11 mm diameter screws (Pharma 11, ThermoFisher Scientific®, Waltham, MA, USA) with a standard screw configuration with two mixing zones through a die with a diameter of 1.75 mm at a screw speed of 30 rpm and the following barrel temperatures: 110–110-120–130-140–150–150–150 °C. In addition, a conveyor belt was used to cool the filament and was set at a sufficient haul-off speed to maintain a filament diameter of 1.75 ± 0.05 mm. Filament diameter was measured regularly using a digital caliper (VWR® International, Radnor, Pennsylvania, United States). The resulting filament was stored in a sealed plastic bag.

Table 1
Composition of formulations used in preformulation studies.

Composition (%, w/w)								
Formulation	HC	EC	HPC	MgS	PEG	KVA	PEO	RL
F1	20	20	40	1	5	14		
F2	20	20	44	1	5	10		
F3	15		24	1			45	15

Table 2
Composition of the final product.

Composition (%, w/w)					
Formulation	HC	PEO	HPC	MgS	RL
F4	15	35	24	1	25

2.2.3. 3D FDM printing

A FlashForge Creator Pro ((Zhejiang Flashforge 3D Technology Co, Zhejiang, China) FDM 3D printer was used for printing the manufactured filaments. Tablet geometry was designed using a computer-aided design (CAD) software (Tinkercad software v.1, Autodesk 2022, California, USA) to create an.stl file (Fig. 2A and 2B) compatible with the Flashprint software v.5.3.1. (Flashprint, Flashforge, Zhejiang Flashforge 3D Technology Co, Zhejiang, China), which was used to adjust the printing parameters (Table 3) and to create a sliced.x3g file which contains the printing instructions (Fig. 2C). Tablets were designed in a full tablet shape (F1 and F2) and a circle shape (F3 and F4). Infill pattern was linear at all times.

2.2.4. Content determination

A content determination was performed for samples mentioned in sections 2.3 and 2.9 using the method described below. All formulations obtained by 3D printing were dissolved in 96 % ethanol: 1 M HCl (90:10, V:V). All samples were subsequently diluted in mobile phase consisting of water: acetonitrile (74:26, V:V) containing 0.036 % (W/V) triethylamine and 0.544 % (W/V) potassium dihydrogen phosphate prior to quantification by High Pressure Liquid Chromatography (HPLC). Samples were analyzed by HPLC comprised of an Agilent 1290 infinity II pump, an Agilent 1290 infinity II vialsampler and an Agilent 1290 infinity II diode array detector. Integration of the peaks was performed with Agilent OpenLab 2.5 software. Separation was achieved on an Agilent Zorbax Eclipse Plus C18 reverse-phase column (100x4.6 mm, 3.5 µm). The mobile phase was pumped at a flowrate of 1 ml/min and the sample injection volume was 40 µl. The column temperature was kept at 30 °C and the detector was set at 246 nm. This method was validated in terms of linearity (1 – 16 µg/mL) and specificity.

2.3. Pre-formulation studies

2.3.1. Identification of optimal processing temperature

F1 was used in a quality by design approach where temperature impact was assessed by ranging extrusion temperatures from 170 °C to 150 °C and 3D printing temperatures from 200 °C to 150 °C, in steps of 10 °C to identify optimum processing temperatures. F3 was used to assess if a lower extrusion temperature (140 °C) would also lead to printable filaments.

2.3.2. Dose-height correlation

F2 was used in a study where contents of tablets (N = 3) with heights ranging from 0.5 mm tot 3.0 mm, in steps of 0.5 mm were determined to assess the dose-height relationship.

2.3.3. Identification of optimal resolution setting

Printing resolution can be set at low, standard, high, and hyper (Table 4), corresponding to different printing parameters.

The impact of all four resolution settings on HC content and visual appearance was assessed with F4 tablets (n = 3).

2.3.4. Uniformity of content

Content uniformity was tested with formulation F4 conform Ph. Eur. uniformity of dosage units (Ph. Eur. 2.9.40) ([Anonymous]. , 2022). Tablets (n = 4) from 3 single-screw and twin-screw batches were used. The target test sample amount for the single-screw batches was set at 12 mg HC per tablet. The acceptance value (Av) was calculated with a reference value (M) of 101.5 % and an acceptability constant of 2.4. The target test sample amount for the twin-screw batches was set at 11 mg. The acceptance value (Av) was calculated with a reference value (M) of 101.5 % and an acceptability constant of 2.4.

2.4. Mechanical strength and dimensional properties

2.4.1. Friability testing

A friability test was performed with the PTF10E friability instrument (Pharma Test, Hainburg, Germany), conform Ph. Eur. 2.9.7 ([Anonymous]. , 2022). F4 tablets (n = 20) were dedusted with nitrogen gas and accurately weighed. The rotational speed was set at 25 rotations per minute. After 100 revolutions, tablets were dedusted and weighed again. According to Ph. Eur., a sample of tablets corresponding to 6.5 g should be used for tablets with an individual weight below 650 mg. Since the tablets weighed < 100 mg, it would take approximately 80 units to meet the 6.5 g target for the friability test. The requirement of Ph. Eur. for the number of samples for this tests seems to be more suitable for large scale manufacturing. 3D printing, however, has the potential to be used for small scale individual manufacturing of personalized medicine. The

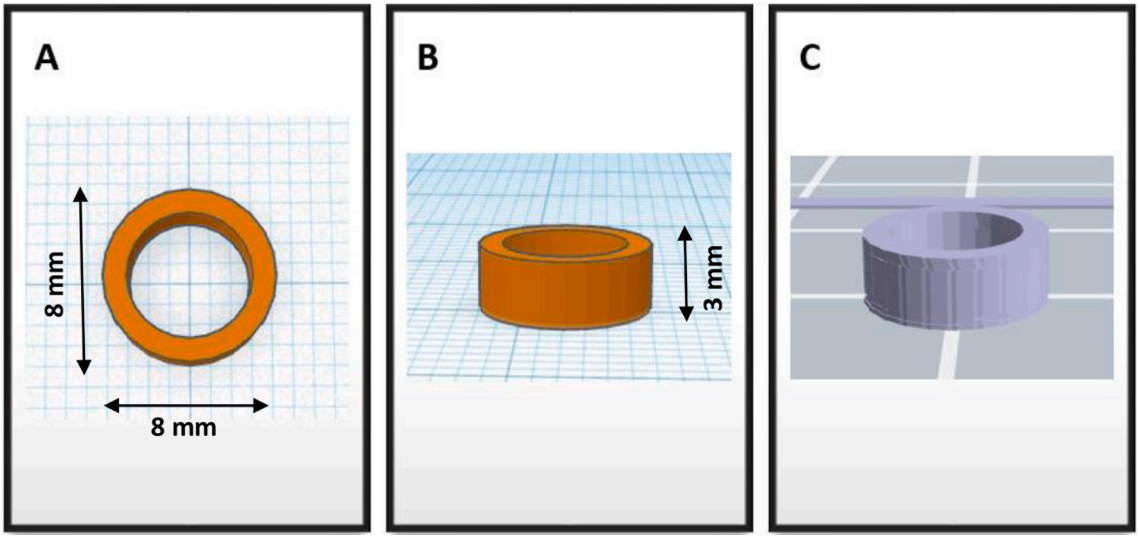

Fig. 2. CAD designs for formulation F3 and F4: tinkercad top view (A), tinkercad side-view (B) and sliced design (C).

Table 3
3D printing settings.

Formulation	Resolution	Layer height (mm)	First layer (mm)	Infill (%)	Diameter (mm)	Height (mm)	Wall (mm)
F1	Standard	0.18	0.27	100	6	1	–
F2	Standard	0.18	0.27	100	6	0.5–3	–
F3	High	0.12	0.20	100	8	3	2.57
F4	High	0.12	0.20	100	8	3	2.57

Table 4
Printing resolution options and corresponding printing parameters.

