Leveraging Pharmaceutical 3D Printing to Fulfill the Unmet Medical Need in Adrenal Insufficiency



Sejad Ayyoubi

Dissertation Statements

Related to PhD thesis

Leveraging pharmaceutical 3D printing to fulfill the unmet medical need in adrenal insufficiency

1. Pharmaceutical 3D printing allows for the modification and personalization of hydrocortisone drug dose and drug release profile; the latter is impossible with conventional compounding techniques. *This thesis.*

2. 3D printed, personalized hydrocortisone-containing dosage forms with different release profiles can be manufactured at acceptable societal costs and should be reimbursed. *This thesis.*

3. 3D printed hydrocortisone-containing dosage forms are of higher quality compared to conventionally compounded hydrocortisone capsules and should therefore be standard of care. *This thesis.*

4. Semi-solid extrusion 3D printing is the most suitable 3D printing technology for implementation in standard hospital pharmacy care. *This thesis.*

5. All excipients used for the development of 3D printed medication must be safe for pediatric patients. *This thesis.*

6. Patients with adrenal insufficiency are entitled to 3D printed hydrocortisone-containing dosage forms as they need a treatment that is personalized and mimics the physiological plasma cortisol concentrations. *Johannsson et al. Cur Med Res Op. 2014 Sep;30(9):1833–1847.*

7. Pharmacy compounding is the only tool to aid patients that are left with unsuitable dosage forms. *Dooms et al. Orph J R Dis vol 13 (2018)*

8. In these times of extreme personnel shortages we must turn to automatic compounding, such as 3D printing, to substantially reduce the workload. *Rodríguez-Maciñeiras et al. Int J Pharm. Vol 671, 2025, 125251.*

9. Pharmaceutical 3D printing should completely replace manual medication manipulation to ensure patient safety. *Chachlioutaki et al. Exp Op Drug Del. Vol 20 (2023).*

10. There are no regulatory barriers for the implementation of 3D printing at the point-of-care in hospital pharmacies. *Annereau et al. Eur J Pharm Sci. 2025, 107340.*

11. “It is more important to know what sort of person has a disease, than to know what sort of disease a person has.” *Hippocrates, 400 BCE.*

Leveraging Pharmaceutical 3D Printing to fulfill the Unmet Medical Need in Adrenal Insufficiency

Het toepassen van farmaceutisch 3D printen ter verbetering van de behandeling van bijnierschorsinsufficiëntie

Thesis

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‘When a home is filled with sincerity,

its people grow in affection.

Whoever plants love in the heart

finds their home bright with its light.’

خانه چون آباد گردد با صفا

اهل آن یابند از هم بس وفا

هر که در دل مهر یاران کاشت است

خانه اش از نور یاران راست است

Rumi

To my parents and brothers
To my wife and son

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Chapter 1

Introduction: aims and outline

Introduction

Patients with adrenal insufficiency, a rare disease, are affected by a lack of suitable oral hydrocortisone formulations. In the absence of authorized treatments, pharmacists are allowed to compound medicinal products to meet the individual patient's needs. Pharmaceutical three-dimensional (3D) printing is a novel pharmacy compounding technique, which allows the pharmacist to adjust the drug dosage, release profile, shape, and taste of a product. In this thesis, different pharmaceutical 3D printing techniques are explored to manufacture suitable hydrocortisone formulations for patients with adrenal insufficiency. Research is performed regarding the formulation development, manufacturing costs, and quality of 3D printed hydrocortisone and we discuss how to implement this technology in regular pharmaceutical care. This chapter gives an overview of the unmet medical need, the manufacturing process of pharmaceutical 3D printing, considerations during formulation development, and clinical and implementational efforts of this technology. We conclude this chapter with the aim and outline of this thesis.

Unmet medical need in adrenal insufficiency

A disease is considered rare when less than 5 per 10,000 people are affected (1). Developing and commercializing medicines for rare diseases can be challenging. The small amount of patients complicates research, clinical trials and attenuates commercial attractiveness (1). These justifications may explain why there is no effective treatment option for 95 % of rare diseases (2). Initiatives from regulatory authorities have been implemented to promote formulation development for rare diseases. In 2020, the European Union (EU) implemented the orphan medicinal product regulation to promote the development of medicines for rare diseases (3). It led to market authorization of 149 medicines with an active orphan designation. It is however a limited effect given the more than 6000 estimated rare diseases and approximately 30 million Europeans living with a rare disease (1).

The lack of suitable formulations has also been described for primary adrenal insufficiency. It is a rare disease, also known as Addison's Disease, with a prevalence of 1-2 patients per 10,000 people (4). The most common cause is autoimmune adrenalitis where antibodies develop against the adrenal cortex, leading to dysfunction. The adrenal cortex is responsible for the production of adrenocortical hormones. Following disease of the adrenal cortex, a decline of adrenocortical hormones such as cortisol, aldosterone and androgens is observed, which is life-threatening when left untreated. Patients usually present themselves with an adrenal crisis in an emergency setting. The nonspecific signs and symptoms such as abdominal pain, nausea, myalgia, weight loss, fatigue, and dizziness lead to a delayed and challenging diagnosis (5).

The cornerstone of the treatment consists of glucocorticoid and mineralocorticoid replacement therapy, usually in the form of oral hydrocortisone and fludrocortisone (6). Long term glucocorticoid replacement therapy consists of three times daily hydrocortisone treatment with 10 mg immediately on waking, 5 mg at midday and 5 mg in the early evening. However, the dose and dosing frequency can be changed as a result of clinical signs and symptoms by the treating endocrinologist during follow-up. Real world data regarding hydrocortisone dosing regimens demonstrates that there is a high variety in daily dosage of hydrocortisone that patients receive (7, 8). Only 42.4 % of patients remained on the conventional three times daily 10 mg, 5

mg, 5mg dosing regimen (7). In this study, 6.3 % of patients received 5 to < 10 mg daily hydrocortisone, 22.9 % received 15 to < 20 mg, and 15.2 % received 25 to < 30 mg. A high variability in the frequency of dosing was also observed, ranging from one to four times daily. There is no biomarker to guide the right dose in glucocorticoid replacement therapy. Treatment is therefore guided by subjective health status alongside clinical assessment of over- or under-replacement symptoms. Clinicians reduce the daily dose when patients present with signs of a glucocorticoid excess, such as weight gain, hypertension, oedema, and poor glycemic control (5). On the other hand, the daily dose is increased in case of a glucocorticoid deficit, which could present as postural hypotension and salt-craving symptoms (5). These variables lead to individualization and therefore to variation in hydrocortisone dose in clinical practice. Long term excess, or overreplacement, is associated with an increased risk of cardiometabolic risks e.g. diabetes and hypertension and a lower quality of life, whereas underreplacement is associated with risks of adrenal crisis, fatigue, nausea, myalgia and joint stiffness (5). A delicate balance and personalization of therapy is therefore required in patients with adrenal insufficiency (9).

The treatment goal is to mimic the physiological circadian plasma cortisol pattern seen in healthy individuals. The current three times daily treatment with hydrocortisone does not mimic the physiological circadian plasma cortisol in patients (10, 11). In normal physiology, the cortisol plasma concentration is highest in the morning and gradually decreases throughout the waking day (**Figure 1)**. However, the current standard of care consists of multiple daily dosing, leading to fluctuating plasma cortisol concentrations. Late afternoon cortisol exposure has been associated with glucose intolerance, abdominal obesity, coronary atherosclerosis, fatigue, and a poor sleep pattern (12-16). In recent years, modified release hydrocortisone formulations became available for the treatment of adrenal insufficiency, demonstrating a more physiological circadian glucocorticoid rhythm (17). Although long-term studies on hard endpoints are lacking, studies have demonstrated that the modified release hydrocortisone formulations lead to a reduction in body weight, reduced HbA1c, overall immune function improvement, and a higher quality of life (18-21). However, modified release hydrocortisone tablets are only available in limited fixed doses, complicating personalization of treatment. There is therefore an unmet medical need for patients with adrenal insufficiency, requiring a personalized, physiological cortisol replacement therapy.

