

# PROCESS OPTIMIZATION OF HOT-MELT EXTRUDED FILAMENTS FOR FDM 3D PRINTING OF PERSONALIZED LOW-DOSE FLUDROCORTISONE ACETATE ORAL DOSAGE FORMS

Quentin Bourcy, Olivier Jennotte, Brigitte Evrard, Anna Lechanteur\*

*Laboratory of Pharmaceutical Technology and Biopharmacy, Department of Pharmacy, Center for Interdisciplinary Research on Medicines (CIRM), University of Liege 4000 Liege, Belgium*

*\*Corresponding author. E-mail address: anna.lechanteur@uliege.be (A. Lechanteur).*

## **Keywords:**

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## **Abstract:**

Low-dose oral formulations are often associated with poor dose accuracy (mass and content non-uniformity) and limited reproducibility. Three-dimensional printing (3DP), particularly Fused Deposition Modeling (FDM), has emerged as a promising strategy to overcome limitations of conventional pharmaceutical compounding for oral therapies. FDM enables precise, digitally controlled deposition for decentralized, on-demand manufacturing at the Point of Care (PoC), but its implementation is limited by the availability of suitable pharmaceutical filaments. Especially at sub-percent drug loadings, achieving homogeneous drug distribution at such low concentrations is a major challenge. Fludrocortisone Acetate (FCA), a micronized corticosteroid administered at microgram daily doses and commonly compounded in Belgium in the absence of authorized products, was selected as a model drug. This study aimed to develop homogeneous low-dose (0.5% w/w) FCA-loaded filaments by Hot-Melt Extrusion (HME) suitable for FDM printing. The effects of adding 1% of a flow regulator (Aerosil® 200) and screw configuration (one vs. two kneading zones) on extrusion process parameters and drug distribution were investigated. Aerosil® 200 improved powder flow and feeding stability, and filament homogeneity resulted from the combined effect of formulation and screw configuration. Optimized filaments showed suitable mechanical properties for FDM and enabled printing of Immediate-Release (IR) oral dosage forms containing 50, 100, and 200 µg FCA. Printed waffle-shaped units complied with European Pharmacopoeia requirements for mass and content uniformity, hardness, and friability. Dissolution confirmed an IR profile, with > 80% FCA released within 45 min. This work demonstrates the feasibility of manufacturing pharmaceutically compliant low-dose dosage forms by combining HME and FDM, offering a reliable alternative to conventional compounding and advancing point-of-care personalized medicine.

## **Abbreviations:**

API, active pharmaceutical ingredient; AV, acceptance value; CV, coefficient of variation; FCA, fludrocortisone acetate; FDM, fused deposition modeling; FTM, Formulaire Thérapeutique Magistral;

GMP, Good Manufacturing Practice; HME, hot-melt extrusion; HPLC-UV, high-performance liquid chromatography ultraviolet detection; HPMC, hydroxypropylmethyl cellulose (Affinisol®); IR, immediate release; PEO, polyethylene oxide (POLYOX®); Ph. Eur., European Pharmacopoeia; PLA, polylactic acid; PoC, point-of-care; Printlet, printed tablet; RSD, relative standard deviation; USP, United States Pharmacopeia; 3DP, three-dimensional printing.

## 1. Introduction

Manufacturing oral low-dose drug products (i.e., containing less than 1 mg of active pharmaceutical ingredient (API) per dosage unit) represents a major challenge. Such products face multiple hurdles during formulation and processing, including difficulties in achieving content uniformity due to low drug concentration, low potency from manufacturing losses, and potential chemical instability from increased surface exposure of micronized drugs to excipients and equipment (Zheng, 2009). These challenges are particularly pronounced in pharmaceutical compounding, where small batch sizes and manual operations further complicate dose accuracy and reproducibility. Several studies have reported significant API losses during pharmaceutical compounding. D'Hondt et al. reported that 77% of total API loss occurs during the trituration, mainly due to equipment surface roughness (D'Hondt et al., 2014). Such losses critically affect the final API content, especially in low-dose preparations, which are inherently prone to variability (Mathaut et al., 2006). To compensate, API overdosing is commonly applied in corticosteroid triturations and low-dose capsules, as recommended in the *Formulaire Thérapeutique Magistral* (FTM) in Belgium (Formulaire Thérapeutique, 2016). Despite this strategy, compounded preparations often fail to meet content standards, potentially leading to subtherapeutic dosing, inadequate disease control, and poor patient compliance (Mathaut et al., 2006; Neumann et al., 2017). This risk was confirmed by a national analysis involving community and hospital pharmacies conducted by the Association of Pharmacists Belgium (Association Pharmaceutique Belge, 2021), which found that 21% of triturations and 23% of 0.1 mg Fludrocortisone Acetate (FCA) capsules fell outside the required content ranges (95–105% and 90–110%, respectively). These findings highlight the need to improve the quality of compounded preparations or develop alternative dosage forms that ensure safe and effective patient care (Curti et al., 2020; Gioumouxouzis et al., 2019; Rowlands et al., 2021).

FCA is a synthetic corticosteroid with potent mineralocorticoid activity. It is mainly used in combination with hydrocortisone for the treatment of endocrine disorders such as primary adrenal insufficiency (Addison's disease) and congenital adrenal hyperplasia (Auer et al., 2023; Vaidya et al., 2025). It is typically administered orally at low daily doses (50–200 µg in adolescents and adults), with dosing individualized based on clinical assessment and serum electrolyte monitoring (Bornstein et al., 2016; Ceccato et al., 2023). Several oral FCA formulations are commercially available. In France, approved products include Fludrocortisone Acetate Accord® (100 µg) and Flucortac® (50 µg) tablets (Haute Autorité de Santé, 2025; VIDAL, 2025), while in the United States FCA tablets are marketed and monographed in the United States Pharmacopeia (USP) (United States Pharmacopeia Convention, 2019). In contrast, no FCA-containing medicinal products are currently authorized in some European countries, including Belgium, creating a significant therapeutic gap. In this context, individualized FCA

dosing relies on extemporaneous compounding of hard capsules in community and hospital pharmacies (Dooms & Carvalho, 2018). Given these limitations, FCA represents a relevant model drug to investigate alternative manufacturing strategies for personalized low-dose oral therapies.

Three-dimensional printing (3DP) has emerged as a promising technology for the development of individualized therapies. Over the past decades, interest in 3DP has grown significantly across multiple disciplines, including medicine, where it has been applied to medical devices, tissue engineering, and pharmaceutical dosage forms (Alhnan et al., 2016; Singh et al., 2020; Wang & Yang, 2021). In the pharmaceutical field, 3DP offers several advantages for individualized formulations, including flexible design, adjustable sizes, modifiable infill density, complex geometries, taste masking, and the incorporation of multiple APIs into a single dosage unit (polypills) (Jennotte et al., 2023; Khaled et al., 2015; Parulski et al., 2023; Tabriz et al., 2021). 3DP technologies are commonly classified into three main categories: light- based printing, inkjet printing, and nozzle-based deposition methods. Among these, nozzle-based technologies include: semi-solid extrusion (SSE), direct powder extrusion (DPE), and Fused Deposition Modeling (FDM), which differ by the nature of the printable material (ink) used (semi-solid formulations, powder/pellet blends, or drug-loaded polymeric filaments, respectively). These technologies show strong potential for decentralized drug manufacturing, particularly in hospital and community pharmacies, where flexible, patient-specific dosage forms and rapid responses to drug shortages are required. Within this context, FDM is one of the most widely used 3DP techniques due to its low cost, ease of use, and high reproducibility. It also reduces the risk of drug exposure and eliminates the need for organic solvents, making it both environmentally and operationally attractive (Daminabo et al., 2020; Rahim et al., 2019). It relies on the controlled extrusion of a thermoplastic filament through a heated nozzle to build solid dosage forms layer by layer from a digital model (Jennotte et al., 2020; Park et al., 2019; Parulski et al., 2021). By enabling on-demand manufacturing at the Point-of-Care (PoC), FDM supports the transition from a “one-size- fits-all” approach toward personalized medicine, allowing adaptation of drug dosage and design to individual patient needs (Park et al., 2019; Tracy et al., 2023). However, the implementation of FDM in pharmaceutical settings remains limited by the availability of suitable drug-loaded filaments (Tan et al., 2018). Unlike SSE or DPE, where drug- loaded cartridges or powder mixtures could be prepared directly at the PoC under strict and well-defined quality requirements, pharmaceutical filaments are not commercially available and cannot be produced on- site. Consequently, filament design and manufacturing represent a critical step for the broader adoption of FDM in community and hospital pharmacies. The development of ready-to-use, industrially produced qualified drug-loaded filaments suitable for direct printing at the PoC is therefore essential to enable decentralized pharmaceutical manufacturing.