Resolution	Print speed (mm/s)	Travel speed (mm/s)	First layer (mm)	Layer height (mm)
Low	70	100	0.30	0.30
Standard	60	80	0.18	0.27
High	50	70	0.12	0.20
Hyper	50	70	0.08	0.20

used number of samples was therefore much lower than Ph. Eur. requirement.

2.4.2. Hardness

The crushing strength of the F4 tablets (n = 20) was determined conform Ph. Eur. Monography 2.9.8., using a MT 50 hardness tester (SOTAX, Aesch, Switzerland) ([Anonymous]. , 2022). An increasing force was applied to each individual tablet, until the tablets fractured.

2.4.3. Filament tensile strength

The mechanical properties of the filaments of formulation F4 were evaluated with a TA-XT2 analyzer (Amatek®, Berwyn, USA) and the TA-1000 N probe set with a 25 mm supporting gap. The filament samples were collected and cut into rods with a length of 5 cm, then placed on the sample holder. Blade movement was set at a speed of 100 mm/s until reaching a maximum distance of 15 mm below the supported sample. The breaking force and the breaking distance data were recorded and analyzed using the Nexigen® plus 3 software (Amatek®, Berwyn, USA). Each batch of filament was tested three times.

2.4.4. Filament diameter

Filament diameter was determined with formulation F4 using three batches (n = 10) at random points using a digital caliper.

2.5. Dissolution study

Dissolution tests were performed in triplicate for three batches of single-screw and twin-screw F4 tablets and one batch of Plenadren® 5 mg using a Ph. Eur. apparatus 2 (ERWEKA DT800, Langen, Germany) at 100 rpm. Adhering to the Ph. Eur. recommendations on dissolution testing (Ph. Eur. 5.17.1.) the following degassed dissolution media were used: simulated gastric fluid (SGF) without enzymes (pH 1.2) and simulated intestinal fluid (SIF) without enzymes (pH 6.8). SGF (500 ml) was used during the first 2 h. SIF (400 ml) was added and kept for the remaining 22 h. Media were maintained at 37 ± 0.5 °C and 4 M NaOH was used to adjust the pH to 6,8 after the addition of the SIF. Samples (1 ml) were withdrawn from the dissolution media at 30 min, and 1, 2, 3, 4, 6, 7, 21, 22, 23 and 24 h. Samples were analyzed with the same HPLC method as described under 2.2.4 Content determination. Dissolution curves were compared using the similarity factor (f2), in line with the EMEA Guideline on the investigation of bioequivalence (European Medicines Agency, 2010). f2 was calculated by the mathematical software DDsolver (China Pharmaceutical University, Nanjing, China) (Zhang et al., 2010).

2.6. Thermogravimetric analysis (TGA)

TGA was performed using a Q-50 Thermographic Analyzer (TA instruments, New Castle, USA) with F4 tablets. Raw materials, powder mixture and crushed filament and tablet (10–30 mg) were placed in open platinum pans. TGA analysis was performed at a constant heating rate of 10 °C/min starting from 25 °C up to 400 °C. Nitrogen was used as a purge gas with a flow rate of 60 ml/min. In addition, HC thermostability was assessed with a heat-and-hold analysis at 150 °C for 30 min with the F4 powder mixture and raw HC. Data were collected with TA Instrument Explorer and analyzed using TA Universal Analysis 2000 (TA instruments).

2.7. Differential scanning calorimetry (DSC)

DSC scans of F4 raw material, filament and tablet were recorded with a Discovery Differential Scanning Calorimeter (TA instruments, New Castle, USA) using nitrogen as purge gas, with a flow rate of 50 ml/min. The samples were weighed (3-10 mg) and sealed in an aluminum pan. A scanning rate of 3 °C/min was employed, after a preheating cycle to 100 °C to remove water of the samples. Data collection and analysis were performed using TA Instrument TRIOS and TA Universal Analysis 2000 (TA instruments, New Castle, USA).

2.8. X-ray powder diffraction (pXRD)

X-ray powder diffraction was performed with F4 raw material, filament and tablet using a Bruker D2 Phaser with a cobalt anode (Bruker, Billerica, Massachusetts). A wavelength of 0.179 nm was utilized and the applied voltage and current were set at 30 kV and 10 mA respectively. The PXRD patterns were recorded (n = 1) from 5° to 60° on the 2 theta scale at a step scan rate of 0.05° per second. Raw material, a powder-mixture, a grinded piece of filament and a grinded tablet were placed in a sample holder prior to analysis. The data was analyzed using the Diffrac.EVA V4.2 software (Bruker, Billerica, Massachusetts).

2.9. Stability study

The stability study was set-up according to the International Council for Harmonisation (ICH) guideline [Q1A(R2)] with formulation F4 tablets (xxxx). Tablets (n = 18) were placed in climate chambers (Memmert HPP260, Schwabach, Germany) at two different conditions of temperature and relative humidity (RH):

(1) 25 °C ± 0.1 °C/60 % RH ± 0.5 % RH
(2) 40 °C ± 0.1 °C/75 % RH ± 0.5 % RH

The study period was set at 4 weeks. Content determination (n = 3) was performed at the start of the study (t = 0), after 7 days (t = 1), after 14 days (t = 2), after 21 days (t = 3) and after 28 days (t = 4). Additionally, a dissolution study (n = 3) was performed at t = 4 to assess if there are changes in the drug release profile. An f2 comparison was made at t = 0 and t = 4 to quantify the similarity between the two time points. Tablet weight and total amount of impurities per time point were

also analyzed.

3. Results

3.1. Pre-formulation studies

3.1.1. Optimal processing temperatures

A significant amount of drug loss is observed at 200 °C for F1, possibly due to HC thermal degradation (Table 5). Drug loss was minimized with a processing temperature of 150 °C, where a content of 90.2 % was found. This processing temperature was used for the final F4 tablets.

3.1.2. Tablet-height – Tablet dose correlation

In order to evaluate the correlation between the height of tablets and the dose of HC within them, F2 tablets have been printed and evaluated. Fig. 3 shows that F2 tablet height is correlated ($R^2 = 0.996$) with tablet content, providing an easy tool for dose adjustment. Although the impact of tablet height on drug release was not assessed, a similar dissolution behavior is expected when maintaining the same surface-area to volume ratio (Reynolds et al., 2002).

3.1.3. Identification of optimal resolution setting

Lower resolution settings lead to a faster printing and traveling speed and a higher layer-height in F4 tablets (Fig. 4). Furthermore, tablets printed with higher resolution settings tend to be more discolored compared to low resolution setting where the formulation is exposed to the printing temperature for a shorter amount of time.

Resolution settings affect the HC content of the final product, 'low' resolution is associated with a higher HC recovery (98.16 %) compared to setting the resolution at 'hyper' (94.56 %) (Fig. 5). 'Low' resolution corresponds to a faster printing and travelling speed of 70 mm/s and 100 mm/s respectively, compared to 'hyper' resolution, where printing and travelling speed are 50 mm/s and 70 mm/s respectively. Printing at low resolution therefore reduces the exposure time of the formulation to the high printing temperature and thus, reduces the degradation risk. This observation is in line with other literature findings and printing speed should be taken into account as a critical process parameter in pharmaceutical FDM 3D printing (Ilyés et al., 2019). Although the intra-batch variation in HC content at low resolution is higher when compared to hyper resolution (0.23 % vs 0.16 % resp.), it is still acceptable. The low variation in contents also indicates a high filament quality for the batch used in this experiment. Furthermore, the high HC recovery of 98.16 % found at low resolution indicates that minimal HC loss and degradation occurred at this setting during manufacturing.