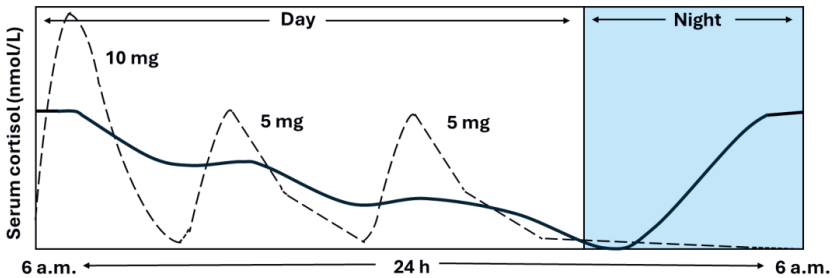


Figure 1. *Sketch of concentration-time profile of plasma cortisol in a healthy person (full line) and in a patient with primary adrenal insufficiency, receiving the standard regimen of three times daily (10 mg morning, 5 mg midday, 5 mg early evening) immediate release hydrocortisone tablets (dashed line).*

This thesis investigates pharmaceutical 3D printing as a pharmacy compounding technique to manufacture hydrocortisone formulations mimicking the physiological plasma cortisol, while enabling personalization of the dosage to ensure optimal treatment.

Pharmacy compounding and manipulation of pharmaceutical products

Extemporaneous pharmacy compounding has been described as a safe and cost-effective alternative when there are no suitable, authorized formulations available (22). Extemporaneous compounding is defined as the practice of preparing medicinal products for an individual patient when there is no commercial alternative available (23). Pharmacists in the Netherlands are allowed by law to manufacture medicinal products for their owns patients when suitable commercial alternatives are lacking (24). Pharmacy compounded capsules and liquids are common examples (25, 26). However, conventional extemporaneous compounding techniques do not allow for the modification of drug release profiles. Pharmacy compounded capsules, for instance, are usually manufactured by filling empty capsules with a mixture of raw unprocessed pharmaceutical powders, limiting the ability to modify the drug release. Pharmaceutical 3D printing does allow for the manufacturing of modified release products, potentially more suitable for patients with adrenal insufficiency (27).

Manipulation of existing formulations is also used as a strategy when suitable, commercially available products are lacking. Studies have shown that 17 % to 37 % of oral medicines given to hospitalized children were manipulated, making it common practice for pediatrics (28, 29). Manipulation of existing medicines, such as crushing or splitting tablets, or opening capsules, could be used with the aim of achieving the right dose (30). However, manipulations are associated with safety risks for patients due to a risk of inaccurate dosing, and can be time-consuming for healthcare workers (31-33). Furthermore, manipulations can negatively affect patient safety due to changes in drug stability, solubility and bioavailability with subtherapeutic or toxic drug levels as a consequence (29). Pharmaceutical 3D printing can be used to manufacture high quality, less time-consuming medicines at the point-of-care, without the risks associated with drug manipulation (34).

Pharmaceutical 3D printing

It was in 1996 when the first paper was published, in which researchers explored 3D printing as a method to fabricate complex polymeric drug delivery systems (35). 3D printing was used to print an object with two colorants, exerting different drug release properties. Research in recent years demonstrated that 3D printing technology allows for the personalization of the drug dose, release profile, shape, and taste of pharmaceutical products. This has led to the maturation of the technology, showcased by market entry of pharmaceutical 3D printers, the first clinical trials that have been performed, and adoption of the technology by hospital pharmacies (27).

Pharmaceutical 3D printing can be used for mass manufacturing or mass personalization of pharmaceutical products (27, 36, 37). Aprecia Pharmaceuticals for instance uses 3D printing to manufacture levetiracetam on an industrial scale (27). Large compounding pharmacies could manufacture, and/or register 3D inks, or 3D printed products on a semi-industrial scale (38). Legislation in the Netherlands allows compounding facilities to supply compounded preparations from one pharmacy to another, given that there is no commercially

available alternative, amongst other requirements (39). In a hospital pharmacy setting, usually a small number of patients are in need of pharmaceutical products that are not commercially available. The research presented in this thesis is therefore focused on 3D printing as a pharmacy compounding method, to manufacture personalized medicine on a small scale.

3D printing is an umbrella term of different technologies that can be classified into seven categories, namely material extrusion, binder jetting, powder bed fusion, vat polymerization, material jetting, directed energy deposition and sheet lamination (27). In pharmaceutics, extrusion-based 3D printing techniques are the most widely investigated techniques, demonstrated by the highest number of publications, clinical trials, as well as implementation in hospital pharmacies (40-44). Direct powder extrusion (DPE), semi-solid extrusion (SSE), and fused deposition modeling (FDM) are extrusion-based 3D printing techniques. The studies presented in this thesis are focused on FDM and SSE 3D printing. In extrusion-based 3D printing, the 3D printer requires a pharmaceutical ink, and a digital design to produce an object (**Figure 2**). Prior to printing, a digital model of the object is designed, which is sliced in layers by 3D printing software in a file. This file contains instructions for the printer to build the desired object. The printer executes the instructions in this file and builds the final object in a layer-by-layer manner. Of the extrusion-based techniques, FDM and SSE are the most researched in (hospital) pharmacy. Both techniques work by softening or melting the ink to produce the final object in a layer-by-layer manner. The main differences in the techniques are the type of pharmaceutical ink and the processing temperatures used.

The pharmaceutical ink for FDM is manufactured by hot melt extrusion (HME), where raw thermoplastic materials and active pharmaceutical ingredient (API) are melted (45). The molten materials pass through a nozzle with a specific diameter and solidify at room temperature, generating a filament. The obtained filament is subsequently fed to the printer and melts again due to heating. The molten material is then deposited layer-by-layer on the platform until the final product is formed. Raw powders are thus exposed to high temperatures, usually above 100 °C, twice in FDM 3D printing (46). In SSE the ink consists of semi-solid materials which are filled in a syringe (47). The filled syringe serves as the ink. The printer heats the syringe and deposits the molten material in a layer-by-layer manner on the platform, similar to FDM. Here, the raw materials may be exposed to high temperatures during pre-mixing and during printing, but lower temperatures are used compared to FDM printing, usually below 100 °C (47).

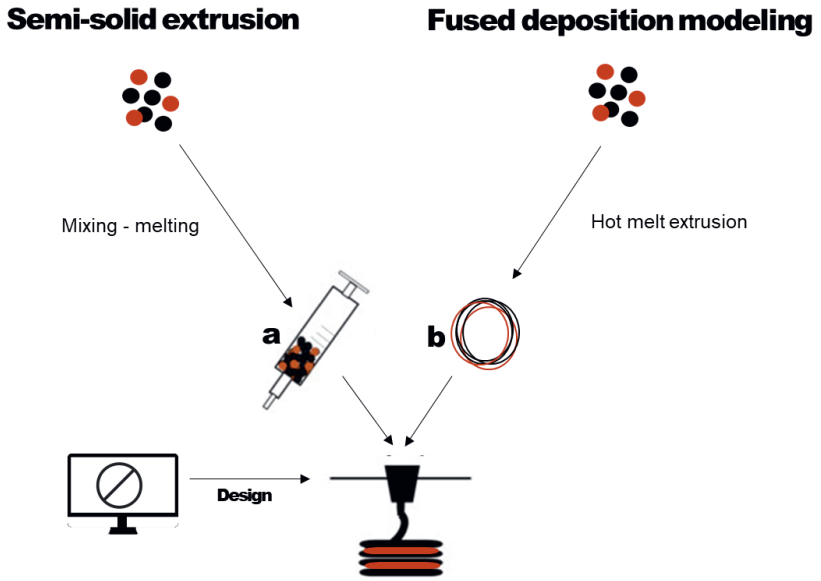


Figure 2. *In semi-solid extrusion, powders are converted to a printable semi-solid material by mixing, and in some cases by applying higher temperatures. The semi-solid material is filled into a syringe (a), which is the ink in SSE 3D printing. In fused deposition modeling solid strands called filaments (b) are used as ink. Filaments are formed by hot melt extrusion, where pressure and high temperatures are applied to form solid strands. The ink and design are fed to the printer, which prints the ink in a layer-by-layer fashion on a platform.*

Zooming out, the manufacturing process steps in solvent-free SSE printing involve the premixing of raw pharmaceutical starting materials, forming a semi-solid material by applying heat, filling the semi-solid into a syringe, inserting the syringe in the printer, feeding a predefined design to the printer, and 3D printing (**Figure 3**). In solvent-based SSE 3D printing additional post-processing, e.g. drying, is required (48). Key formulation development considerations are the selection of excipients, the processing temperatures, and the design used to manufacture the final product. The starting materials should be carefully selected as they can influence critical quality attributes of the final product, such as dissolution profile and mechanical strength (49). For instance, by increasing the concentration of soluble diluents such as mannitol, a faster drug release can be realized (50). Rational excipient selection should be based on the quality target product profile to meet the intended therapeutic goals (51). Other formulation development considerations, related to the manufacturing process, are shown in **Figure 3**.