These filaments are produced by Hot-Melt Extrusion (HME) and are composed of thermoplastic polymers, excipients (e.g., plasticizers, glidants), and the API (Bandari et al., 2021; Shaqour et al., 2020; Tan et al., 2018). During HME, the mixture is heated and conveyed along twin screws within the barrel and then extruded through a cylindrical die to form a filament (Goyanes et al., 2015; Zhang, Yang, et al., 2017). Nonetheless, several formulation challenges must be addressed to ensure the production of high-quality printable filaments Quodbach et al. (2022). These challenges include the limited availability of pharmaceutically acceptable thermoplastic polymers, precise control of filament diameter, and achieving suitable mechanical and rheological properties for consistent feeding and extrusion (Aho et al., 2019; Pereira et al., 2020).

Numerous studies have demonstrated the feasibility of producing printable filaments incorporating a wide range of APIs. Reported drug loadings typically range from a few percent (5%) up to 20–30% (w/w), depending on the polymeric matrix, formulation strategy, and release kinetics. This range is generally considered optimal to balance therapeutically relevant doses with the mechanical properties required for reliable FDM processing. For example, Viidik et al. successfully produced filaments containing 20–40% (w/w) APIs, including theophylline and indomethacin (Viidik et al., 2021), while the highest loading reported in the literature reached 60% (w/w), as described by Verstraete et al. (Verstraete et al., 2018). HME filaments containing 20% (w/w) hydrocortisone and 10% (w/w) dexamethasone have also been reported, confirming the feasibility of extrusion-based processing for corticosteroids (Domsta et al., 2024; Parulski et al., 2024). In contrast, the production of filaments containing very low-dose APIs remains largely unexplored. To date, no studies have reported the development of FCA-loaded filaments suitable for FDM printing. One example of a low-dose filament involves pramipexole at 0.1% (w/w), for which homogeneous filaments were obtained after a complex multistep pretreatment, including granulation by roll compaction and subsequent blending of placebo and API-loaded granules during extrusion (Chamberlain et al., 2022). However, the filaments were not further processed by 3DP, highlighting the practical limitations of such approaches for PoC applications.

In this context, FCA was selected as a model drug to investigate the feasibility of producing homogeneous, low-dose filaments by HME suitable for FDM. The primary objective of this study was to optimize the filament formulation and the extrusion process to achieve reproducible drug loading, adequate mechanical properties, and compositional homogeneity at low API level. The optimized filaments were subsequently used for FDM printing of Immediate-Release (IR) solid oral dosage forms, whose pharmaco-technical properties were evaluated in accordance with the European Pharmacopoeia (Ph. Eur.) requirements for uncoated tablets.

## 2. Materials and methods

### 2.1. MATERIALS

FCA was purchased from Pharma Chemicals (Wauthier-Braine, Belgium). Affinisol® HPMC 100LV (HPMC, hydroxypropyl methylcellulose, Tg: approx. 115 °C, cellulosic polymer soluble in water, gifted by IFF Pharma Solutions, USA) was used as matrix former. Polyethylene oxide (PEO, POLYOX® WSR N10, MW 100,000, gifted by Colorcon, UK), a semi-crystalline polymer (Tg = -67 °C and Tm = 65–70 °C) was used for its plasticizing effect. Aerosil® 200 Pharma (SiO<sub>2</sub>, hydrophilic fumed silica) was acquired from Evonik Industries AG (Essen, Germany) and was used for its flow-regulating properties.

## 2.2. METHODS

### 2.2.1. FILAMENTS PRODUCTION

A cellulosic polymer (HPMC 100LV) was selected and combined with polyethylene oxide (PEO N10) at a fixed ratio of 70:30 for all formulations ([Table 1](#)). Each batch of filaments was produced by HME to identify the optimal formulation incorporating 0.5% (w/w) of the active pharmaceutical ingredient. 1% Aerosil® 200 Pharma was incorporated into the blend ([Table 1](#)) to assess its impact on powder flow and filament homogeneity, as well as its potential influence on extrusion behavior. Physical mixtures were prepared by triturating the components using a mortar and pestle. A 5% overage relative to the API content was incorporated to compensate for FCA loss, in accordance with Belgian regulatory requirements outlined in the FTM for corticosteroid trituration ([Formulaire Thérapeutique, 2016](#)).

The powder blends were extruded using a Pharma 11 twin-screw extruder (Thermo Fisher Scientific, Germany) configured with one or two kneading zones ([Table 1](#)) and operated at 20 RPM (Annex A). A temperature gradient ranging from 90 °C to 140 °C was applied along the barrel and a gravimetric MiniTwin 20 feeder (Kubota Brabender Technologie, Germany) was used to feed the powder mixture into the barrel. To control the filament diameter, an air-cooled conveyor belt (Thermo Fisher Scientific, Germany) was integrated into the extrusion line. This system allowed adjustment of the pulling speed to control filament diameter. A digital caliper was used to monitor the filament diameter in real time, with a target diameter of 1.75 mm.

Process data were collected online via a computer equipped with the software “CX-SUPERVISOR-RUN-ME-V3” and the data logging application 11 mm version 3.30 V1.5, which was connected to the extruder.

**Table 1**  
HME formulations.

| Formulation | FCA (%) | HPMC 100LV (%) | PEO N10 (%) | Aerosil® 200 (%) | Kneading zones |
|-------------|---------|----------------|-------------|------------------|----------------|
| F1          | 0.5     | 69.65          | 29.85       | /                | 2              |
| F2          | 0.5     | 68.95          | 29.55       | 1                | 2              |
| F3          | 0.5     | 68.95          | 29.55       | 1                | 1              |

### 2.2.2. MECHANICAL TESTING

The mechanical properties of the filaments were evaluated using a three-point bending test, adapted from the Repka-Zhang method, on a TA-XT2 Texture Analyzer (Ametek, Berwyn, USA) equipped with a TA- 1000 N probe set and a 25 mm supporting gap ([Zhang et al., 2019](#)). Six filament samples were collected, cut into 7 cm rods, and positioned on the sample holder. The blade was driven downward at a speed of 10 mm/s until reaching a maximum displacement of 15 mm below the supported sample. The breaking force, breaking distance and Young's modulus were recorded at room temperature and analyzed using Nexygen® Plus 3 software (Ametek, Berwyn, USA).

### 2.2.3. FUSED DEPOSITION MODELING THREE-DIMENSIONAL PRINTING

The 3DP process was performed using formulation F3 with a Good Manufacturing Practice (GMP) compliant 3D printer (M3DIMAKER 2, FabRx, UK) equipped with a FDM printhead. The printed object, a cylindrical structure, was designed using Tinkercad® (Autodesk, San Rafael, USA) and converted into.gcode files using Repetier-Host® software (version 2.3.2; Willich, Germany) in combination with the open- source slicing software Slic3r® (version 1.3.0). This process enabled the fabrication of a structure referred to as the “waffle shape” (Fig. 1), as described in a previous work (Parulski et al., 2024). The printing parameters were as follows: infill density 30%; no top, bottom, or perimeter layers; speed 5 mm/s; nozzle temperature 145 °C; bed temperature 50 °C; layer height 0.2 mm; and nozzle diameter 0.25 mm.

The solid oral dosage form manufactured using 3DP technology, such as FDM, is referred to as a 3D printed tablet (printlet) (Goyanes et al., 2017). The dimension of the printlets (Table 2) were adjusted to achieve a target mass of 10 mg, 20 mg, and 40 mg per unit, corresponding to doses of 50 µg, 100 µg, and 200 µg of FCA, respectively. These doses were selected to align with the therapeutic range (Bornstein et al., 2016; Ceccato et al., 2023). For each printing sequence, 20 units were consecutively printed on the build plate. The total printing times were 431 s, 685 s, and 2,098 s for the 50 µg, 100 µg, and 200 µg dosage forms, respectively. The corresponding filament consumption was 10.8 cm, 18.6 cm, and 34.6 cm for the 50 µg, 100 µg, and 200 µg dosage forms, respectively. These values were estimated by the slicing software prior to printing and include a small, nearly constant amount of material used for printer priming and initial extrusion.