3.1.4. Observed impurities

Impurities were not expected at processing temperatures of 150 °C as the HC melting and degradation temperature is 226.0 °C (Rojek and Wesolowski, 2017). Impurities were observed in the HPLC graphs of F4 tablets (supplementary material, appendix A). Some peaks are above the identification (0.2 %) and qualification (0.5 %) threshold based on the ICH guideline 'ICH Q3B (R2) Impurities in new drug products' (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Guidance for Industry Q3B Impurities in New Drug Products (Revision 2). ICH Harmonized Tripartite Guidelines. [Internet]., 2006). F3 was developed with a higher amount of PEO in order to be able to manufacture at a lower processing temperature. F3 was extruded at 140 °C and printed at 150 °C which led to a lower amount and concentration of impurities (supplementary material, appendix A), 4 impurities were observed at extrusion and printing temperatures of 150 °C vs 1 impurity at an extrusion temperature of 140 °C and a printing temperature of 150 °C. Degradation seems to be temperature-dependent.

Table 5
Hydrocortisone contents at different processing temperatures for F1.

Temperature (°C) Extrusion	3D printing	HC content (%) ± SD
170	200	70.9 ± 1.2
170	190	76.0 ± 1.0
170	180	80.1 ± 0.3
170	170	89.7 ± 0.5
160	160	85.4 ± 1.2
150	150	90.2 ± 2.1

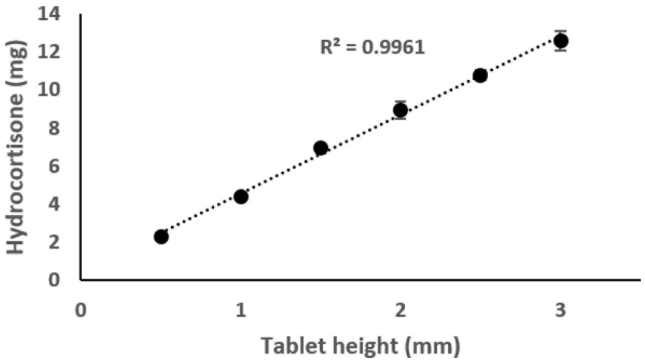

Fig. 3. F2 tablet height and tablet content correlation.

3.1.5. Concluding remarks on pre-formulation studies

F1 and F2 were not identified as the final formulation due to the fact that they did not have the desired 24 h sustained release effect and/or they did not meet the Ph. Eur. dissolution requirement of > 80 % release (supplementary material, appendix B). F4 tablets did comply to Ph. Eur. recommendations of drug release and was therefore chosen as the final formulation which was used for the experiments described below. F3 was solely designed to reduce the processing temperature, aiming at an impurity level below the 'identification threshold', after impurities were observed with F4. Impurities above the identification threshold were still observed in F3, further researched was therefore not pursued with this formulation.

3.2. Uniformity of content

Twelve units from three batches were used for the determination of the content uniformity in this experiment. Nevertheless, a content uniformity with an average HC content of 101.66 ± 1.60 % was found (full data provided in supplementary material, Appendix B). The calculated acceptance value (Av) was 4.01 which was well below the requirement of Av= ≤15, indicating that intra-batch, as well as inter-batch, tablets have a uniform content and are reproducible.

3.3. Physical properties

The friability of the tablets met the Ph. Eur. requirement of < 1.0 % mass loss (Table 6). Some tablets adhered to the drum wall during testing. According to Ph. Eur., a sample of tablets corresponding to 6.5 g should be used for tablets with an individual weight below 650 mg. Since the tablets weighed < 100 mg, it would take approximately 80 units to meet the 6.5 g target for the friability test. The requirement of Ph. Eur. for the number of samples for this tests seems to be more suitable for large scale manufacturing. 3D printing, however, has the potential to be used for small scale individual manufacturing of personalized medicine. The used number of samples was therefore much lower than Ph. Eur. requirement. HME-FDM printed tablets have different physical properties compared to compressed tablets which may indicate that current guidelines on tablet friability may not be suitable for 3D printed tablets, in general HME-FDM tablets do not tend to be abrasive (Quodbach et al., 2022).

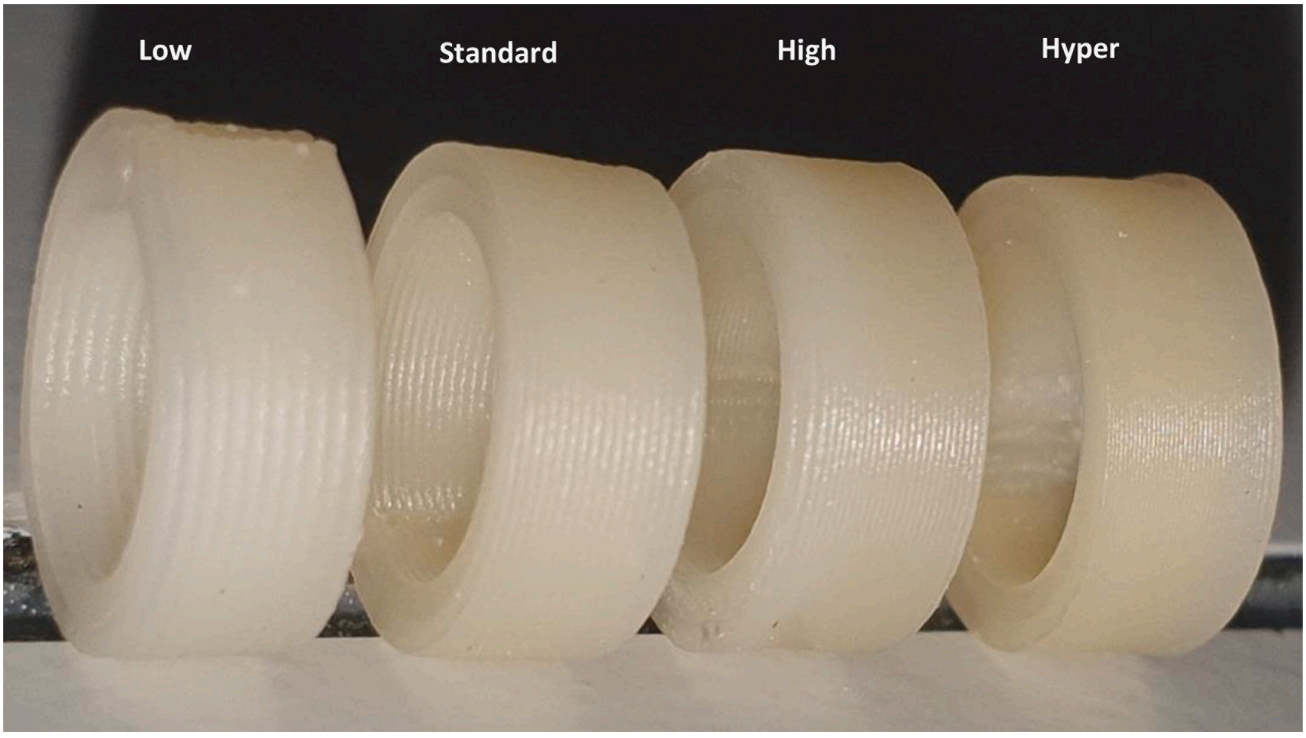

Fig. 4. F4 tablets printed with low, standard, high and hyper resolution setting (left to right). Difference in layer-height is clearly visible with more layers at higher resolution.