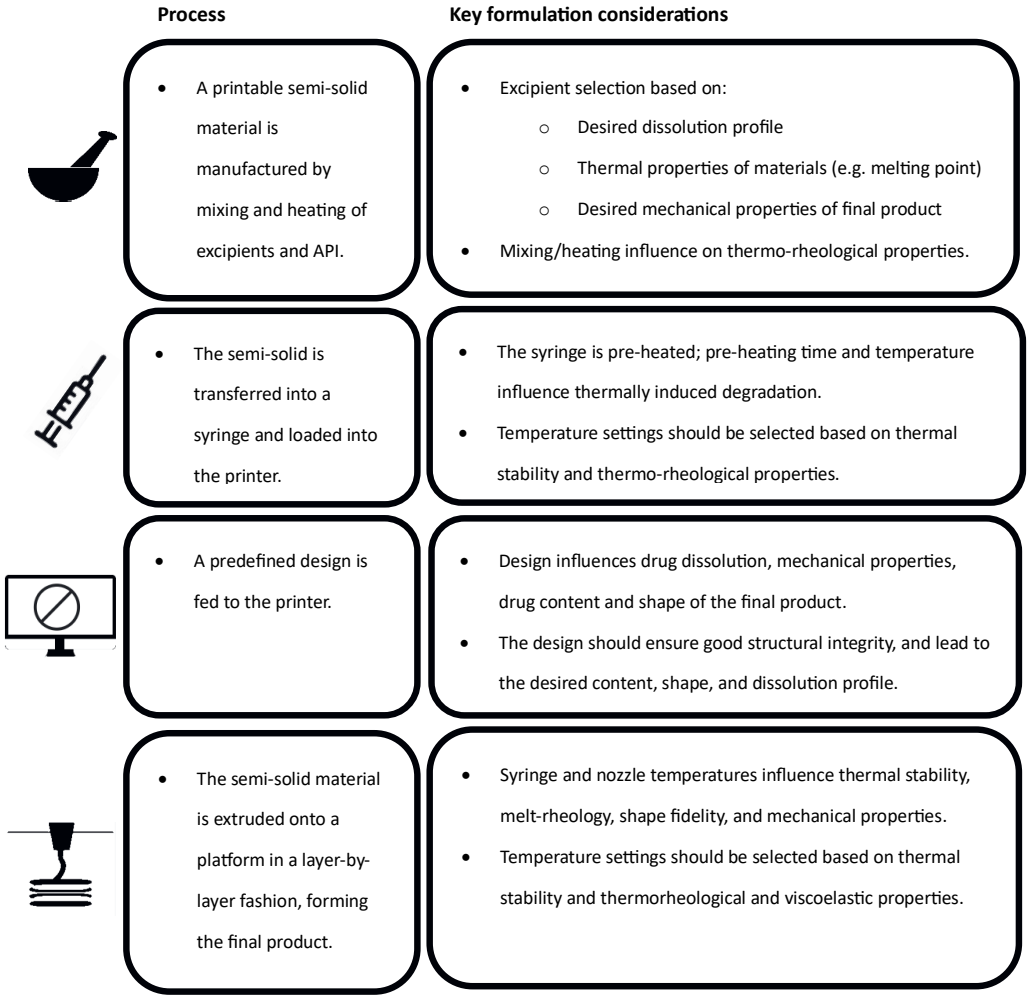


***Figure 3**. Key formulation development considerations In the solvent-free SSE 3D printing process .*

The mixture of active pharmaceutical ingredients combined with suitable excipients should lead to good melt-rheological properties in order to be printable. Usually, thermoplastic materials are used that melt or soften below printing temperatures in order to be printable (52). The viscosity of the mixture is determined by the physicochemical properties of the excipients as well as the used processing temperatures. Usually highly viscous semi-solid materials are used to prevent sedimentation of particles and ensure a homogeneous mixture. Viscosity is therefore a critical material attribute (CMA). If the viscosity of the semi-solid material is too high, the solid material can cause nozzle blockage and cannot be printed (53-55). On the contrary, if the viscosity is too low, the formulation will flow out of the syringe as a liquid, making it impossible to form a tablet shape (55). Ideally, the material should exhibit thixotropic behavior, where it behaves like a lower viscous fluid during printing under higher pressure and temperature, while quickly recovering after the print is finished (56). This ensures good structural integrity of the final product during solidification. Another CMA in SSE 3D printing is the particle size of dispersed particles in the semi-solid material (57). The particle size should be small enough to ensure good passing thought the printer nozzle in order to be printable. Furthermore, SSE inks should not contain air bubbles, as it can lead to defects in structure, weight, dissolution, and content-uniformity. Air bubbles may also affect the relaxation behavior of the semi-solid material (58).

The ink used in FDM is associated with different CMAs compared to SSE. For instance, filaments need to have a homogeneous diameter in order to be printable and to prevent product defects (57). If the filament diameter is too big, it cannot be fed to the printer. Too small diameters lead to feeding issues or weight and content variations in the final product (56). An inhomogeneous filament diameter may lead to printing failure due to feeding issues or impact product quality due to over-extrusion at thicker filament parts, and under-extrusion at thinner parts. Furthermore, mechanical properties, such as hardness and elasticity also play a role. If the filament is too brittle, it can break during printing, causing a failure (59). Overly flexible filaments are at risk of coiling up inside the feeding zone, which leads to print failures (59). The thermo-rheological properties described for SSE inks are also applicable for FDM (57). The filament should melt above printing temperatures and quickly solidify after printing at room temperature. Researchers have put efforts to identify acceptance criteria for the mentioned CMAs for printable inks (59, 60). However, due to the high variability of excipients, processing temperatures, pressure settings and hardware (e.g. type of printer, nozzle diameter, syringe material) that can be used, developing suitable inks usually seems to remain a trial-and-error process.

The design produced by 3D printing software is a key manufacturing process step as it enables to manufacture a personalized dosage. The design allows adjustment of the surface area to volume ratio which can be used to control the tablet weight and drug dose(61-63). The drug dosage can therefore easily be adjusted by designing a specific tablet volume or height in 3D printing software, without changing the formulation. Studies have demonstrated that personalized dosages can be manufactured within a high dose range with high accuracy. Personalized doses can be manufactured with high accuracy and a high dose range, with SSE 3D printing, dosages from 0.5 mg up to 600 mg can be printed (49, 64).

Besides the ability to print personalized doses for individual patients, 3D printing also allows for the modification of the drug release profile. Researchers have developed 3D printed products releasing the drug in 15 minutes (65). Others report sustained drug release profiles with gradual drug release up to 24 hours with

the aim of reducing the number of tablets and improving drug adherence (66-68). It is also possible to delay the release of the API, by 3D printing a core-shell tablet. The drug release can be delayed from three to six hours (69, 70). This could potentially improve pharmacotherapy for patients where a timed-release is necessary, such as in congenital adrenal hyperplasia, where patients need a nighttime cortisol dose (71). 3D printing therefore allows pharmacists to manufacture oral medicines for individual patients, which was not possible before with conventional manufacturing techniques such as capsule filling or formulating liquids.