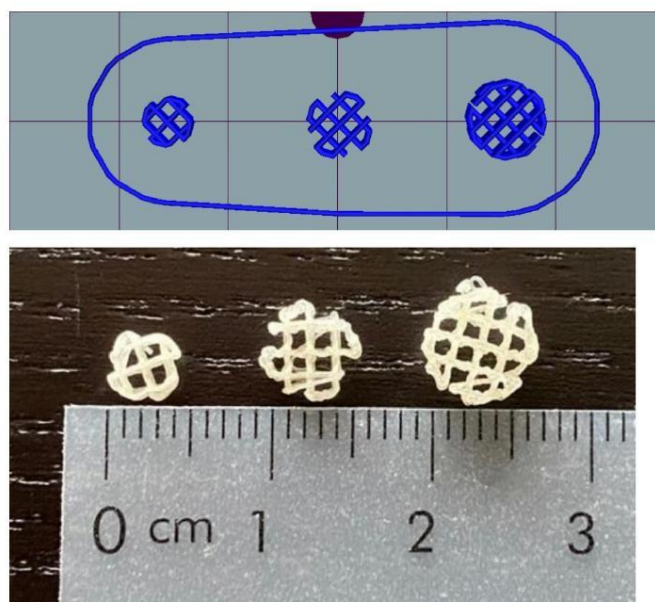


Fig. 1. Design 3d (above) and picture (down) of the printlet named “Waffle Shape”.

**Table 2**  
Characteristics of the 3D object.

| Weight (mg) | FCA (µg) | Diameter (mm) | Height (mm) |
|-------------|----------|---------------|-------------|
| 10          | 50       | 4.25          | 1.70        |
| 20          | 100      | 5.75          | 2.30        |
| 40          | 200      | 6.80          | 2.72        |

#### 2.2.4. CAPSULES COMPOUNDING

Thirty opaque capsules containing 200 µg of FCA were prepared according to the procedure described in the FTM. A trituration containing 0.5% FCA was prepared by dilution with an excipient blend composed of 99.5% mannitol and 0.5% colloidal anhydrous silica, using a mortar and a pestle. The excipient mixture was progressively added until the volume corresponding to 30 capsules size 3 was reached. The powders were homogenized in a mortar and the capsules were filled volumetrically by levelling.

#### 2.2.5. DETERMINATION OF DRUG CONTENT

The drug content was evaluated at three stages of the manufacturing process: in the powder mixture prior to HME, in the filament after extrusion, and in the printed dosage form following 3DP. For the powder mixture, five samples were withdrawn from different locations within the blend and subsequently analyzed. Regarding the filament, ten samples were collected by cutting sections at equal intervals along its length. The printed tablets were dissolved in a water/acetonitrile mixture (60:40 V/V) prior to analysis by high-performance liquid chromatography with UV-detection (HPLC-UV).

The HPLC-UV analysis was performed using a reverse-phase system (Agilent® 1100, Santa Clara, USA) operated with OpenLab CDS IC ChemStation software (version C.01.05). The mobile phase consisted of water and acetonitrile in a 60:40 (V/V) ratio. Separation was achieved on a Spherisorb® ODS2 C18 column (250 mm × 4.6 mm I.D., 5 µm particle size). The flow rate was maintained at 1.5 mL/min, and the column temperature was set to 30 °C. The injection volume was 100.0 µL, the total run time was 15 min, and FCA was detected at approximately 8 min with a wavelength of 240 nm. All analyses were performed in triplicate. The present method was successfully validated using the accuracy profile approach and E-noval® software (V3.0, Arlenda, Liège, Belgium), with an LOD of 0.09133 µg/mL and an LOQ of 0.5184 µg/mL.

#### 2.2.6. CHARACTERIZATION OF PRINTED TABLETS

##### 2.2.6.1. Uniformity of mass

Mass uniformity was assessed in accordance with the Ph. Eur. (11th Edition, monograph 2.9.5). To assess the uniformity of mass of the printed dosage forms, twenty units of each dosage form (50, 100, and 200 µg), produced using the final formulation (F3) under the process conditions described in [Section 2.2.1](#), were taken. Each unit was individually weighed using a microbalance (Excellence Plus XP26, Mettler Toledo, Schwerzenbach, Suisse). The mean weight, standard deviation (SD), and relative standard deviation (RSD) were calculated. For tablets with a mean mass below 80 mg, no more than two individual units were permitted to deviate by more than ± 10% from the mean mass, and none were allowed to deviate by more than ± 20%. This test was performed in triplicate for each dosage.

##### 2.2.6.2. Content uniformity

The content uniformity test is required when the amount or proportion of the active substance is less than 25 mg or 25%, as is the case for the printed forms produced. Content uniformity was assessed on ten printed units from each dosage form using F3, under the process conditions described in [Section 2.2.3](#), in accordance with the Ph. Eur. (11th Edition, monograph 2.9.40). The quantification of FCA was performed using a HPLC-UV method described in [Section 2.2.5](#). The compliance is

determined by calculating an acceptance value (AV) based on Equation (1), which must be less than 15.0.

$$\text{Acceptance Value} = |M - \bar{X}| + ks \quad (1)$$

Where:

M is a reference value which depends on X.

$\bar{X}$  is the mean of the individual content, expressed as a percentage of the theoretical value of FCA.

k is an acceptability constant (if n = 10, then k = 2.4).

s is the sample standard deviation

#### 2.2.6.3. Mechanical properties (friability and hardness)

To evaluate the mechanical properties of the printlet, friability and hardness tests were performed based on Ph. Eur. methods (11th Edition, monographs 2.9.7 and 2.9.8, respectively).

For the friability test, twenty printed units from each dosage were randomly selected from batches produced. This number has been fixed based on previous work (Parulski et al., 2023). The units were dusted, weighed, and placed in a friability tester (Friabilator USP F2, Sotax®, Switzerland). The apparatus was operated at 25 RPM for 4 min. After testing, the units were dusted and reweighed, and the percentage weight loss (%) was calculated. According to the Ph. Eur., the friability limit for uncoated tablets is not more than 1.0% weight loss.

Hardness testing was conducted on ten printlets from each dosage form using a hardness tester (MultiTest 50, Pharmaton®, France). Each unit was positioned horizontally on the lower base, and compressive force was applied laterally until fracture. The crushing strength was recorded for each unit, and the results were expressed as mean, minimum, and maximum values. No specific acceptance criteria for hardness are defined by the Ph. Eur.

#### 2.2.6.4. In vitro drug release studies

Dissolution studies were conducted under sink conditions using two compendial methods: the USP Apparatus II (paddle method) and USP Apparatus IV (flow-through cell), both operated on Sotax® systems (AT7 and CE 7smart, respectively; Allschwil, Switzerland). For the paddle method, the stirring speed was set at 50 RPM, and the temperature was maintained at 37 °C. The dissolution medium consisted of 360 mL of 0.01 N HCl. For the flow-through method, the small-volume cell for tablets was used with a standard flow rate of 16 mL/min, and the dissolution medium consisted of 60 mL of 0.01 N HCl in closed-loop configuration. Both tests were run over a 4 h period. The saturation solubility of FCA was determined using the flask-shaking method in 0.01 N HCl, the selected dissolution medium. The measured solubility of crystalline FCA powder in this medium was  $31.91 \pm 0.60 \mu\text{g/mL}$ .

At predetermined time points (0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, and 4 h), 1 mL aliquots were withdrawn and replaced with an equal volume of fresh medium. Comparisons were made against gelatin capsules prepared as described in Section 2.2.4. Samples were analyzed by HPLC-UV as detailed in Section 2.2.5 to quantify the release of FCA over time from the dosage forms. The release kinetics of the units printed with F3 were monitored to assess their compliance with conventional IR specifications, which require that at least 80% of the active substance be released within 45 min, according to Ph. Eur. Each dissolution test was performed in triplicate for both apparatuses.

## 3. Results and discussion

### 3.1. FILAMENTS EXTRUSION

#### 3.1.1. DEVELOPMENT OF FORMULATION

As explained in the introduction, no commercially available pharmaceutical filaments for FDM are currently on the market. Although the literature on this topic is extensive, reported formulations rely on a wide range of excipients, including various polymers, plasticizers, fillers, and taste maskers, etc., reflecting the absence of standardized filament compositions. Building on our experience in the development and optimization of drug-loaded filaments via HME ([Jennotte et al., 2022](#); [Parulski et al., 2022, 2024](#); [Thiry et al., 2016](#)) we designed a model excipient composition intended to be adaptable to different APIs. This composition is based on a primary blend of a cellulosic polymer and polyethylene oxide in defined proportions, enabling the incorporation of up to 20% (w/w) additional excipients and API loadings ranging from 0.5% to 25% (w/w). This formulation has previously been successfully applied to hydrocortisone, and the present study extends its applicability to fludrocortisone acetate.

To select such composition and excipient ratio, various excipients were initially screened with different API (data not shown). For instance, poly(vinyl) alcohol (PVA) as main thermoplastic polymer and sorbitol as plasticizer were mixed with FCA. Obtained filaments were not adapted to FDM printing mainly due to too high flexibility. Subsequently, Affinisol® 100LV and PEO N10 were combined in a 70:30 ratio ([Table 1](#)), providing a balance between mechanical strength and flexibility while ensuring stable filament production and reliable FDM printability.