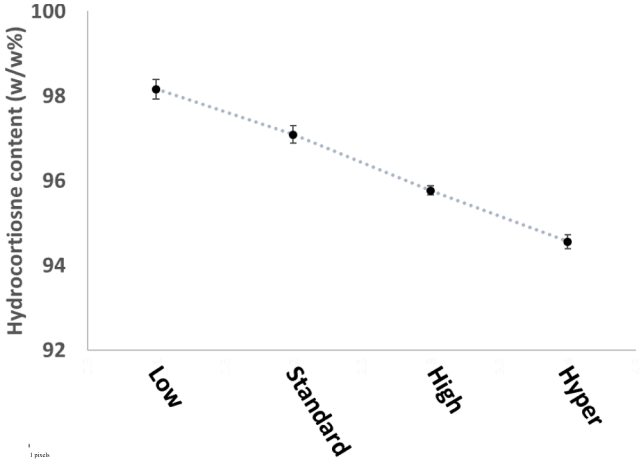

Fig. 5. Hydrocortisone content at different resolution settings for F4 tablets.

Table 6
Friability and hardness of F4 tablets.

Formulation	Tablet friability (%)	Tablet hardness (N) ± SD	Tablet diameter ± SD (mm)	Tablet height ± SD (mm)
F4	0.06	35.5 ± 9.1	7.90 ± 0.08	3.12 ± 0.09

The results for tablet hardness (Table 6) suggest that tablet mechanical strength is comparable to other HME-FDM based tablets (Karalia et al., 2021; Brambilla et al., 2021). The observed breaking force of 35.5 N may be an underestimation as tablets were intact after hardness testing (Fig. 6). The registered breaking force was most likely the point where tablets started to bend a little which led to a crack on the tablet surface (Fig. 6B).

The average force needed to break filaments was comparable for the single screw filaments (6.03 N ± 0.6) and the twin screw filaments (6.16 N ± 0.7). Average filaments elongation at breaking point was 4.85 mm ± 0.5 for the single screw filaments and 5.20 mm ± 0.4 mm for the twin screw filaments (Table 7). Young's modulus average was 1895.93 mPa ± 103.34 for the single screw filaments and 2094.63 mPa ± 439.17 for the twin screw filaments. Other mechanical properties and full data such as filament diameter, maximum bending stress at maximum force, and elongation at maximum force are provided in the supplementary material, Appendix C.

Twin screw filaments had a higher variation in filament diameter compared to single screw filaments. Average filament diameter was between 1.74 mm and 1.80 mm which is close to the required filament diameter of the FDM printer. The utilized FDM printer requires a filament diameter of 1.75 mm (Flashforge, 2022).

3.4. Dissolution

F4 single-screw and twin-screw tablets comply to the Ph. Eur. recommendation of > 80 % drug release within 24 h (Fig. 7A). Drug release data (Fig. 7B) show a low intra-batch variability at 24 h (<2.78 %) of F4 tablets. There is however, a high inter-batch variability in the single screw extrusion products, where one batch specifically has a higher HC release (11.19 mg) in 24 h compared to the other 2 batches which have less variation between them (10.18 mg and 9.83 mg). Plenadren® 5 mg tablets produce a stable HC release in 24 h, the DR effect is clearly visible (Fig. 7A) as an initial burst in HC release, after which a stable sustained release effect is established. Inter-batch differences in dissolution profiles may arise due to differences in filament diameter. Filaments are manually pulled from the extruder which introduces filament diameter variability leading to variation in tablet weight and content, and hence drug release profile. For instance, the average tablet weight of batches 2 and 3 were 82.61 ± 0.36 mg and 82.17 ± 0.52 mg respectively, while batch 1 had an average weight of 85.13 ± 0.80 mg (full data provided in supplementary material, Appendix D). Variation in filament diameter may also depend on the operator as pulling the

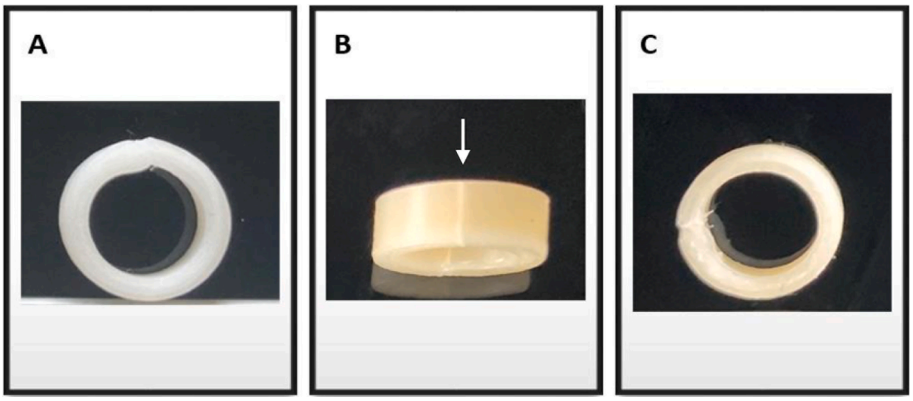

Fig. 6. 3D printed tablets before hardness test (A) and after hardness test (B, C).

Table 7
Mechanical properties of F4 single screw and twin screw filaments.

Batch	Breaking Force (N)	Breaking elongation (mm)	Young's modulus (mPa)	Average filament diameter (mm) ± SD
Single screw filaments				
1	6.23	4.51	1980.9	1.80 ± 0.05
2	6.46	4.66	1926.0	1.78 ± 0.04
3	5.39	5.37	1780.9	1.76 ± 0.07
Average ± SD	6.03 ± 0.6	4.85 ± 0.5	1895.93 ± 103.34	1.78 ± 0.06
Twins screw filaments				
1	6.64	4.91	1940.8	1.80 ± 0.08
2	6.46	5.02	2588.8	1.78 ± 0.15
3	5.39	5.68	1751.3	1.74 ± 0.13
Average ± SD	6.16 ± 0.7	5.20 ± 0.4	2094.63 ± 439.17	1.77 ± 0.12

filament out of the extruder was a manual procedure and manufacturing was performed by three different operators. An f2 of 54.69 was observed when comparing the batch with the lowest release in 24 h vs the batch with the highest release. A similarity factor > 50 corresponds with an average difference of < 10 % at all specified time points (Diaz et al., 2016).

3.5. Thermogravimetric analysis

TGA analysis revealed that the raw materials are thermally stable at extrusion and printing temperatures of 150 °C (Fig. 8A), with a slight weight change due to water evaporation at 100 °C. The observed thermal degradation of HC starts at 225 °C, this is in line with literature (Center, 2022). TGA thermographs of the powder mixture, drug-loaded filament and tablet show no weight loss at 150 °C (Fig. 8B). Degradation pathways that do not include weight loss may play a role in the earlier observed impurity formation. The heat-and-hold analysis was performed on raw HC and the powder mixture, no weight change was observed when exposed to 150 °C for 30 min (Fig. 8C and D). This does not correspond with the degradation observed earlier. Degradation due to higher temperatures related to friction and shear forces during the production process may also play a role (Censi et al., 2018; Matić et al., 2020). Furthermore, single-screw extruder elements like the barrel, screw and hopper are made from mild steel and the nozzles are made of brass which may have also contributed to the observed impurities.

3.6. PXRD

PXRD analysis of the raw materials revealed that HC, MgS and PEO were highly crystalline, while HPC and RL are amorphous materials (Fig. 9A). The crystalline peaks of the physical mixture, filament and tablet can mainly be attributed to HC. A lower peak intensity is observed in the tablet and filament compared to the physical mixture, suggesting that a fraction of the HC is in an amorphous form (Fig. 9B). Lower peak intensity may also arise as a result of a lower absolute amount of HC in samples, results should therefore be interpreted with caution. Although the applied temperatures during the manufacturing process are below the HC melting point, amorphization may still happen due to drug dissolution in case of a good drug-polymer miscibility, rather than exclusively melting of the active pharmaceutical substance (API) (Liu et al., 2013).