Pharmaceutical 3D printing further allows for the manufacturing of polypills and modification of shape and taste of medicines (72, 73). One study combined five APIs into one tablet with immediate and sustained release profiles (72). This concept could greatly benefit drug adherence in geriatrics where polypharmacy is common (74). The taste and shape masking abilities with 3D printing could be used to enhance palatability and drug adherence in the pediatric population. One study tested the acceptability of chewable tablets with different flavors and colors produced by SSE in pediatric patients. Patients preferred the printed tablets over the pharmacy compounded isoleucine capsules (62). Furthermore, 3D printed mini tablets were developed to overcome difficulties in swallowability in the pediatric population (75, 76). Mini tablets are defined as tablets with a diameter of ≤ 3 mm (77). Studies have demonstrated that small-sized tablets (2-3 mm) may be accepted from birth (78). The trend shows that the larger the tablet, the lower the percentage of pediatric patients aged from neonates to 6-year-olds that are able to swallow the tablets whole.

3D printing has already entered clinical trials and implementation studies. Two clinical studies demonstrated a lower plasma-variation and closer to target concentrations of 3D printed isoleucine tablets versus pharmacy compounded isoleucine capsules (44, 62). Other clinical research illustrate the combination of two drugs into one tablet or capsule, using 3D printing (44, 79). One study has also demonstrated bioequivalence of 3D printed drugs compared to the originator, showing that the 3D printed formulation was not inferior to the commercial product (42). In community pharmacy setting, researchers have shown that manufacturing personalized medicine with a 3D printer, compared to manual capsule filling, is faster and more cost-effective (34). Researchers also conducted interviews with relevant stakeholders such as pharmacies and pharmaceutical authorities to investigate the implementation of pharmaceutical 3D printing for magistral compounding. Stakeholders identified hospital pharmacies and compounding facilities as suitable places for pharmaceutical compounding as they already have the knowledge, experience, trained personnel, facilities and expertise to manufacture pharmaceutical products (80). Pharmacists in general show a positive perception regarding the concept of formulating and dispensing personalized 3D printed medicine (81, 82).

In light of the aforementioned possibility to personalize medicine on a small scale, we believe that pharmaceutical 3D printing is especially suitable as an extemporaneous pharmacy compounding method.

Aim and outline of this thesis

The overall aim of this thesis is to use 3D printing as an extemporaneous pharmacy compounding method to manufacture hydrocortisone formulations with an added clinical value for patients with adrenal insufficiency against acceptable societal costs. The research in this thesis is based on the hypothesis that using 3D printing, a personalized sustained release treatment, better fitting the need of the individual patient can be developed and manufactured at the point-of-care, against acceptable societal costs and high quality. To test this, we explored FDM and SSE 3D printing to manufacture sustained release formulations. Furthermore, we developed a costing framework to assess the manufacturing costs of a 3D printed tablet. Finally, 3D printing was benchmarked in terms of costs and quality, against conventional methods to personalize medicine.

Chapter 2 presents a study where FDM 3D printing was used to explore whether it is possible to develop a pharmaceutical product with sustained release profiles. Building on that knowledge**, Chapter 3** describes the use of the same technology, but this time applied to hydrocortisone for patients with adrenal insufficiency. 3D printed sustained release hydrocortisone tablets were developed and tested against compendial standards. However, unknown impurities were found due to high processing temperatures with FDM.

To avoid impurity formation, we changed technologies to SSE 3D printing. In **Chapter 4**, we screened excipients for SSE 3D printing regarding safety and printability. We identified safe and suitable excipients that can be used for SSE 3D printing at low processing temperatures.

There has been thus far no scientific literature on the costs of 3D printed pharmaceuticals. **Chapter 5** describes research that aimed to elucidate the manufacturing costs of the sustained release hydrocortisone product presented in **Chapter 3**. Furthermore, an open access costing framework, including a calculation tool, was developed for easy calculation of manufacturing costs of 3D printed products, regardless of the technique.

Finally, in **Chapter 6** we successfully printed hydrocortisone immediate and sustained release hydrocortisone tablets using low processing temperatures with SSE. Here, we also present a systematic comparison of the quality of 3D printed tablets versus conventional pharmacy compounding techniques. Furthermore, the manufacturing costs for both FDM and SSE printed hydrocortisone tablets were identified. Cost and quality data are necessary to evaluate and position the novel technology in hospital pharmacy.

The findings of this thesis are discussed and placed in a broader context in the general discussion, presented in **Chapter 7,** which is followed by the summary (**Chapter 8)**.

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2

Chapter 2

3D printed spherical mini-tablets: geometry versus composition effects in controlling dissolution from personalised solid dosage forms

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Abstract

Oral dosage forms are by far the most common prescription and over-the-counter pharmaceutical dosage forms used worldwide. However, many patients suffer from adverse effects caused by their use of "one-size fits all" mass produced commercially available solid dosage forms, whereby they do not receive dedicated medication or dosage adjusted to their specific needs. The development of 3D printing paves the way for personalised medicine. This work focuses on personalised therapies for hypertensive patients using nifedipine as the model drug. 3D printed full solid Mini-tablets and channelled spherical mini-tablets with enhanced surface area (1.6-fold higher) were printed using modified PVA commercial filaments loaded by passive diffusion (PD), and Kollidon VA64 (KVA) and ethylcellulose (EC) based filaments prepared by hot-melt extrusion (HME). Drug loading ranged from 3.7% to 60% based on the employed technique, with a 13-fold higher drug loading achieved with the HME compared to PD. Composition was found to have a more significant impact on drug dissolution than geometry and surface area. Both KVA and EC-based formulations exhibited a biphasic zero-order drug-release profile. Physicochemical characterization revealed that nifedipine was in the amorphous form in the KVA-based end-products which led to a greater dissolution control over a 24 h period compared to the EC-based formulations that exhibited low levels of crystallinity by PXRD. The proposed 3D printed spherical mini-tablets provide a versatile technology for personalised solid dosage forms with high drug loading and dissolution control, easily adaptable to patient and disease needs.

Introduction

The ideal scenario for healthcare would be for all patients to receive personalised pharmacotherapy based on the patient's profile [such as age, weight, genetic and pharmacokinetic profile (e.g. eGFR)] and disease characteristics (such as co-morbidities) instead of a 'one size fits all' treatment (Harvey et al., 2012). The development of new techniques, such as 3D printing (3DP), in the field of pharmaceutical technology paves the way for personalised medicine, as 3D printed medicines are unique formulations that can be adapted to patients' needs (Awad et al., 2018a). Some of the advantages of 3D printed medicines include control of the dose in an accurate manner (Skowyra et al., 2015), and the ability to incorporate multiple active pharmaceutical ingredients (API) into one dosage form that can result in enhanced adherence in cancer (Serrano et al., 2019b) and polymedicated patients (Khaled et al., 2015). The release profiles of each individual API within a specific formulation can also be defined (Fina et al., 2020; Gioumouxouzis et al., 2020; Khaled et al., 2015; Pereira et al., 2020; Tan et al., 2019). Lastly, modification of colour, taste, and geometry of 3D printed medicines is also possible (Konta et al., 2017). Overall, 3D printed personalised medicines can lead to greater patient compliance, better pharmacotherapy, and thus to safer and more effective health outcomes (Januskaite et al., 2020; Konta et al., 2017; Serrano et al., 2019a). It has also been used in novel applications such as printing of medicines with unique designs (Isreb et al., 2019), opioid medicines with alcohol-resistant and abuse-deterrent properties (Nukala et al., 2019; Ong et al., 2020), and also as an anti-counterfeit measurement for personalised products (Trenfield et al., 2019).

From the seven 3D printing categories described by the American Society for testing and materials (ASTM) scheme, the most commonly used techniques in 3D printing of medicines are binder jetting, vat photopolymerisation including stereolithography and digital light processing, and material extrusion that includes fused deposition modelling (FDM), which utilises thermoplastics, and semisolid extrusion (SSE), based on the use of gels and pastes (Awad et al., 2018b). Ensuring the appropriate 3DP method is selected for the intended API is critical to avoid manufacturing and technical issues. With FDM technology (a nozzle based deposition system), high temperatures are used during printing, in order to melt the mixture of API and excipients (Konta et al., 2017). There are several FDM 3D printers, but with a similar mechanism of action (Fig 1A). The printing resolution with an FDM printer ranges from 0.05-0.5 mm (Femmer et al., 2016). However, due to the high temperatures required for FDM, it is less suitable for thermolabile drugs. The low availability of thermoplastic materials with good melt viscosity for extrusion remains another limitation (Konta et al., 2017) and the development of suitable filaments for FDM is key to the success of this technique.