A patent application was filed on the composition comprising this combination of excipients.

#### 3.1.2. IMPACT OF A FLOW REGULATOR ON FEEDING AND EXTRUSION PERFORMANCE (F1/F2)

In order to optimize the FCA-loaded filament, 1% of flow regulator (Aerosil® 200) has been added to the formulation containing Affinisol® 100LV and PEO N10 (70:30 ratio) and FCA 0.5% w/w. F1 corresponds to the formulation without flow regulator and F2 with. As previously described, achieving uniform API distribution along the filament length is particularly challenging at the very low drug loading employed in this study. This risk is primarily influenced by the powder feeding behavior during extrusion, as fluctuations in material input may lead to local variations in API concentration. To address this challenge, the addition of a flow regulator was investigated as a strategy to enhance feeding stability and, consequently, filament homogeneity. Aerosil® 200, an anhydrous colloidal silica, was therefore incorporated to evaluate its effect on the feeding rate and the extrusion process. Aerosil® 200 is widely used in pharmaceutical manufacturing for its ability to improve powder flowability and prevent particle agglomeration, two factors known to influence blend homogeneity and API distribution ([Majerová et al., 2016](#)). As reported by Saraf et al., glidant such as colloidal silica has already been used in formulations for HME. However, authors mentioned the lack of literature data on the impact of silica on the quality attributes ([Saraf et al., 2024](#)).

In order to fully study the impact of the addition of Aerosil® 200, real-time data collection during HME was collected. Indeed, real-time data collection is essential for a comprehensive understanding of the process, where most transformations occur inside the barrel of the extruder, beyond direct visual observation. In this context, several critical process parameters were continuously monitored. First, the feed rate of the gravimetric feeder, operating synchronously with the extrusion process, was

recorded. The feed rate, expressed in grams per hour (g/h), corresponds to the mass flow of material entering the barrel. In addition, die pressure, reflecting the resistance of the molten material at the die; die melt temperature, indicating the temperature of the melt at the die; and torque, representing the mechanical energy required to maintain constant screw speed and therefore reflecting the overall process load, were continuously monitored. Fig. 2a presents the corresponding feed rate profiles for the triplicate runs under both formulation conditions: the left panel shows the mixture without flow regulator (F1), whereas the right panel corresponds to the formulation containing 1% Aerosil® 200 (F2). Fig. 2b shows the real-time extrusion profiles of die melt temperature, die pressure, and torque for three batches of formulations F1 (left) and F2 (right), represented by red, green, and blue curves, respectively.

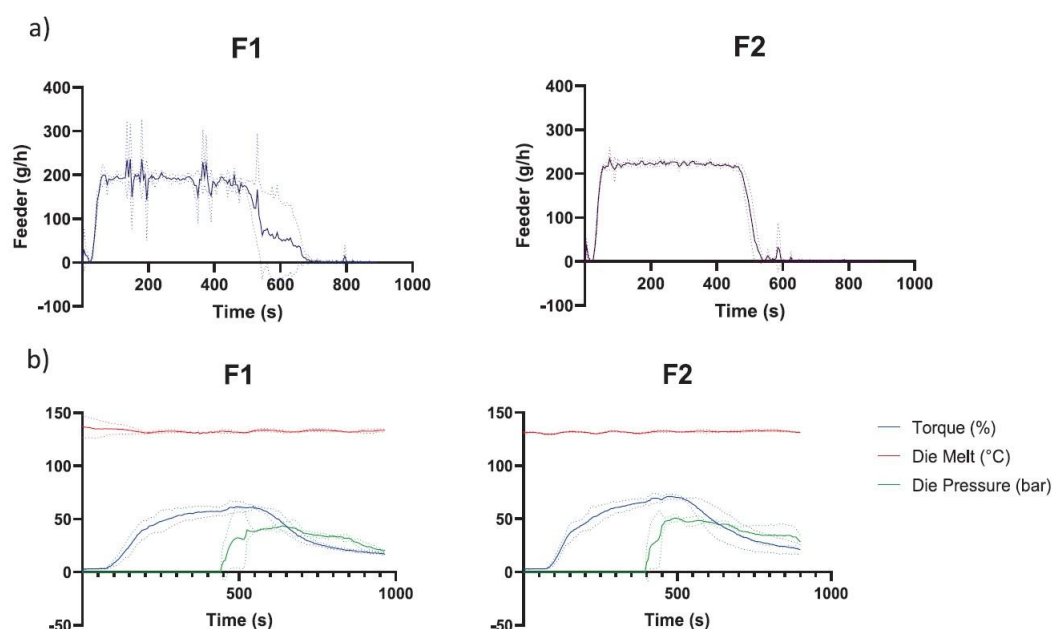


Fig. 2. Extrusion process data in real time; a) quantity spilled by the gravimetric feeder in gramme per hour with the F1 (left) and F2 (right). b) torque; die melt and die pressure with the F1 (left) and F2 (right).

Fig. 2a compares the feeding profiles (g/h) of F1 and F2 during HME. A marked improvement in feeding stability was observed for F2. In contrast, F1 exhibited pronounced fluctuations and irregular deviations from the target feed rate, indicating poor flowability and inconsistent material delivery. Such feeding instabilities are known to induce variations in residence time and may ultimately contribute to filament diameter fluctuations. Conversely, F2 maintained a stable feed rate of approximately 221 g/h until depletion of the batch at around 500 s, reflecting improved feeder performance and enhanced powder flow properties. This enhancement was corroborated by bulk and tapped density measurements, as reflected by a lower Hausner index for F2 (1.18) compared with F1 (1.24), corresponding to good and fair powder flowability, respectively. This improved feeding behavior resulted in the production of longer filaments with reduced diameter variability from the same initial amount of powder (30 g) (Table 3). Indeed, the continuous and controlled material delivery also enabled a clean process cutoff, whereas the erratic feeding observed for F1 led to irregular filament thicknesses and incomplete extrusion, rendering the filaments unsuitable for subsequent FDM printing. Moreover, less residual powder blend remained in the gravimetric feeder at the end of the process for F2, indicating a more complete material consumption, which further explains the greater filament length obtained with this formulation.

Beyond feeding behavior, the extrusion process parameters (Fig. 2b) provided further insight into the impact of formulation on melt behavior. F1 and F2 exhibited comparable die melt temperature profiles that remained stable throughout the extrusion process, indicating consistent thermal behavior between the two formulations. In contrast, the torque and die pressure profiles revealed clear differences between the formulations, indicative of distinct rheological properties and melt flow behavior. Both formulations showed similar torque evolution, with a peak observed around 500 s; however, F1 reached a maximum torque of 61%, whereas F2 displayed a slightly higher peak of 71% (Table 3). This suggests that the incorporation of Aerosil® 200 (F2) increased the melt viscosity relative to F1. This higher torque reflects an increased energy demand during extrusion, consistent with previous reports describing colloidal silica as a viscosity-enhancing agent in molten systems (Rowe et al., 2010). Regarding die pressure, maximum values were higher for F2 ( $51 \pm 4$  bar) than for F1 ( $43 \pm 4$  bar), in agreement with the observed increase in melt viscosity following the addition of the flow regulator. The onset of pressure rise occurred earlier for F2 (418 s) compared with F1 (475 s), suggesting improved and more consistent powder feeding, thereby reducing the time required to reach stable extrusion conditions. Despite the higher torque observed for F2, these improvements in feeding behavior indicate enhanced overall processability under the tested conditions. The addition of 1% Aerosil® 200 therefore appears to facilitate extrusion by improving powder conveyance and slightly accelerating the onset of extrusion. Collectively, these findings highlight the critical influence of formulation composition on extrusion behavior and underscore the importance of real-time process monitoring for achieving robust and reproducible HME operations.