3.7. DSC

The DSC thermographs of the F4 powder mixture, filament and tablet

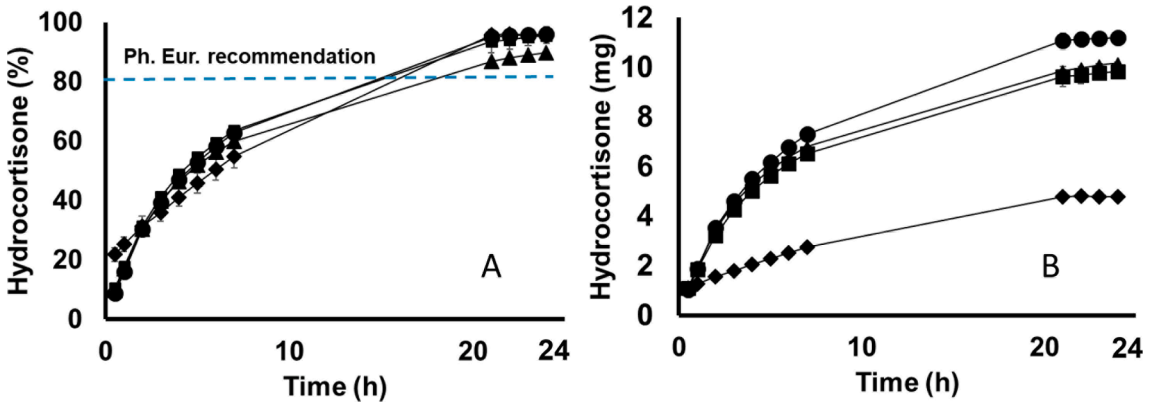

Fig. 7. Drug release profiles in mg (A) and in % (B) of three single screw extrusion F4 batches (● ■ ▲) and Plenadren® 5 mg (◆).

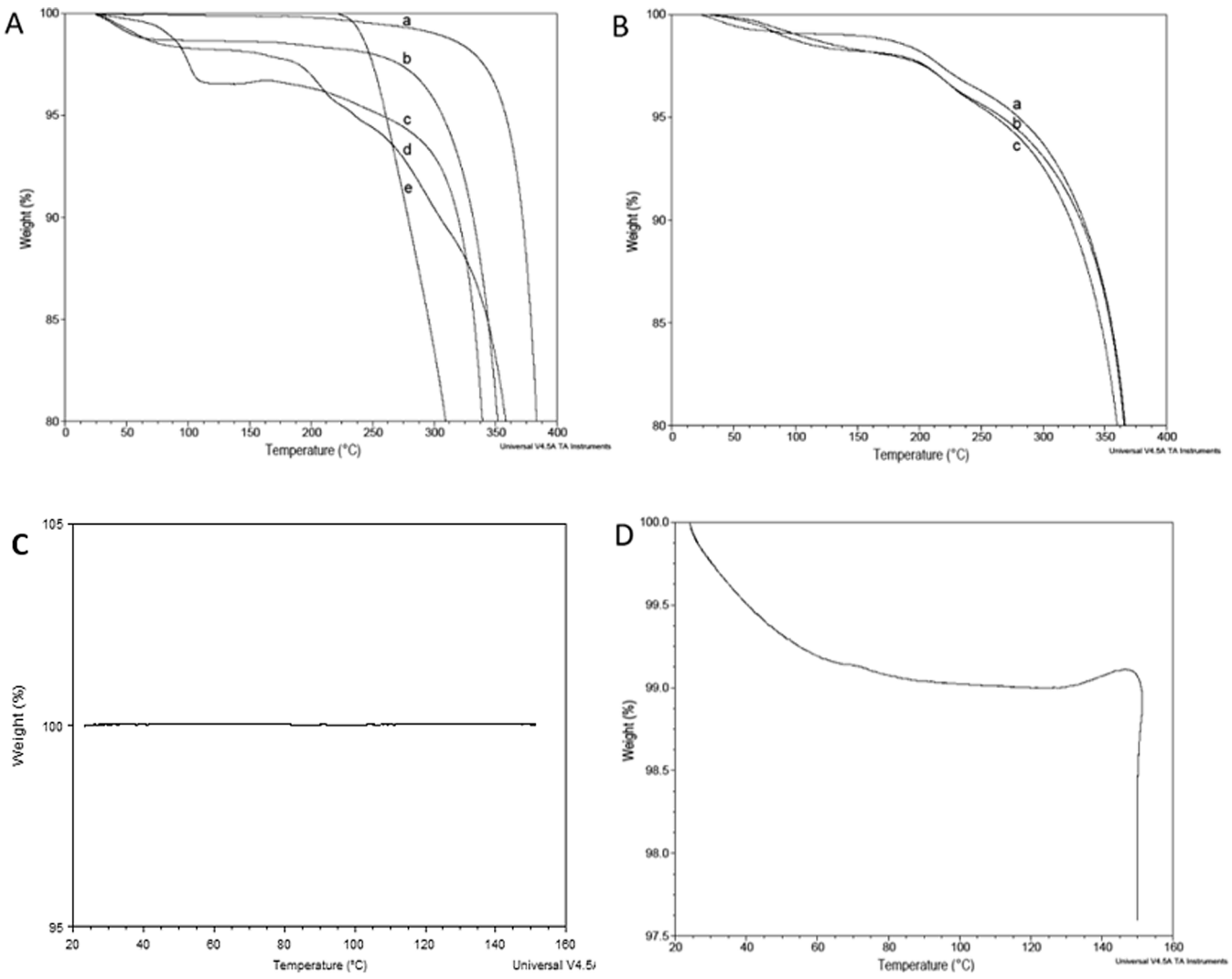

Fig. 8. TGA curves for A: PEO (a), HPC (b), MgS (c), RL (d), hydrocortisone (e); B: powder mixture (a), F4 tablet (b) and the drug-loaded F4 filament (c); C: heat-and-hold hydrocortisone; D: heat-and-hold powder mixture.

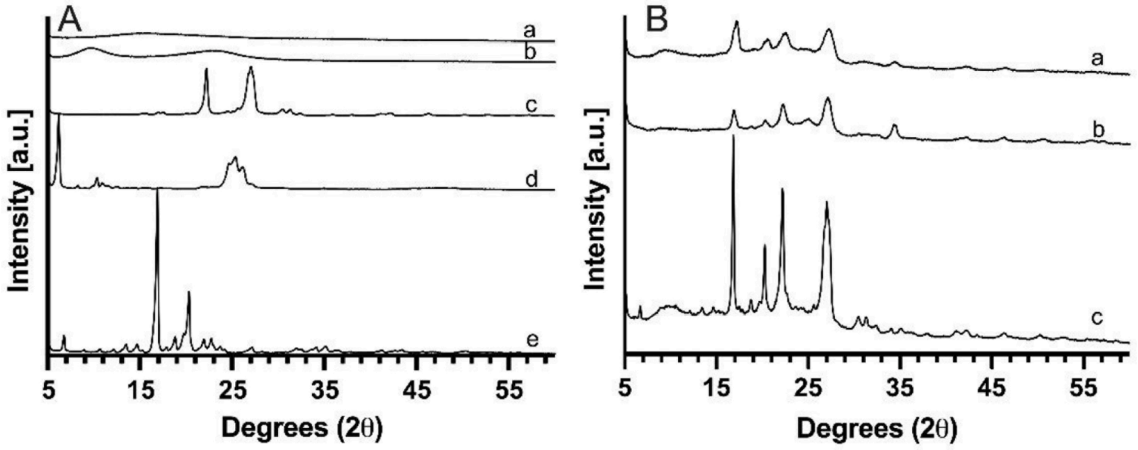

Fig. 9. XRPD diffractograms of A) the raw materials; a) Eudragit RL PO, b) HPC, c) PEO, d) MgS, e) hydrocortisone and of B) processed samples; a) 3D printed F4 tablet, b) filament F4 and c) powder mixture F4.