Filaments can be engineered either by hot-melt extrusion (HME) or by passive diffusion after immersion in a saturated solution containing the API (Cerda et al., 2020). For the latter approached, commercial filaments can be used for first drug loading and then printing. A wide variety of filaments with unique properties are on the market, although none that are loaded with drugs are yet approved for pharmaceutical use. It is also possible to create specific and unique filaments with different ratios of API/excipients through HME (Tiwari et al., 2016). A hot-melt extruder consists of a feeding system, one or two screws, a heating system and an extruder head with an orifice which gives shape to the extrudate (Fig. 1B) (Maniruzzaman et al., 2012; Wilson et al., 2012).

Powder combinations of API-excipients can be inserted in the feeding system after which the screw pushes the mixture towards the extruder head. Before reaching the extruder head, the mixture melts as it passes the heating system. The melted mixture eventually reaches the die and hardens outside of the extruder, obtaining a defined filament ideally with the correct diameter to be fed into the FDM printer.

HME allows for the manufacture of high drug loaded filaments (Verstraete et al., 2018). The formation of amorphous solid dispersions during the melting process, can lead to an improved water-solubility and oral bioavailability of poorly soluble APIs, as well as control of API release from the polymeric matrix (Tiwari et al., 2016). A suitable miscible combination of API(s) with low glass transition temperature (T_g) polymers, such as polycaprolactone, can lead to a reduction of the overall melting temperature of the powder mixture and hence, reduces the risk of API degradation by high temperatures. The challenge with HME remains to create a 'printable' filament with the correct diameter, rheological properties, mechanical strength, and elastic modulus to avoid blockages during printing (Elbadawi et al., 2020a; Elbadawi et al., 2020b; Nasereddin et al., 2018). As an alternative, direct powder extrusion has emerged as a new technology to avoid the need of creating a printable filament (Fanous et al., 2020; Goyanes et al., 2019; Ong et al., 2020).

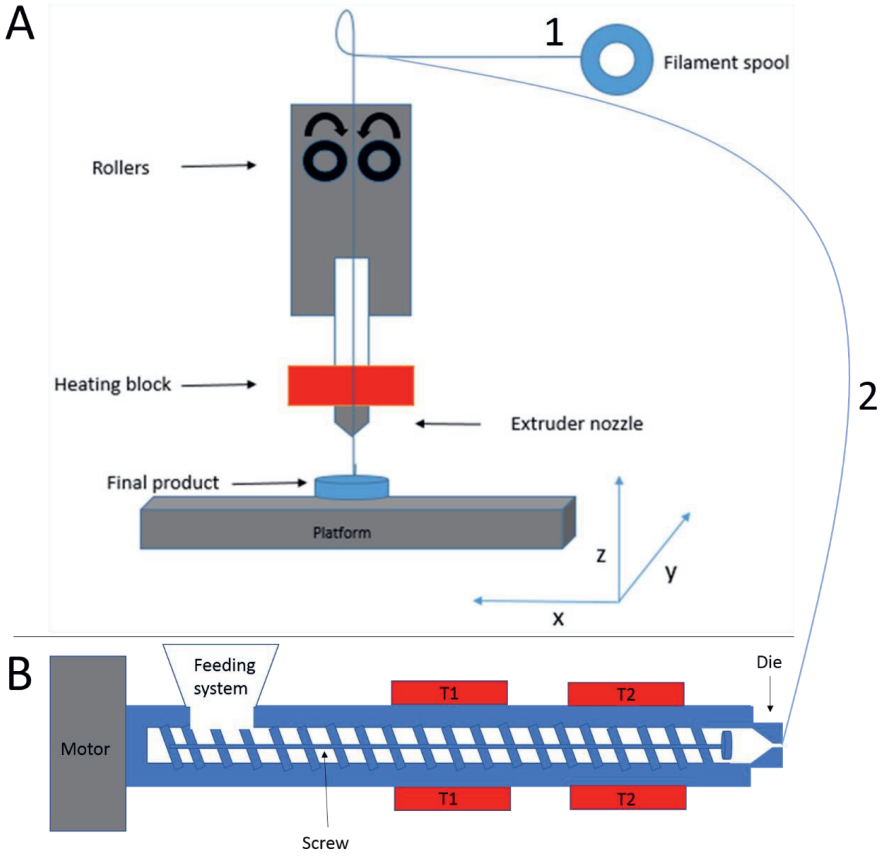


Figure 1: Schematics of FDM 3D printing (A) and Hot melt extrusion (B).

On the other hand, passive diffusion is a drug loading method based on the immersion of prefabricated filaments in an API saturated solution. This method is easy, but requires highly potent drugs where low drug loadings are adequate, as drug loading does not typically exceed 2% of API within the filaments (ranging from 0.06% w/w to 1.9% w/w) (Goyanes et al., 2014; Goyanes et al., 2015a; Skowyra et al., 2015). However, recent studies indicate that the application of the Hansen solubility theory to understand which polymer and solvent combination is more suitable has allowed filaments with higher drug loadings to be obtained by passive diffusion (≥ 3%) (Cerda et al., 2020).

Here, we have chosen a calcium channel blocker, nifedipine (NFD), a BCS class II agent, mainly used for the management of hypertension and angina pectoris (Gajendran et al., 2015) as a model drug. NFD is a suitable model drug for 3D printing considering that dose adjustment is essential for proper management of hypertension and only a limited range of doses are commercially available. NFD has good permeability and low aqueous solubility (Gajendran et al., 2015), and is a photolabile drug with a melting point of 172–174 °C

(Da Silva Leite et al., 2013). The oral bioavailability of nifedipine is variable due to its low solubility (Cavallari et al., 2016). Personalised 3D printed NFD formulations are not yet available and the challenge is to ensure that the formulations meet the regulatory agencies requirements, while at the same time remain patient friendly oral dosage forms that can improve the patient's quality of life. Here we have manufactured mini-tablets as flexible personalised dosage forms loaded with NFD using FDM 3D printing. Mini-tablets allow for facile dose adjustments as well as the ability, if required, to combine different APIs loaded in different tablets within the same capsule in order to avoid physicochemical interactions. We have designed spherical mini-tablets with different geometries with enhanced surface area and with different compositions to investigate the impact of these parameters on the final characteristics of the 3DP solid dosage forms utilising either commercially available filaments loaded by passive diffusion (PD) or in-house manufactured filaments prepared using HME based on different polymer compositions. The impact of geometry design on the drug release profile was explored by designing and printing channelled mini-tablets for the first time with a 1.6-fold higher surface area than tablets without channels. The physicochemical characteristics of the manufactured 3DP mini-tablets were finally tested and compared in terms of content uniformity, morphology, thermal properties, drug loading, and dissolution characteristics.

1. Materials and methods

1.1. Materials

NFD was purchased from Industria Chimica Italiana (>95%, Bergamo, Italia). PEG 4000 and magnesium stearate were purchased from Sigma–Aldrich (Madrid, Spain). Hydrosupport filaments with 1.75 mm diameter (>96% polyvinyl alcohol and polyethylene glycol) was a gift from 3D-Fuel (Donegal, Ireland). Klucel hydroxypropyl cellulose (HPC) grade LF and Aqualon ethylcellulose (EC) N10 were kindly donated by Ashland (Madrid, Spain). Kollidon VA 64 (KVA64) was purchased from BASF (Ludwigshafen, Germany). Size 0 hard gelatine capsules were a gift from Capsugel (Madrid, Spain). Adalat OROS 30 mg (Bayer, Leverkusen, Germany) and nifedipine retard 20 mg tablets (Stada, Bad Vilbel, Germany) were included as commercialised formulations for comparison purposes. The composition of Adalat OROS coated tablet is polyethylene oxide, hypromellose, magnesiusm stearate, sodium chloride, cellulose acetate, macrogol, hydroxypropyl cellulose and propylene glycol, while the generic uncoated nifedipine retard tables are comprised of microcrystalline cellulose, maize starch, monohydrate lactose, polysorbate 80, magnesium stearate, hypromellose, macrogol 4000, titanium oxide. Any other reagents were used without further purification.