**Table 3**  
 Summary of the extrusion process parameters for F1 and F2.

|                                             | F1           | F2           |
|---------------------------------------------|--------------|--------------|
| Feeder rate (g/h) (50–450 s)                | $190 \pm 16$ | $221 \pm 5$  |
| Filament length (cm)                        | $498 \pm 53$ | $664 \pm 60$ |
| Mean torque max (%)                         | $61 \pm 5$   | $71 \pm 3$   |
| Time before the mixture reaches the die (s) | $475 \pm 40$ | $418 \pm 24$ |
| Mean die pressure max (bar)                 | $43 \pm 4$   | $51 \pm 4$   |

### 3.1.3. IMPACT OF A FLOW REGULATOR ON FCA HOMOGENEITY (F1/F2)

In the absence of dedicated regulatory guidelines for extrusion-based pharmaceutical intermediates intended for additive manufacturing, quality requirements must be defined based on existing pharmaceutical standards. Several authors have highlighted that current regulatory frameworks do not yet fully address the specificities of materials and dosage forms produced using 3DP technologies in practice (Ahmed et al., 2025; Beitler et al., 2022; Parramon-Teixido et al., 2025). In this context, and in the absence of specific guidance, the Food and Drug Administration recommends applying the same quality standards and control requirements as those used for conventional pharmaceutical manufacturing processes (Jamróz et al., 2018; Mohapatra et al., 2022; Norman et al., 2017). From a quality-by-design perspective, the drug-loaded filament constitutes a critical intermediate in FDM, as its composition, mechanical properties, and homogeneity directly condition the quality of the final printed dosage forms. In particular, ensuring uniform API distribution within the filament matrix is a prerequisite for achieving reproducible dosing, especially for clinically relevant low-dose applications. Given the intended use of this approach in hospital and community pharmacy settings, the FCA content in the extruded filaments was therefore required to fall within a strict acceptance range of 95–105%. In order to ensure compliance with these predefined quality requirements, the impact of the HME process on FCA content was investigated. FCA concentrations were quantified in both the initial powder blends and the corresponding extruded filaments. Consequently, FCA content uniformity was

evaluated across three independent extrusion batches produced under two formulation conditions (F1 and F2), both processed using two kneading zones.

Mean FCA content values complied with the predefined acceptance criteria for both formulations and processing stages. For F1, mean drug content was  $99.25 \pm 2.48\%$  in the powder blend and  $97.56 \pm 3.28\%$  in the corresponding filament, while F2 showed mean values of  $101.50 \pm 1.91\%$  and  $96.97 \pm 2.84\%$  for the powder and filament, respectively. The incorporation of Aerosil® 200 in F2 resulted in slightly higher mean drug content in powder blend and a modest reduction in standard deviation compared with F1.

However, compliance with mean drug content specifications does not necessarily reflect uniform API distribution along the filament length, particularly at very low drug loadings. To visualize potential variations, the ten individual measurements used to calculate the mean values were represented according to their position along the filament length. Fig. 3 presents the API content values obtained for three independent batches of F1 and F2, with individual measurements shown as blue dots. The red lines indicate the predefined acceptance limits, while the green line corresponds to the mean API content of the corresponding powder blend.

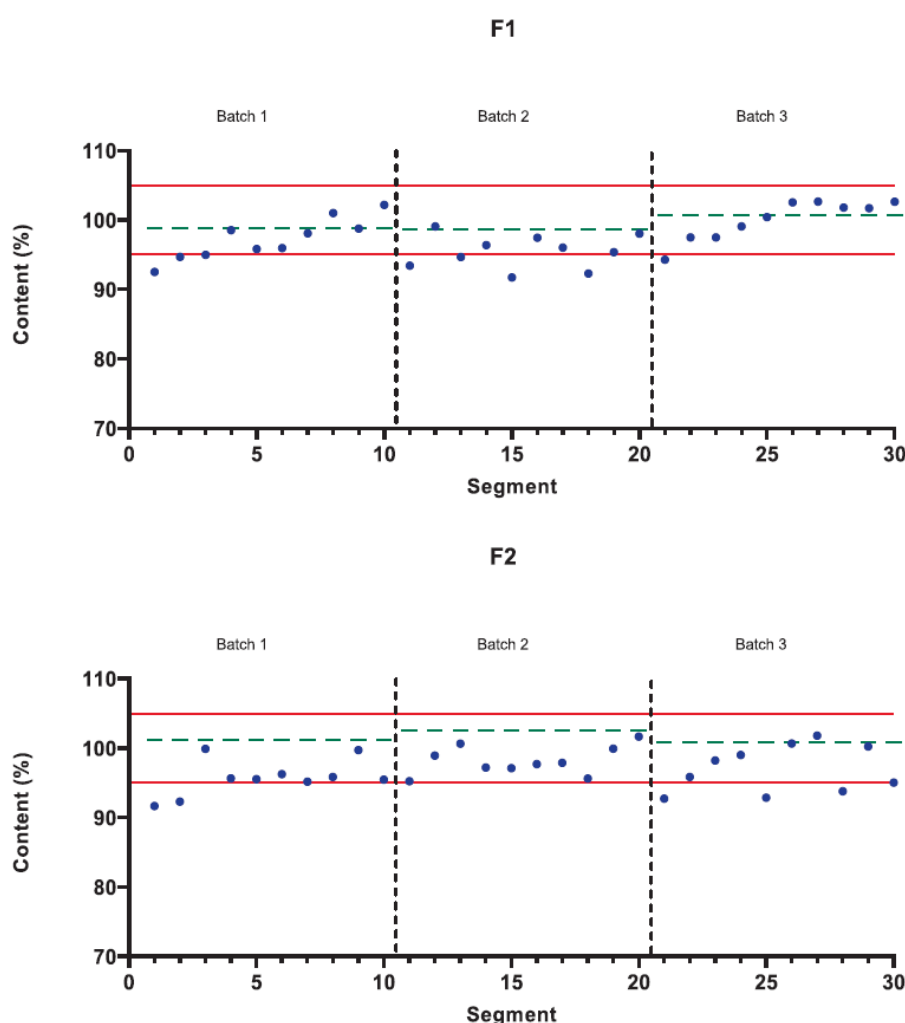


Fig. 3. Point-by-point analysis of fludrocortisone acetate content along three independent filament batches of F1 (top) and F2 (bottom). Blue dots represent API content at defined sampling points, while red and green lines indicate specification limits (95–105%) and initial powder blend concentration, respectively.

Although the average API content remained within the predefined specifications, the analysis of FCA content along the filament length revealed pronounced local deviations, with several sampling points falling outside the acceptance range. These results highlight the presence of heterogeneities that are

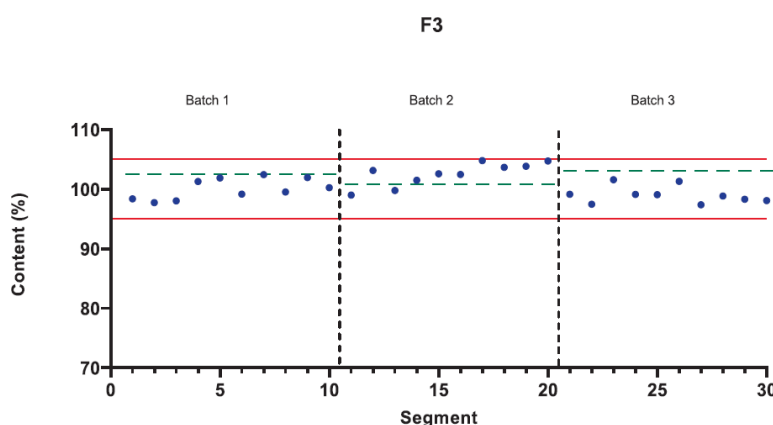
not captured by mean content values alone, a phenomenon that becomes particularly critical at sub-percent drug loadings. For both formulations, slight point-to-point variations in API content were observed along the filament, without any consistent increasing or decreasing concentration trend. Instead, the fluctuations appeared randomly distributed along the filament length, complicating interpretation and indicating that local variations with no systematic pattern observed between sampling positions.

The incorporation of 1% Aerosil® 200 resulted in only a slight reduction in standard deviation compared with F1 and did not translate into a measurable improvement in FCA distribution along the filament. Although Aerosil® 200 is widely used as a glidant to enhance powder flowability, its primary benefit under the present processing conditions appears to be related to improved feeding behavior, resulting in extrudates with a more consistent diameter and slightly greater length; however, its impact on drug content uniformity remains limited. These findings underscore the inherent difficulty of ensuring longitudinal content uniformity in low-dose HME filaments and highlight the need for improved formulation strategies and process control to support reliable downstream FDM printing.

#### 3.1.4. IMPACT OF THE NUMBER OF KNEADING ZONES DURING THE EXTRUSION PROCESS

Given that FCA content uniformity along the filament length did not comply with the predefined acceptance criteria, additional process- related factors potentially influencing API distribution during HME was investigated. One critical parameter is the intensity of shear and thermal stress imposed within the extruder, which is largely governed by the number and configuration of kneading zones. These zones play a key role in melt mixing but are also associated with elevated shear forces and prolonged exposure to high temperatures, which may adversely affect API integrity and distribution. To investigate whether reducing processing intensity could improve filament homogeneity, an additional formulation (F3) was extruded using a single kneading zone and compared with formulation F2, which was processed under identical conditions except for the use of two kneading zones (Table 1).