show an endothermic event at 60.7 ± 1.0 °C (Fig. 10), corresponding to the melting behavior of PEO (Cantin et al., 2016). Raw HC exhibited a sharp melting point at 217–220 °C corresponding to literature findings and demonstrating the presence of the drug in crystalline form (Center, 2022). The endothermic HC peak is absent in the F4 powder mixture, filament and tablet which, especially for the powder mixture, is

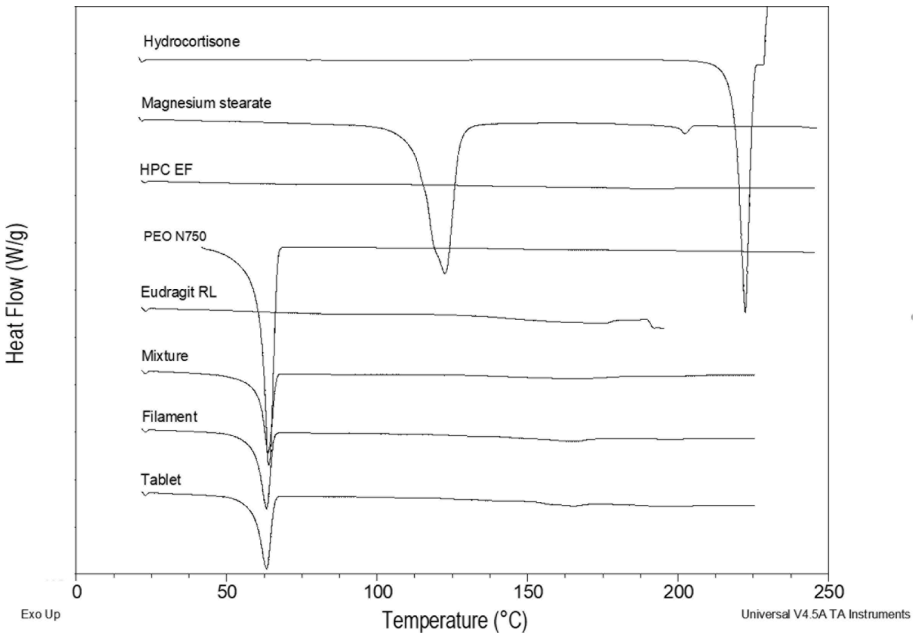

Fig. 10. DSC thermographs of hydrocortisone, magnesium stearate, PEO N750, Eudragit RL, HPC, mixture, F4 filament and 3D printed F4 tablet.

unexpected and in contrast to XRD data which shows crystalline material. A repetition of the experiment resulted in similar data, future studies should be performed to understand this observation. Glass transition temperatures for eudragit RL and HPC are 67.9 ± 1.0 °C and 126.2 ± 1.0 °C respectively, which is in line with literature findings (Tan et al., 2020; Mohammed et al., 2012). Both polymers seem to have a high amorphous content as no endothermic events are observed.

3.8. Stability study

Stability study data show that formulation F4 tablets are stable within 4 weeks at room temperature (25 °C, 60 % RH) as well as in more extreme conditions (40 °C, 75 % RH) (Fig. 11). The differences between lowest and highest HC content values are < 10 % relative to t = 0 content in both conditions (Fig. 11).

The average amount of impurities found at 40 °C, 75 % RH are higher by 1 % (full data provided in supplementary material, appendix E), suggesting that the formulation should be stored at 25 °C, 60 % RH even though there may be no significant difference. Concentrations of individual impurities are above the identification threshold of 0.2 % set by ICH Q3B (Fig. 12).

The sustained drug release effect is a critical product quality attribute of this formulation. The sustained release effect of F4 tablets remains intact after exposure to 25 °C 60 % RH for 4 weeks (Fig. 13). A similarity factor (f2) of 61.1 was found, corresponding to an average difference of < 10 % at all time points.

3.9. From proof of concept to scale-up

Moving towards clinical trial material, it is important to assess whether the proof of concept product, F4 tablets, maintain the same quality when produced with a twin-screw extruder instead of the single screw extruder.

3.9.1. Uniformity of content

Ph. Eur. requires n = 10 samples for content uniformity, 12 units from three batches were used for the determination of the content uniformity in this experiment. An average HC content of 100.41 ± 5.54 % was found (full data provided in supplementary material, Appendix B). The calculated acceptance value was 12.21 which is below the requirement of Av= ≤15, indicating that intra-batch, as well as Inter-batch, tablets have a uniform content and are reproducible. The twin

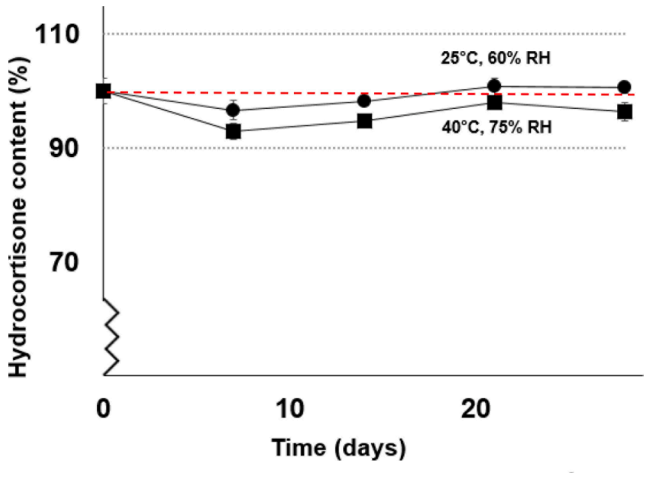

Fig. 11. Stability data of F4 tablets tested over four weeks at 25 °C 60 % RH (●) and 40 °C, 75 % RH (■).

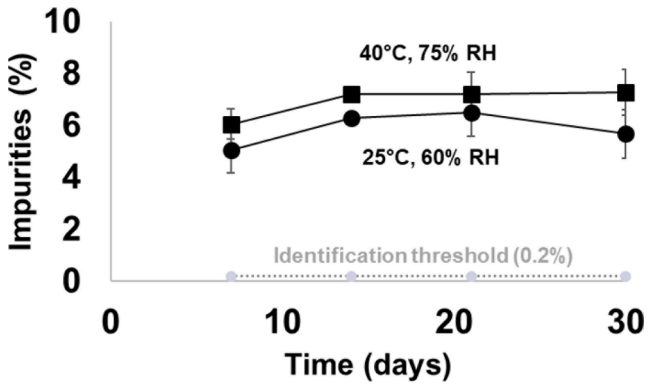

Fig. 12. Average amount of total impurities observed over four weeks at 25 °C 60 % RH (●) and 40 °C, 75 % RH (■).

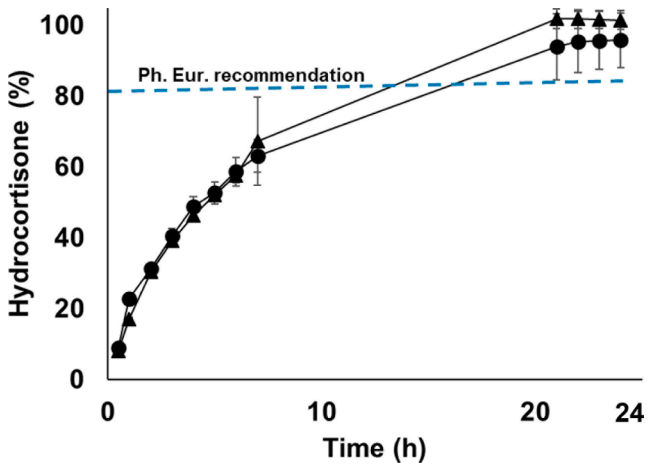

Fig. 13. Dissolution profile of F4 tablets stored at 25 °C, 60 % RH after o days (▲) and 28 days (●).

screw based tablets had an average weight of 86.21 ± 4.66 mg, whereas the single screw tablets had an average weight of 85.96 ± 0.87 mg. Variation in HC content and tablet weight was lower for the single screw product, most likely due to a lower variation in filament diameter which was 1.78 ± 0.06 mm compared to 1.77 ± 0.12 mm for the twin screw based product.