1.2. Methods

1.2.1. Preparation of NFD loaded filaments

Passive diffusion

Based on preliminary solubility studies, a saturated solution of NFD in ethanol was prepared (30 mg/ml). Hydrosupport filaments (1 m in length and 1. 75 mm in diameter) were completely immersed in the saturated solution (100 ml) for 8 hours at room temperature to allow the NFD to passively diffuse into the filament. Previous studies have shown that NFD exhibited the highest diffusion rate across hydrosupport filaments compared with rigid polyvinyl alcohol and rigid poly lactic acid commercial filaments (Cerda et al., 2020). Diffusion times greater than 8 hours led to chemical degradation of NDF in solution and consequently to a lower drug loading. After 8 hours, the filament was dried in an oven at 40 ºC overnight to ensure evaporation of the ethanol, followed by drying at 100 ºC for an extra hour prior to printing at room temperature in order to increase the mechanical strength of the filaments and facilitate the printing process (Cerda et al., 2020).

HME

Mixtures of NFD, Aqualon EC N10, PEG 4000, magnesium stearate (MgS), Kollidon VA 64 (KVA64) and Klucel HPC LF were extruded into filaments by HME for subsequent 3D printing with FDM. The different compositions prepared at 20 g batch sizes were extruded at different temperatures as detailed in Table 1. EC, HPC and KVA64 were used to create a defined release polymeric matrices. PEG 4000 was included as plasticiser, and magnesium stearate as lubricant to promote the homogenous transit of the powder mixture through the extruder. Ball milling (IKA Ultra-Turrax® Tube Drive Disperser) was used to blend the feed powder mixture for 2 min at 6,000 rpm after which the mixture was sieved through a 12-US mesh (1.68 mm) screen prior to extrusion. HME of the mixture was performed with a Noztek touch single-screw extruder (Shoreham, UK) at 30 rpm.

Table 1: Compositions of HME formulations and extrusion temperatures for the manufacture of the NFD filaments. The "cp" annotations in the formulation code stand for "channelled Mini-tablet".

	Composition (%, w/w)						Extrusion zone temperature (ET)	
Formulation code	NFD	EC	HPC	PEG 4000	MgS	KVA64	First ET (T1) (ºC)	Second ET (T2) (ºC)
1 (EC30)	30	20	44	5	1	0	110	165
2 (EC40)	40	10	44	5	1	0	110	165
3 (EC50)	50	10	34	5	1	0	110	165
4 (cpEC50)	50	10	34	5	1	0	110	165
5 (EC60)	60	10	24	5	1	0	110	165
6 (cpPKVA150)	50	0	34	5	1	10	0	155
7 (KVA250)	50	0	24	5	1	20	0	145

1.2.2. 3D FDM printing

Geometry design

The Mini-tablet geometry was designed using a computer-aided design (CAD) software (Tinkercad software v.1, Autodesk 2019, Barcelona, Spain) to create a .stl file compatible with the Flashprint software v.4.6.0. (Flashprint, Flashforge, Zhejiang Flashforge 3D Technology Co, Zhejiang, China) to adjust the printing parameters (Fig. 2). Mini-tablets were designed with spherical shape with a diameter of 6 mm in order to fit within a size 0 hard capsule. The total surface area of each mini-tablet was calculated using Meshlab v.1.5.2. (Visual Computing Laboratory, CNR-ISTI, Italy) to be 133.1 mm^2.

Channelled mini-tablets were also engineered with the aim of increasing the surface area that was exposed to the dissolution media. Three channels were designed into the 6 mm tablet in all the three axes: Y, X and Z. The Y channel was 2 mm in diameter while the other two channels were 1 mm in diameter to maintain the

structural integrity of the mini-tablet. In addition, four lateral channels (with a diameter of 1 mm) were also incorporated in each quarter of the tablet. A schematic design of the final geometry is illustrated in Figure 2. Based on the calculations of Meshlab software, the surface area of the channelled mini-tablets was increased by 1.6-fold (221.8 mm^2) relative to the original non-porous/non-channelled tablets.

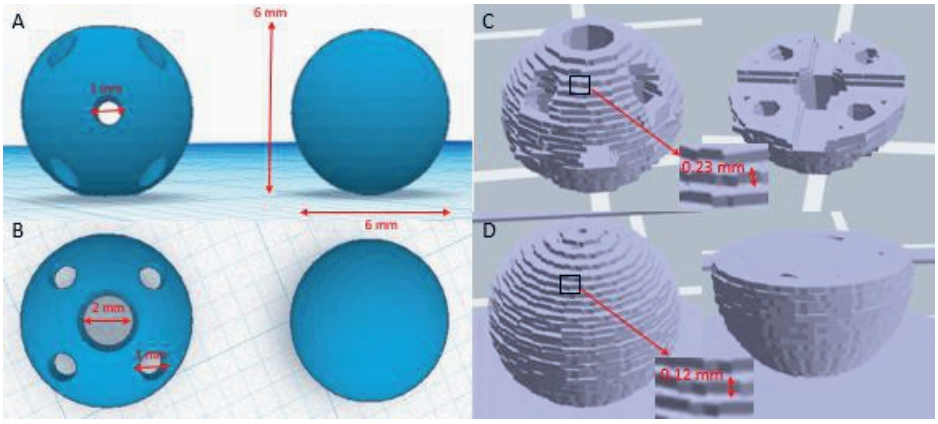


Figure 2. Geometric design of the solid and channelled mini-tablet of NFD formulations. A) Lateral CAD view; B) Top CAD view (Tinkercad software v.1); C) Sliced model of channelled Mini-tablet and D) Sliced view of full infill Mini-tablet (Flashprint software v.4.6.0.).

FDM printing settings and geometry design

A FlashForge Creator Pro (Zhejiang Flashforge 3D Technology Co, Zhejiang, China) FDM 3D printer was used to print the mini-tablets. The platform temperature was set at 50 °C and the printing temperature was set at 223 °C for all formulations. NFD degradation was minimal at this temperature (corroborated by TGA, Fig 6). Lastly, the print and travel speed were both set at 10 mm/s. Other relevant settings are summarised in Table 2 for all formulations.

*Table 2: Printing settings for all NFD formulations. Key:*cp: channelled mini-tablet. The infill of all tablets was 100%.*

Formulation	Layer height (mm)	First layer (mm)
PD	0.12	0.20
1 (EC30)	0.23	0.23
2 (EC40)	0.23	0.23
3 (EC50)	0.23	0.23
4 (cpEC50)*	0.23	0.23
5 (EC60)	0.23	0.23
6 (cpKVA150)*	0.12	0.20
7 (KVA250)	0.12	0.20

1.2.3. Content uniformity and drug loading

Drug loading in mini-tablets and filaments was assessed for the PD formulation and for the EC50 formulation. Mini-tablets (n=10) obtained by passive diffusion were dissolved in mobile phase consisting of (methanol: water: acetonitrile (36:55:9, v:v)) and mini-tablets obtained from HME filaments were dissolved in acetonitrile. All the samples were then diluted in mobile phase prior to quantification by HPLC.

1.2.4. Dissolution studies

Dissolution tests were performed in triplicate using a United States Pharmacopoeia (USP) apparatus 2 (ERWEKA DT 80, Heusenstamm, Germany) at 100 rpm (United States Pharmacopeia and National Formulary, USP38-NF33). The employed dissolution media were: USP simulated gastric fluid (SGF) without enzymes (pH 1.2) with 0.5% sodium lauryl sulfate and USP simulated intestinal fluid (SIF) without enzymes (pH 6.8) with 0.5% sodium lauryl sulfate as described in the USP (United States Pharmacopeia and National Formulary (USP 38-NF 33). Reagents: Test Solutions. Rockville). SGF (400 ml) was used during the first 2 hours. SIF (500 ml) was added and kept for the remaining 22 hours and media were maintained at 37 ± 0.5 °C. NaOH (30% v/v) was used to adjust the pH to 6.8 after the addition of the SIF. Samples (2 ml) were withdrawn from the dissolution media and filtered through a hydrophilic 0.45 µm filter (Millipore, Millex-LCR, Massachusetts, US) at 5, 10, 15, 30 and 45 minutes 1, 1.5, 2, 3, 4, 6 and 24 hours. Samples were diluted with mobile phase (1:2 v/v) consisting of methanol: water: acetonitrile (36:55:9, v:v), and subsequently analysed by HPLC comprised of a Jasco PU-1580 pump, a Jasco AS-2050 Plus autosampler and a Jasco UV-1575 UV-visible detector. Integration of the peaks was performed with Borwin 1.5 software. NFD was separated on a Thermo BDS Hypersil C18 reverse-phase column (200 x 4.6 mm, 5 µm). The mobile phase was pumped at a flow rate of 1 mL/min and the sample injection volume was 20 µL. The column temperature was kept at 25º C and the detector was set at 240 nm. The detection limit was 0.12 µg/mL while the quantification limit was 0.4 µg/mL (Cerda et al., 2020).