The FCA content in F3 was quantified relative to the target drug loading of 0.5% (w/w). Fig. 4 summarizes the FCA content measured along three independent F3 filaments, together with the mean drug content of the corresponding powder blends and the predefined acceptance limits (95–105%). For F3, mean FCA content values of  $102.12 \pm 1.83\%$  were measured in the powder blends and  $100.54 \pm 2.24\%$  in the corresponding filaments, demonstrating good agreement with the target concentration and satisfactory drug recovery following extrusion.



All the data points shown in Fig. 4 indicate improved filament homogeneity compared with the

previous formulations (F1 and F2). The variations observed along the filaments were less pronounced, and no sampling point across the three F3 filaments exceeded the predefined acceptance limits. Given the very low API loading, achieving this level of homogeneity remains a significant technical challenge, highlighting the importance of optimizing screw design and mixing intensity in HME- based formulations. To support this interpretation, the real-time process data collected under these conditions, including die melt temperature, die pressure, and torque, are presented in Fig. 5, while Table 4 summarizes the corresponding process parameters for formulations F2 and F3.

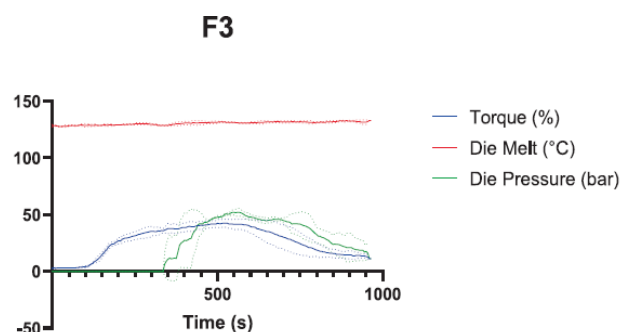


Fig. 5. Extrusion process data in real time: torque; die melt and die pressure with F3.

**Table 4**  
 Summary of the extrusion process parameters for F2 and F3.

|                                             | F2       | F3       |
|---------------------------------------------|----------|----------|
| Filament length (cm)                        | 664 ± 60 | 644 ± 23 |
| Mean torque max (%)                         | 71 ± 3   | 42 ± 3   |
| Time before the mixture reaches the die (s) | 418 ± 24 | 382 ± 42 |
| Mean die pressure max (bar)                 | 51 ± 4   | 52 ± 2   |

Process parameter analysis comparing F2 and F3 revealed clear differences in extrusion behavior. As shown in Table 4, F3 exhibited lower mechanical resistance during processing, as reflected by a reduced mean maximum torque of  $42 \pm 3\%$ , compared with  $71 \pm 3\%$  for F2. This decrease is attributable to the reduced number of kneading zones, which are known to impose high shear stresses and increase material residence time within the barrel (Lang et al., 2014).

With respect to die pressure, maximum values were comparable for F2 and F3, suggesting similar melt viscosity and flow behavior under the investigated conditions. However, a slightly earlier onset of pressure increase was observed for F3 compared with F2. Although this difference remains limited and within experimental variability, it suggests a trend toward faster material conveyance when using a reduced number of kneading zones, likely due to lower mechanical constraints within the barrel. Despite these differences in processing behavior, both formulations yielded comparable filament lengths, suggesting similar overall material throughput when a flow regulator was present. Real-time monitoring of F3 further confirmed stable melt temperature throughout extrusion, with relatively steady torque and pressure profiles. Overall, the reduction in the number of kneading zones resulted in lower mechanical demand during extrusion while maintaining stable processing conditions. In combination with the improved longitudinal API homogeneity observed for F3, these HME processing characteristics supported its selection for subsequent experiments.

### 3.1.5. EVALUATION OF MECHANICAL PROPERTIES OF THE FILAMENT

Assessing the mechanical properties of pharmaceutical filaments is essential for predicting their

printability in FDM 3D printing. Three parameters are particularly informative: breaking force, distance at break, and Young's modulus. Breaking force represents the maximum load sustained before failure and is relevant to the stresses exerted by the printer's drive gears. Distance at break describes ductility and the ability of the filament to tolerate bending during feeding. Young's modulus characterizes stiffness and resistance to deformation, which are key factors for ensuring consistent advancement through the printer's mechanical system (Parulski et al., 2021; Zhang et al., 2019; Zhang, Feng, et al., 2017). Although no official standards currently exist for characterizing filament mechanics, Korte and Quodbach proposed practical threshold values to distinguish filaments that are reliably printable from those prone to breakage or feeding issues. According to their work, printable filaments should exhibit a Young's modulus above 300 N/mm<sup>2</sup> and a distance at break above 1.125 mm; below these thresholds, filaments become difficult to handle and feed (Korte & Quodbach, 2018; Kreft et al., 2024). Based on these criteria, filaments F3 demonstrated excellent mechanical performance. The measured breaking force reached  $4.60 \pm 0.52$  N, indicating substantial tensile strength. The distance at break was  $4.62 \pm 0.49$  mm, confirming high ductility and tolerance to bending and feeding stresses. The Young's modulus was determined to be  $1653 \pm 117.82$  N/mm<sup>2</sup>, far exceeding the recommended minimum value. Taken together, these results provide a robust quantitative basis confirming that filament F3 meets and surpasses all recommended printability criteria for FDM processing.

### 3.1.6. STABILITY OF FCA DRUG CONTENT IN FILAMENTS DURING STORAGE

The filaments intended for FDM printing (F3) were stored in sealed plastic bags, protected from light, at room temperature. To assess the stability of FCA content over time, drug loading was quantified in each batch at three time points: immediately after production (T0), after four months, and after twelve months of storage (Fig. 6a and b, respectively). The mean FCA content at T0 was  $100.54 \pm 2.24\%$ . After four months, the average content was  $98.30 \pm 1.69\%$ , and after twelve months  $99.64 \pm 1.55\%$ , with no indication of a downward trend over the one-year storage period. Moreover, after twelve months of storage, the three batches of F3 filaments were re-evaluated using the three-point bending test to assess potential deterioration in printability. The values were  $1517.49 \pm 168.84$  N/mm<sup>2</sup> for Young's modulus,  $3.57 \pm 0.29$  N for load at break, and  $3.10 \pm 0.41$  mm for breaking distance.

All mechanical parameters showed a decrease compared with the values measured at the time of production. Nevertheless, the filaments remained suitable for FDM printing, indicating acceptable retention of mechanical performance after long-term storage. These observations are consistent with previously reported data in the literature. For example, Ilyés et al. demonstrated that pharmaceutical filaments stored under ambient conditions typically exhibit a gradual reduction in stiffness and an increase in brittleness over time, while still retaining sufficient mechanical integrity for FDM processing (Ilyés et al., 2019). Likewise, Nascimento et al. reported that drug-loaded filaments show moderate mechanical ageing during storage but remain printable as long as the polymer matrix does not undergo extensive moisture-induced degradation (Nascimento et al., 2024). These findings demonstrate that FCA remained stable even if the packaging is very simple and of low resistance against humidity since no significant loss of API occurred over time. Overall, the filaments exhibited suitable long-term stability, supporting their potential use for decentralized or on-demand pharmaceutical manufacturing.