3.9.2. Impurities

Less impurities above 0.2 % were found in the twin screw product (n = 2) compared to the single screw extruder (n = 4) (supplementary material, appendix A). This may be explained by the lower transit time in the twin screw extruder which is designed for powder processing, whereas the single screw extruder was designed for pellet processing.

3.9.3. Drug release profile

Twin screw drug release profiles also comply to Ph. Eur. recommendation of > 80 % drug release within 24 h (Fig. 14A). Intra-batch 24 h release variability is < 2.62 % which is comparable to the single screw variability (<2.78 %). The inter-batch variability is ± 0.42 mg after 24 h whereas the variability for the single screw extruder is much higher (±0.71 mg). The twin screw extruder was set up with kneading and mixing zones which may have led to a better inter-batch homogeneity. Similar to the single screw extruder product, a stable 24 h sustained release profile was established with an average drug release after 24 h of 9.58 ± 0.42 mg (Fig. 14B). Single screw F4 tablets were translatable as proof of concept product to the twin screw extruder, where a similar drug release profile was found, indicated by a similarity factor 63.3 %, corresponding to an average difference of < 10 % at all time points.

3.9.4. Impurities in twin screw F4 tablets

Impurities were observed in the HPLC graphs for both single screw based products as well as twin screw based products (supplementary material, appendix A). Less impurities > 0,2% (n = 2) were observed for the twin screw extruder compared to the single screw extruder (n = 4). A possible explanation may be the lower transit time in the twin screw extruder which is designed for powder processing, whereas the single screw extruder was designed for pellet processing.

4. Discussion

A novel 3D printed 10 mg sustained release HC formulation (M3DICORT) has been developed in this research. Filaments were successfully extruded and printed below the HC melting point of 217–220 °C. Utilizing processing temperatures below the melting point was crucial as degradation was observed at processing temperatures around the melting point. 3D production at relatively low processing temperatures was possible by the addition of Eudragit RL PO which has a Tg 67.9 °C of and PEO which has a melting point of approximately 60.7 °C.

It is well known that developing printable filaments is the most challenging aspect in pharmaceutical FDM printing (Nasereddin et al., 2018; Korte and Quodbach, 2018; Goyanes et al., 2016; Tabriz et al., 2021). In order to be printable, filaments need to have a certain hardness so they do not break during feeding, and at the same time, have enough flexibility to adequately be pushed towards the printer nozzle. However, too flexible filaments deform during the feeding process and do not reach the nozzle. Many articles have been published on mechanical properties of filaments but a detailed definition of 'printable filaments' is not yet described. Trial and error seems to remain the main method for formulating printable filaments. Nevertheless, our filaments had a Young's modulus between 1700 mPa and 2600 mPa, suggesting that filaments that have similar Young's modulus values have a balanced stiffness and flexibility and therefore have a higher chance of being 'printable'. Filament tensile strength and 'elongation at breaking' parameters are comparable to other findings in literature (Zhang et al., 2017).

There was, however, a degree of variability in filament diameter intra-batch as well as inter-batches leading to variation in tablet weight and in the amount of HC released in 24 h. An f2 of > 50 for the intra-batch drug release profiles was found, indicating an average difference of < 10 % over all specified time points. Filament diameter has a high impact on the tablet weight and on the drug release profile. For instance, a lower filament diameter may lead to less material deposited during printing and therefore, a lower tablet weight. Literature findings indicate that the introduction of a melt pump may be a good solution to reduce variations in filament diameter and improve the quality of the final product (Quodbach et al., 2021). Removing the kneading zones may also lead to a more consistent filament output in the twin screw extruder set-up. Filament diameter variation may also be influenced by

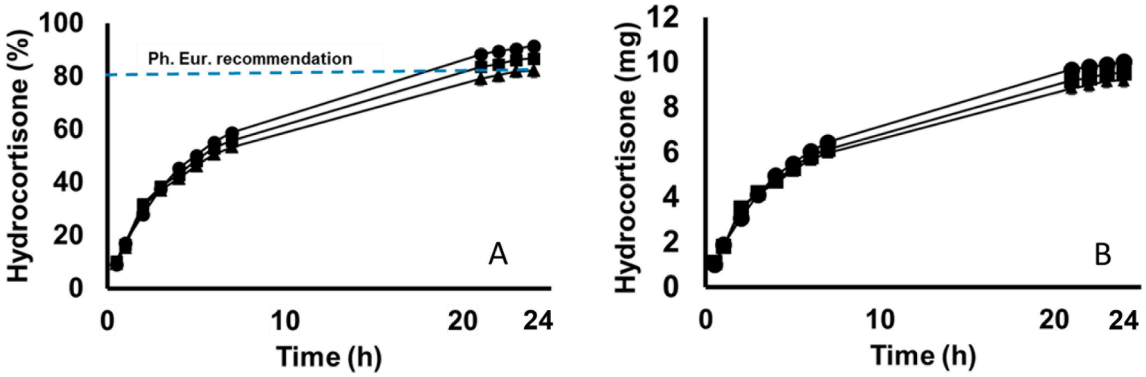

Fig. 14. Drug release profiles in % (A) and in mg (B) of three twin screw extrusion batches (● ■ ▲).

the operator as pulling the filament out of the extruder is a manual process. Results of the HC content analysis indicate a good intra-batch variability, as well as inter-batch variability with a relative standard deviation of < 1.7 % for both parameters. There was however, a high observed variability in content when comparing the content uniformity samples with the dissolution study samples. This may be operator-related, content uniformity samples produced by an operator who was more experienced had a higher content and lower variation compared to dissolution study samples where a less experienced operator was responsible for manufacturing (12.20 ± 0.19 mg vs 11.01 ± 0.72 mg respectively). Operator training and experience should be taken into account as critical process parameters in HME-FDM 3D printing where filaments are manually processed. Automating this process by adding a winder may be a simple solution to reduce filament diameter variations, and subsequently to improve the quality of the final product (Ponsar et al., 2020).

3D printing resolution seem to be a critical process parameter in FDM 3D printing. Resolution is defined by printing and traveling speed, and layer-height. A low resolution setting is associated with a higher HC content, indicating that increasing printing and traveling speed and increasing layer-height tend to lower the risk of API degradation. In future 3D drug development of HME-FDM 3D printed tablets, printing and traveling speed should be as high as possible in order to reduce API exposure time to high temperatures. Although this should be balanced with other quality parameters such as mass uniformity and reproducibility as an increase in printing speed may result in a lower tablet mass due to shorter times for material deposition per layer (Pires et al., 2020).

Twin screw filaments had a higher diameter variation compared to single screw based filaments. It is well established that single screw extruders have a constant output due to the linear relationship between screw speed and extrudate mass flow (Feuerbach and Thommes, 2021). Twin screw extruders however, have kneading and mixing zones which introduce fluctuations in material output and therefore, a higher diameter variation. The proof of concept formulation presented in this research was well translatable from single screw, equipment to advanced twin-screw equipment, maintaining the most critical product quality attributes such as the dissolution profile, demonstrated by a similarity factor of 63.3 %.