The dissolution data obtained were fitted using the following kinetic equations (Costa and Sousa Lobo, 2001; Siepmann and Siepmann, 2013): zero order (Eq. 1), first order (Eq. 2), Hixson–Crowell (Eq. 3), Korsmeyer–Peppas (Eq. 4) and Higuchi (Eq. 5):

$$Q_t = Q_0 + K_0 t \qquad \textit{(Eq. 1)}$$

$$LogQ_t = logQ_0 + K_1 t 2.303 \qquad \textit{(Eq.2)}$$

$$W_0^{1/3} - W^{1/3}_t = K_s t \qquad \textit{(Eq. 3)}$$

$$Log(Mt/M\infty) = log\ K_{kp} + nlogt \qquad \textit{(Eq. 4)}$$

$$Q = tDC_s(2C\text{-}C_s) \qquad \textit{(Eq. 5)}$$

where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, Q_0 =0), W_0 is the initial amount of drug in the tablet, W_t is the remaining amount of drug in the tablet; $Mt/M\infty$ is the fraction of drug release at time t; D is the diffusion constant, C is the initial drug concentration, C_s is the drug solubility in the matrix medium and Q is the amount of drug release per time, t, per unit area; K_1 is the first order release constant, K_0 is the zero order release constant, K_s is a constant incorporating the surface-

volume relation; K_{KP} is a constant that describes the structural and geometric characteristics of the drug dosage form; n is the release exponent which describes the drug release mechanism. The n has a value of 0.5, 0.45 or 0.43 when the particle shape is a thin film, a cylinder or a sphere respectively which indicates Fickian release controlled by diffusion (Serrano et al., 2016). Anomalous non-Fickian transport is observed when n is between those values and 1 ($0.5 < n < 1$ for thin films, $0.45 < n < 1$ for cylinder and $0.43 < n < 1$ for spheres). Values of n=1 correspond to zero order release (Lao et al., 2011). The choice of release profile that best fits the release data is determined based on the obtained regression coefficient (R^2) (Costa and Sousa Lobo, 2001; Mamani et al., 2012; Serrano et al., 2016).

1.2.5. Scanning Electron Microscopy (SEM)

A scanning electron microscope (JSM 6335F JEOL, Japan) was used at 15.0 kV, after the samples were sputtered coated with pure gold (Q150RS Metalizador QUORUM, UK) for 180 seconds. Micrographs were obtained from filaments, 100% fully printed mini-tablets and tablets printed only up to 50% of the total geometry in order to investigate the geometry of the core.

1.2.6. Friability and hardness test

A friability test (Pharmatest PTF friability tester, Hainburg, Germany) at 100 rotations and a hardness test (Pharmatest PTB 311, Hainburg, Germany) was undertaken for the mini-tablets according to the USP (United States Pharmacopeia and National Formulary (USP 38-NF 33). General Chapters: <1216> TABLET FRIABILITY. Rockville; United States Pharmacopeia and National Formulary (USP 38-NF 33). General Chapters: <1217> TABLET BREAKING FORCE. Rockville). The tests were performed with the PD formulation (n=10) and for the EC50 formulation (n=10).

1.2.7. Solid state characterisation

Solid state characterisation was performed on 3D printed filaments and mini-tablets, unprocessed excipients and nifedipine. Physical mixtures between drug and excipients were prepared in an agar mortar and pestle and were also analysed. A thin slice (1-2 mm) of the 3D printed filaments and mini-tablets was cut and analysed to avoid grinding.

Fourier-transform infrared (FTIR) spectroscopy

FTIR analysis of printed mini-tablets was carried out with a Luminar 5030 Spectrometer (Brimrose, America). The following settings were used: wavelength range 1100 – 2300 cm^{-1}, 10 scans, and detector gain of 2 (except when analysing raw NFD powder, in which a detector gain of 1 was used). Spectragryph (version 1.2.9, Oberstdorf, Germany) software was used for the interpretation of the spectra.

X-ray powder diffraction (pXRD)

Powder X-ray analysis was performed using a Miniflex II Rigaku diffractometer with Ni-filtered Cu Kα radiation (1.54 Å). The tube voltage and tube current used were 30 kV and 25 mA, respectively. The PXRD patterns were recorded (n=3) from 5° to 40° on the 2 theta scale at a step scan rate of 0.05° per second (Serrano et al., 2016). Full mini-tablets and filaments were loaded in an open holder to avoid altering the PXRD signal by grinding (n=3). The NFD PXRD peak used was at 16.6 2θ degrees, which was selected due to the lack of interference with other peaks in the diffractogram. Rigaku Peak Integral software was used for the determination of the peak intensity for each sample using the Sonnefelt-Visser background edit procedure.

Modulated temperature DSC (MTDSC)

MTDSC scans were recorded on a QA-200 TA instrument (TA instruments, Elstree, UK) calorimeter using nitrogen as the purge gas. A section of the mini-tablets and filaments was cut, weighed (4-6 mg) and sealed in an open aluminium pan. A scanning rate of 5 °C/min, amplitude of modulation of 0.796 °C and modulation frequency of 1/60 Hz were employed. The temperature range was set between 10 °C to 200 °C (Serrano et al., 2018). Calibration of the instrument was carried out using indium as standard. Glass transition temperatures reported (n = 3) are the midpoint of the transition.

Thermogravimetric analysis (TGA)

Thermogravimetric analysis (TGA) was performed using a Q-50 TA instrument (TA instruments, Elstree, UK). Samples were placed in open aluminium pans (2-6 mg) and analyses were performed at a constant heating rate of 10°C/min between a temperature range of 25 °C and 300 °C (Rolon et al., 2017).

Dynamic Vapour Sorption (DVS)

Water sorption kinetic profiles were obtained using DVS (Advantage, Surface Measurement Systems, Alperton, UK) at 25.0 ± 0.1°C for the EC50 and KVA250 formulations. Water was used as the probe vapour. Samples were dried at 0% relative humidity (RH) for 1 h and then subjected to step changes of 10% RH up to 90% RH, and the reverse for desorption. The sample mass was allowed to reach equilibrium, defined as dm/dt ≤0.002 mg/min over 10 min, before the RH was changed. Sample weights were between 70 and 80 mg corresponding to one whole mini-tablet to avoid altering the structure.

Data processing and statistical analysis

Statistical analysis for the dissolution study data was performed via one-way ANOVA test using Minitab v.16 (Minitab Ltd, Coventry, UK) followed by Tukey's test considering p-values for statistical significance to be below 0.05. Linear regression analysis was performed using the method of least squares by Microsoft® Excel 2010 software (Microsoft Corporation, Redmond, WA, USA). The adequacy of the fit was assessed based on the regression coefficient (R^2). Comparison and modelling of dissolution curves were undertaken using the mathematical software DDsolver (China Pharmaceutical University, Nanjing, China) (Zhang et al., 2010).

Dissolution results were plotted using Microsoft® Excel 2010 software. A multivariate data analysis was performed using The Unscrambler® X software (CAMO Software, Oslo, Norway) in order to assess the influence of the excipients on the NFD release using dissolution study data (Matji et al., 2019). A principal component analysis (PCA), a partial least square (PLS) analysis, and a multilinear regression (MLR) were performed based on the dissolution data.