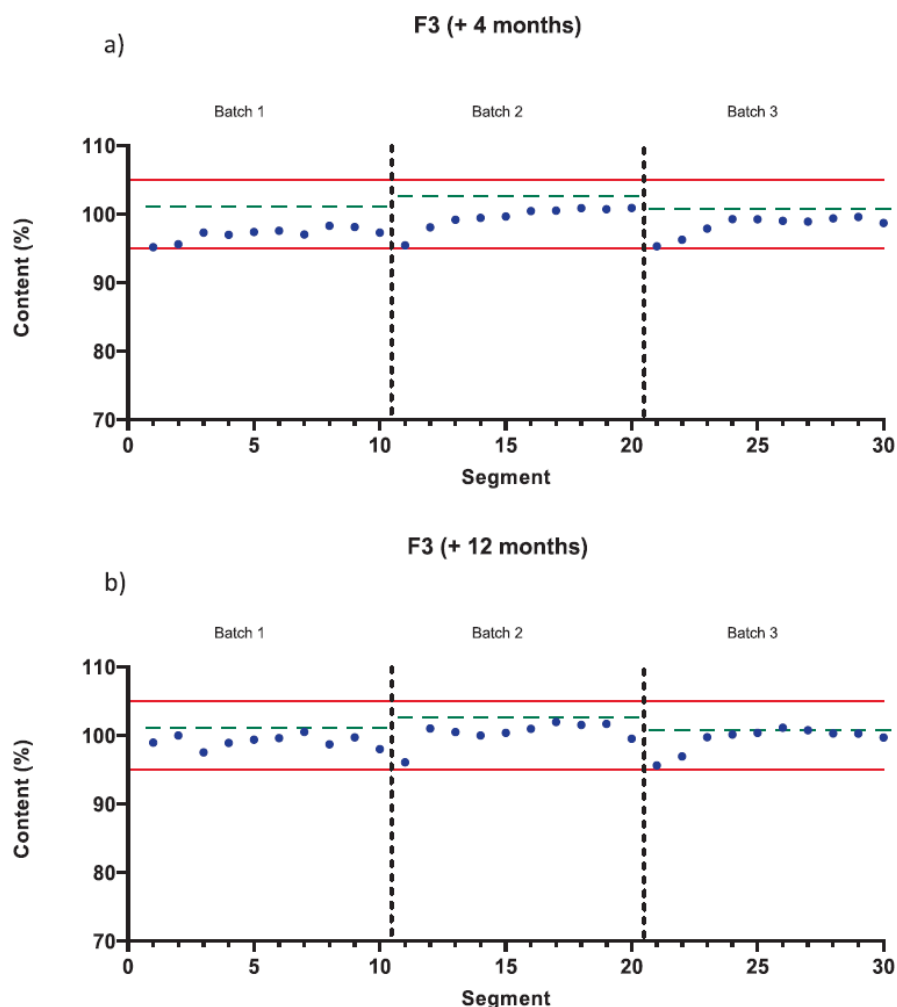


Fig. 6. Point-by-point analysis of FCA content along three independent F3 filament batches after 4 (a) and 12 months (b) of storage. Blue dots represent API content at defined sampling points, while red lines indicate the specification limits (95–105%) and the green line corresponds to the initial powder blend concentration.

### 3.2. PHARMACEUTICAL QUALITY ASSESSMENT OF PATIENT-TAILORED 3D-PRINTED DOSAGE FORMS

The printability of selected filaments (F3) was investigated. The design selected for this study was a geometric shape called 'waffle shape' (Fig. 7) (Parulski et al., 2023). According to the literature, the surface- area-to-volume ratio of 3D-printed structures plays a crucial role in modulating drug dissolution and release performance (Windolf et al., 2021). The waffle design was printed at three different dosage levels (50 µg, 100 µg, and 200 µg of FCA) to assess the feasibility of personalized dose adjustment using this approach. These doses corresponded to printed units weighing 10 mg, 20 mg, and 40 mg, respectively.

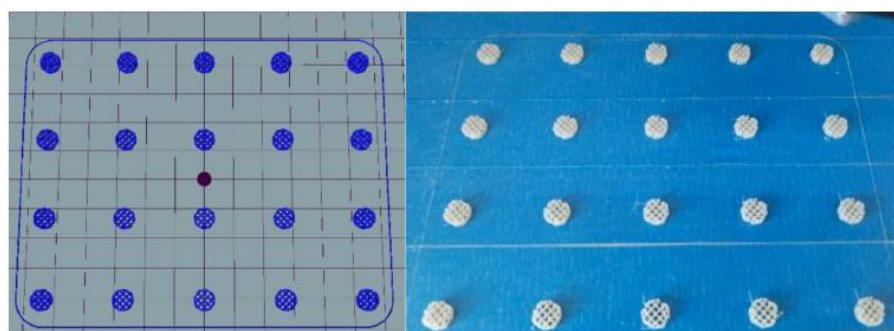


Fig. 7. Production of printlets containing 200 µg of fludrocortisone acetate, arranged in a sequence of 20 units on the build plate (.gcode schematic on the left; corresponding photograph on the right).

#### 3.2.1. UNIFORMITY OF MASS

The individual mass of each printed unit remained within  $\pm 10\%$  of the mean value, in accordance with Ph. Eur. specifications for solid oral dosage forms weighing less than 80 mg (monograph 2.9.5, 11th Edition; Fig. 8). Achieving this specification was particularly challenging given the small size of the printed units. Nevertheless, all printed formulations across the three FCA dose levels exhibited satisfactory mass uniformity, with coefficients of variation (CV) of  $2.18 \pm 0.98\%$  (10 mg),  $1.80 \pm 0.22\%$  (20 mg), and  $3.91 \pm 0.38\%$  (40 mg). Mass variability was mainly associated with fluctuations in filament diameter, as even minor deviations in thickness directly affect the mass of the extruded material during printing, since filament feeding is controlled on a length basis rather than by mass (Korte & Quodbach, 2018; Macedo et al., 2022). This effect becomes more pronounced in higher-dose forms, where larger amounts of material are deposited, explaining the higher CV observed for the 200 µg FCA dosage forms. Indeed, the total filament length required to print 20 units was 10.8 cm, 18.6 cm, and 34.6 cm for the 50 µg, 100 µg, and 200 µg API dosage forms, respectively. As an additional reference, three control batches were printed using the same .gcode sequence and with a standard polylactic acid (PLA) filament, resulting in a lower CV of  $0.63 \pm 0.11\%$  consistent with previous report (Ponsar et al., 2020). Overall, these results support the conclusion that improved filament diameter control directly enhances mass uniformity in printlets and, consequently, the overall quality of the drug product. Filament diameter consistency may be further optimized during scale-up of the HME process under GMP conditions which will ultimately lead to extremely low mass variation between mini-printed waffles.

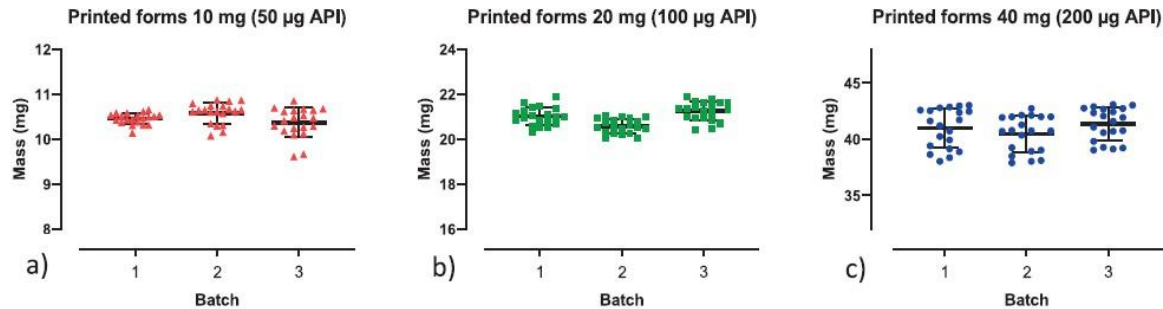


Fig. 8. Masses (mg) ( $\pm$  standards deviations ( $n = 20$ )) of three batches of 3D waffle shapes (a) 10, (b) 20 and (c) 40 mg with the F3.

**Table 5**  
Content and acceptance values ( $\pm$  standards deviations ( $n = 10$ )) for the content uniformity of 3D waffle shapes (50, 100 and 200  $\mu\text{g}$ ).

|                   | Content (%)      | VA     |
|-------------------|------------------|--------|
| 50 $\mu\text{g}$  | $97.74 \pm 1.69$ | 4.0    |
| 100 $\mu\text{g}$ | $96.77 \pm 1.27$ | 4.8    |
| 200 $\mu\text{g}$ | $98.44 \pm 2.73$ | 6.6    |
| Ph. Eur.          |                  | < 15.0 |

**Table 6**  
Friability (%) and force (N) ( $\pm$  standards deviations ( $n = 10$ )) of 3D waffle shapes (50, 100 and 200  $\mu\text{g}$ ).

| API               | Friability Weight loss (%) | Hardness Breaking forces (N) |
|-------------------|----------------------------|------------------------------|
| 50 $\mu\text{g}$  | 0.1                        | N.A                          |
| 100 $\mu\text{g}$ | 0.1                        | $6.7 \pm 1.5$ Min-max: 5–9   |
| 200 $\mu\text{g}$ | 0.1                        | $10.5 \pm 2.6$ Min-max: 7–15 |
| Ph. Eur.          | < 1.0                      | /                            |

3.2.2. CONTENT UNIFORMITY

The content uniformity of the 3D-printed waffle-shaped dosage forms containing 200, 100, and 50  $\mu\text{g}$  of FCA was satisfactory, with acceptance value (AV) of 6.6, 4.8 and 4.0, respectively below the Ph. Eur. limit of 15.0 (Table 5). These results confirm a uniform API distribution across all printlets.

3.2.3. MECHANICAL PROPERTIES OF PRINTLETS (FRIABILITY AND HARDNESS)

The difference in total weight before and after the friability test was precisely 0.14%, 0.096%, and 0.087% for the 3D-printed waffle-shaped dosage forms containing 50, 100, and 200  $\mu\text{g}$  of FCA, respectively (Table 6). No visible cracks or fractures were observed, and all printed units complied with the Ph. Eur. limit of 1.0% weight loss (11th Edition, monograph 2.9.7). The plasticity behavior of FDM-printed structures contributed to their compliance with friability specifications. The printlets demonstrated satisfactory friability values, ensuring adequate resistance to handling and transport without material loss.