Friability and hardness results indicate that F4 tablets are not susceptible to abrasion and have adequate hardness properties for safe packaging, transportation and storage, in line with other literature findings on FDM based 3DP tablets (Karalia et al., 2021; Bhatt et al., 2021). A 'high' resolution setting may have also aided in the good mechanical properties, as a high resolution leads to more layers built into the final product. A higher layer-height is associated with a larger risk of introducing air pockets within and/or between layers, and reducing the tensile strength of the product (Farashi and Vafaee, 2022). Conventional hardness testing does not seem to be suitable for our HME-FDM 3DP tablets as they did not break, but due to their flexible nature, they did bend a little. HME-FDM prepared tablets usually have an excellent hardness, in some cases even better compared to directly compressed tablets (Ilyés et al., 2019; Zhang et al., 2017; Henry et al., 2021). FDM-HME tablet hardness is influenced by infill-density, choice of excipients, structural geometry, layer-height and layer-to-layer adhesion (Karalia et al., 2021; Zhang et al., 2020).

F4 tablets demonstrated a stable 24 h drug release profile similar to the registered Plenadren® formulation. Tablet height correlates strongly with tablet dose which provides an easy tool for accurate dose adaptation based on patients' needs. Although this has not been demonstrated with the 3D printed formulations, the circle design seems to be a suitable for adapting tablet dose without altering drug release profile due to the surface area-volume ratio remaining constant when producing a larger circle (Reynolds et al., 2002). Dose individualization is not only specifically useful in adrenal insufficiency, where cortisol need varies greatly inter-individually, but also broader as pharmaceutical healthcare tends to move towards a personalized approach.

Stability study data indicate that formulation F4 tablets are stable within 28 days at normal conditions (25 °C, 60 % RH) as well as in accelerated conditions (40 °C, 75 % RH) with < 10 % content deviation at all time points compared to initial content. HC degradation was limited during 28 days and drug release profile remained intact with an f2 of 61.6. Impurities were observed at all time points indicating that they were formed during the manufacturing process rather than due to exposure at stability study conditions.

Many concepts of 3D printed medicines have been shown in the literature at this moment. The aim of this research was to develop 3D printed HC with the intention of clinical implementation. Before clinical testing in patients, adequate product quality needs to be demonstrated. One of the limitations of this research was that the HPLC method was not validated. A validated HPLC method is crucial in ensuring product quality. A full validation was not performed as F4 was not considered the final formulation due to the observed impurities. In future studies, after establishing the final formulation, a full validation of the HPLC method will be performed. Furthermore, prior to clinical implementation of M3DICORT, evidence is needed that adequate in-vivo plasma concentrations can be realized with the proposed HC formulation. A major challenge that lies ahead prior to clinical assessment of this product is the observed HC degradation which seems to be temperature dependent. Although TGA data do not reveal a weight change at processing temperatures for at least 30 min, impurities were detected by HPLC. Some peaks are > 0.2 % with respect to the HC peak, necessitating identification and qualification of these impurities conform 'ICH Q3B impurities in new drug products'. This is a very costly and time-consuming process. Our findings in terms of hydrocortisone thermal instability are not surprising. It has been demonstrated before that hydrocortisone thermal degradation kinetics increase at a higher exposure temperature. In one study, researchers have shown 37 % degradation of hydrocortisone succinate (Solu-Cortef®) solution for injection or infusion after 24 h of storage at 60 °C (Mihovec et al., 2022). Other studies have demonstrated similar findings, the findings regarding the impurities cannot be compared to our own findings due to differences in the analytical method (Genete et al., 2012; Shilu et al., 2021; Saira and Sadia, 2020; Zhang et al., 2016). Not much is known regarding the toxicity of the several degradation products found in the these studies. 21-deoxycortisol seems to be an important degradation product, which is a naturally occurring hormone in adrenal steroidogenesis (Hotha et al., 2020; Engels et al., 2019). In the effort to fasten the development to perform a clinical trial, identification and qualification of the found impurities was not pursued. Rather, efforts will be focused on limiting the processing temperature and exposure time of the formulation to higher temperatures, which may be less time-consuming. More feasible strategies to mitigate impurity formation may be to increase the screw speed, which reduces the transit-time of the formulation inside the extruder and thereby decreases the degradation risk (Ghosh et al., 2012). Furthermore, removing kneading zones may also aid in reducing degradation due to a higher local residence time (Matić et al., 2020). Our data indicate that lower processing temperatures and a lower transition time leads to a lower amount of impurities > 0.2 %. Another strategy to reduce impurities to < 0.2 % is by reducing processing temperatures with FDM or by switching to semi-solid (SSE) 3D printing, which may be a better alternative. Low temperature HME-FDM is possible and has been demonstrated earlier with manufacturing temperatures as low as 90 °C (Kollamaram et al., 2018). In the case of SSE, filament development is not necessary, reducing the API exposure time to high temperatures and thus, reducing the risk of degradation and impurity formation (Seoane-Viaño et al., 2021). Furthermore, in SSE low temperatures are utilized, making this technique an attractive alternative to HME-FDM 3D printing.

M3DICORT has the potential to improve health outcomes for patients with adrenal insufficiency compared to the standard of care. The easy dose individualization option for the proposed tablets has the potential to also improve disease in children where very specific dosages

are needed. Earlier research has demonstrated that > 60 % of children aged 4–8 years, and > 96 % of children aged 9–12 years can successfully swallow tablets with a diameter of 6 – 10 mm (Bracken et al., 2020). The proposed tablets have a diameter of 8 mm, making them also suitable for children, with the benefit of once-daily dosing.

5. Conclusion

To our knowledge, M3DICORT is the first 3D printed HC formulation specifically developed for patients with adrenal insufficiency. Multiple critical process parameters have been identified in this research such as (Simon et al., 2010) operator qualification, (Nowotny et al., 2021) printing resolution, and (Oprea et al., 2019) filament diameter. Furthermore, we found that critical quality attributes stated in the European Pharmacopeia, such as friability and hardness, may not always be suitable for 3D HME-FDM printed tablets. Instead, mechanical strength of filaments is a critical quality attribute here, influencing filament printability. Furthermore, this technology is suitable for low volume manufacturing whereas the European Pharmacopeia is focused on large scale manufacturing. The novel 3D printed HC tablet may have a significant impact on the pharmaceutical treatment of patients with adrenal insufficiency. The current standard of care, consisting of thrice daily HC, fails to mimic physiological cortisol plasma concentrations and is therefore suboptimal. The Plenadren® does this to a higher level, but is not always available for patients due to the high costs, also, dose personalization is not possible. HME-FDM seems to be suitable for manufacturing personalized medicine for patients with AI. Children with AI may also benefit from the tablets which have a suitable swallowing size for children > 4 years, with the additional benefits of once-daily dosing and accurate dose individualization.

This research lays a strong foundation for the further development and production of the proposed formulation for clinical use. Although there is room for pharmacists in the Netherlands to compound magistral preparations for individual patients, clinical assessment of the proposed M3DICORT formulation is necessary to proof that adequate in-vivo plasma concentrations can be established. Prior to clinical assessment, HC degradation and impurity formation need to be mitigated. Furthermore, validation and qualification of the production process is necessary before going into clinical trials. The demand for personalized medicine will grow in parallel with the rising trend in the availability of patient data, driven by innovations such as pharmacogenetics, digital diagnostics and artificial intelligence. This research has shown that HME-FDM is an excellent manufacturing technique which can be used to meet this growing demand by enabling pharmacists to produce personalized medicine for individual patients.

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CRediT authorship contribution statement

S. Ayyoubi: Conceptualization, Data curation, Formal analysis, Writing – original draft. **E.E.M. van Kampen:** . **L.I. Kocabas:** Data curation. **C. Parulski:** Data curation, Formal analysis. **A. Lechanteur:** . **B. Evrard:** . **K. De Jager:** Data curation. **E. Muller:** Data curation. **E.W. Wilms:** . **P.W.C. Meulenhoff:** Conceptualization. **E.J. Ruijgrok:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2022.122466.

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