The hardness test reflected the compression resistance of the printed dosage forms, providing an indication of their mechanical robustness during routine handling. Since all units shared the same composition and internal architecture, differing only in dimensions, a decrease in breaking force was observed with reduced size. The 50  $\mu\text{g}$  FCA dosage forms did not exhibit a measurable breaking force; instead, they underwent gradual compression between the instrument jaws without a detectable drop-force peak, preventing quantification. The measured hardness values were relatively low compared with those typically reported in the literature. For example, Patil et al. reported a breaking force of  $47.33 \pm 5.70$  N for 3D-printed tablets produced from a filament composed primarily of HPMC-AS and PEG 4000 (Patil et al., 2025). The mechanical strength of 3D-printed structures is mainly influenced by the polymers used and the adhesion between successive layers, which can be enhanced by increasing infill density to improve cohesion and resistance (Karalia et al., 2021). However, the Ph. Eur. does not specify hardness criteria for solid oral dosage forms. These mini waffles-printed forms are intended to be swallow or crushed either by children or adults population.

### 3.2.4. DRUG DISSOLUTION RATE

The aim of the printlets was to reproduce the release behavior of compounded FCA capsules, corresponding to an IR profile with at least 80% of the drug dissolved within 45 min. To evaluate the dissolution performance of both printlets (orange lines) and compounded capsules (blue lines), tests were conducted under sink conditions to avoid solubility limitations. Two dissolution apparatuses were employed: USP Apparatus II (paddle) and USP Apparatus IV (flow-through cell). In Apparatus II, six printlets were required to achieve a quantifiable concentration due to the low API content, whereas a single unit was sufficient in Apparatus IV, which allows testing in smaller volumes.

The drug release from the 3D-printed dosage forms exhibited an IR profile, with  $89.07 \pm 6.04\%$  of FCA dissolved within 45 min (Fig. 9). Nonetheless, the dissolution rate was slower than that of the compounded capsules, in which FCA was rapidly liberated following gelatin shell disintegration. In the printed units, drug release was primarily governed by the polymer matrix behavior in the dissolution medium, which tended to slow down the release kinetics and complicate the attainment of an IR profile when using FDM technology. The two polymers used, HPMC 100LV and PEO N10, are known to influence drug release kinetics. HPMC exhibits a swelling behavior upon hydration, forming a viscous gel layer that restricts drug diffusion and reduces the effective surface area (Colombo et al., 1999). However, the low infill density of the printed structures appeared to mitigate this gel-forming effect. As reported in the literature, matrix tablets with 100% infill containing HPMC typically display sustained-release behavior, whereas lower-infill geometries facilitate faster drug release (Totaro et al., 2025). PEO N10 is a water-soluble polymer that also exhibits swelling and erosion behavior, and its presence likely contributed to a further delay in drug diffusion. The combined influence of polymer composition and structural design underscores the critical role of both formulation strategy and geometry in achieving the desired release profile in FDM printlets.

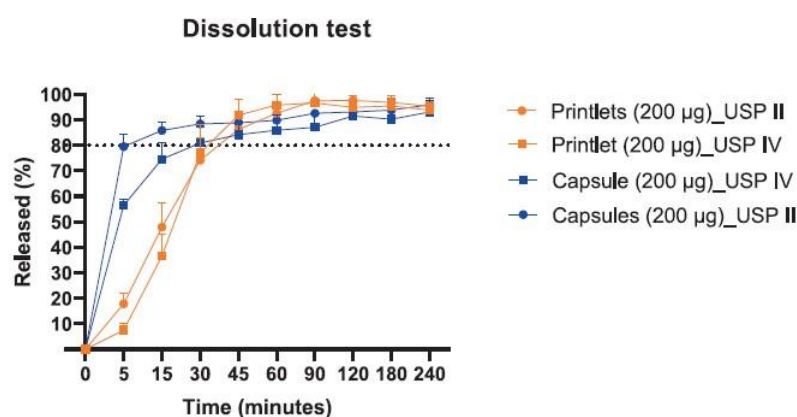


Fig. 9. Fludrocortisone acetate concentration (mean  $\pm$  SD) in 0.01 N HCl as a function of time, obtained during in vitro dissolution testing of capsules\* and printlets containing 200 µg of FCA. Results are shown for USP Apparatus II (paddle method, round) and USP Apparatus IV (flow-through cell, square). \*Not corrected for capsule mass; refers to the label claim (200 µg).

## 4. Conclusion

This study highlights the technical challenges associated with the development of low-dose pharmaceutical formulations using HME, a process in which achieving longitudinal API homogeneity

remains particularly challenging. Through the investigation of excipient blend flowability and process parameters, this study demonstrates that, under the investigated conditions, uniform drug distribution at sub-percent loadings cannot be achieved solely through enhanced powder flow or feeding stability but critically depends on the control of extrusion intensity and screw design. The incorporation of a flow regulator improved powder flow and feeding stability, but this alone was insufficient to ensure homogeneous API distribution along the filament.

Improved homogeneity was achieved only when feeding stability was combined with a reduced number of kneading zones, highlighting the importance of controlling material feeding, mechanical and thermal stresses on low-dose formulations during HME. The optimized formulation (F3), processed with a single kneading zone, yielded filaments with consistent FCA content, reproducible extrusion profiles, and mechanical properties compatible with FDM requirements.

Using these optimized filaments, 3D-printed oral dosage forms were successfully manufactured and met pharmaco-technical quality requirements, including mass and content uniformity, friability, and dissolution immediate-release behavior, in accordance with European Pharmacopoeia standards. These results confirm that, when appropriately controlled, filament-based manufacturing can support accurate dosing even at microgram range drug loadings.

Beyond demonstrating printability, this work underscores the intrinsic complexity of HME as a pharmaceutical manufacturing process and provides practical insights into blend optimization and screw configuration strategies to mitigate content uniformity issues. It is important to note that this study does not focus on filament composition (i.e., the excipient blend), but rather on the operational aspects of hot-melt extrusion that must be controlled to enable industrial-scale production. While formulation optimization is a crucial step in filament development, it is not addressed in this work, as it has already been fully established internally. While FDM 3D printing holds promise as a future tool for decentralized and personalized medicine, its routine implementation in hospital and community pharmacy settings will require the availability of standardized, drug-loaded filaments as pharmaceutical starting materials. In this context, the present study contributes to addressing key technical barriers and supports the development of robust HME-based approaches for low-dose personalized therapies.

#### **CRedit authorship contribution statement**

**Quentin Bourcy:** Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Olivier Jennotte:** Writing – review & editing, Methodology. **Brigitte Evrard:** Writing – review & editing, Project administration, Funding acquisition. **Anna Lechanteur:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

#### **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

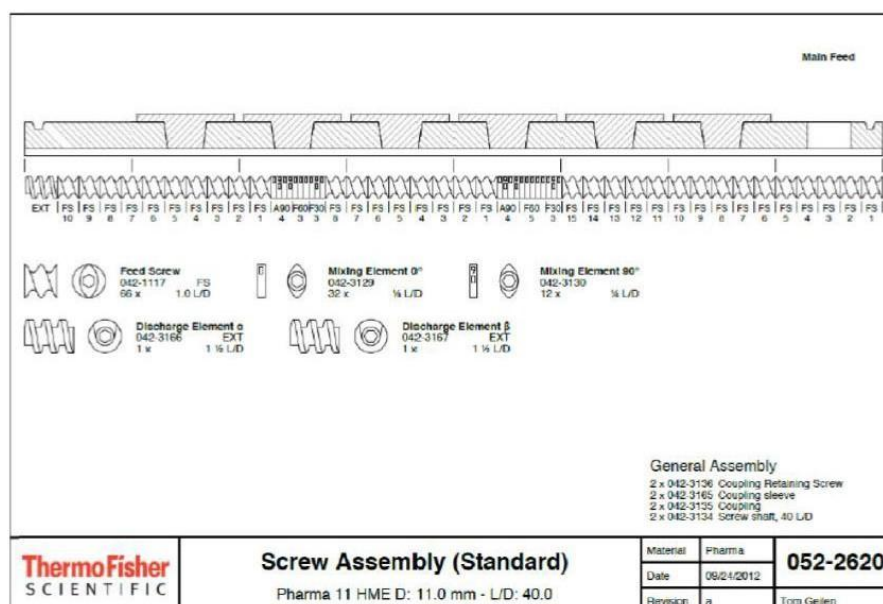
Data will be made available on request.

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## Annex.

A) Screws configuration.



## Data availability

Data will be made available on request.

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