2. Results

2.1. Filament manufacturing and morphology

The morphology of all formulations is illustrated in Fig 3 & 4. The appearance of the PD mini-tablets showed a very smooth surface with minimal printing defects. In contrast, the HME-derived formulations had rougher surfaces with more printing defects, probably due to the quality of the manufactured filaments used for printing. The geometry of the channelled cpKVA150 spherical mini-tablets is more complex and consists of 7 internal channels within a 6 mm diameter sphere, which affected the quality of the printed geometry (Figure 4). The diameter of the commercial filaments loaded by PD was 1.75 mm (± 0.05 mm), which is within the specification limits required for the employed 3D printer. However, higher variability was observed in the diameter of the in-house manufactured filaments (ranging from 1.46 – 1.57 mm), which can explain the larger morphological defects (Supplementary material, table S1 for diameters). The layer height of the EC-based formulations was 2-fold higher than PD and KVA-based formulations. EC-based filaments showed the highest deviation from the specification limit in terms of filament diameter, hampering the printing process. The layer height was increased to ensure a better flow of the molten polymer inside the printer. However, the higher the layer height, the higher the risk of losing resolution and altered surface area during printing. When higher layer heights were selected for the HME filaments, the extruded mixture as printed was not homogenous. Additionally, the density of the PD loaded filament was 2-3 fold higher than that obtained by HME, which is explained by the porous structure of the latter. This also impacted on the quality of the finished product considering the small size of the spherical mini-tablets (6 mm in diameter). The final weight of the printed mini-tablets was 3-6 times greater when printed from PD filaments (Supplementary material, Table S1) compared to HME mini-tablets. The porous structure observed in some of the extruded filaments is likely a result of lack of structural integrity and entrapped air due to the lack of a venting unit in the extruder used for their preparation. However, at greater magnifications, some crystals were observed on the surface of the printed mini-tablets, indicating either deposition of crystalline material on the surface or crystallisation post-processing.

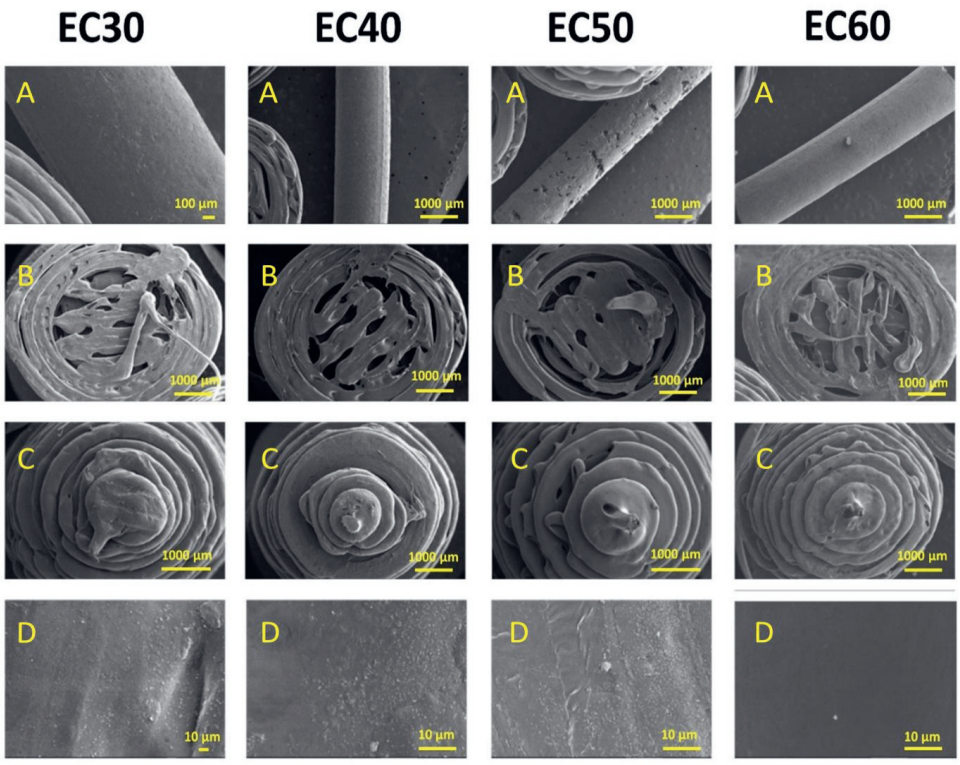


Figure 4: SEM micrographs for the EC30, EC40, EC50 and EC60 formulations containing EC as excipient. Key; A: loaded filaments, B: Mini-tablets printed up to 50% of total geometry, C: Fully printed mini-tablets and D: Surface of the mini-tablets.

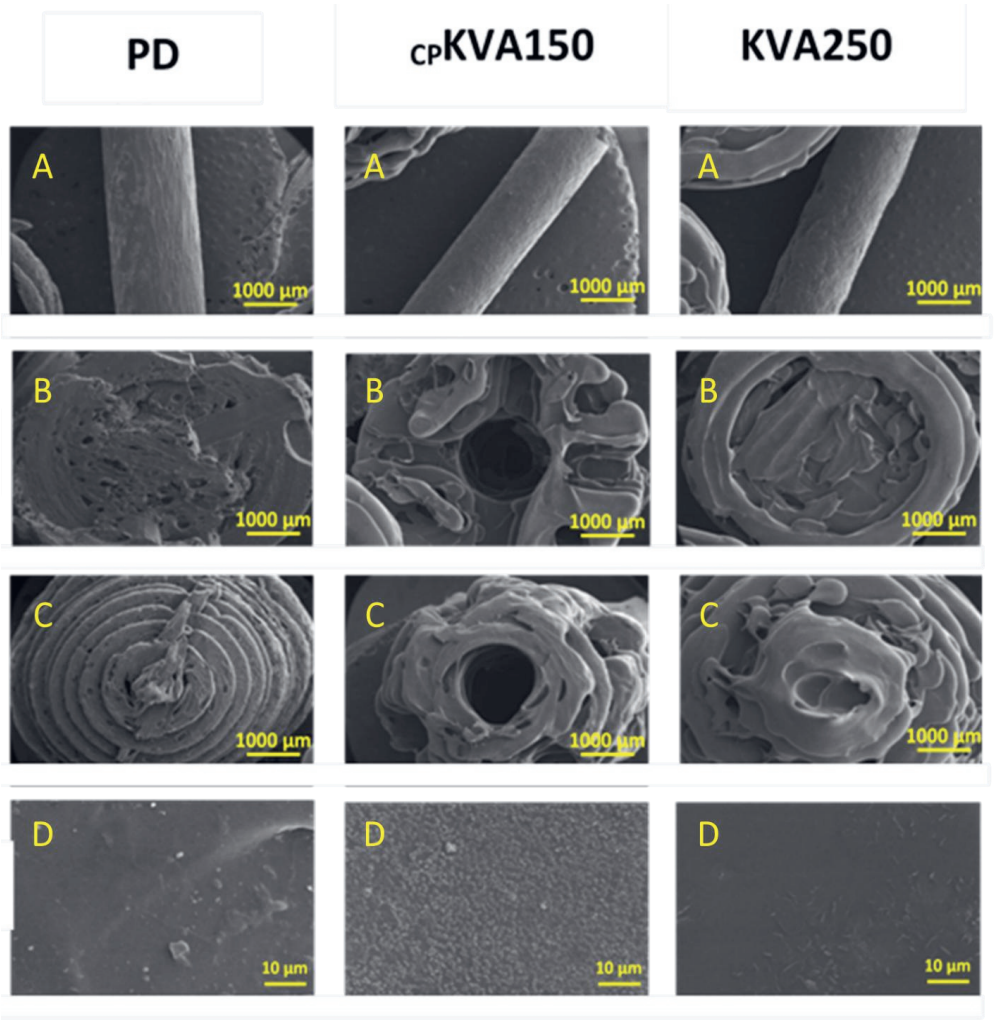


Figure 5: SEM micrographs for the PD formulation, cpKVA150 formulation and KVA250 formulation. Key: A: Loaded filaments, B: Mini-tablets printed up to 50%% of total geometry; C: Fully printed mini-tablets D: Mini-tablet surface morphology.

2.2. Friability and hardness test

For comparison purposes, the physical strength was evaluated for PD and EC50 formulations. Friability tests indicated no weight loss for the mini-tablets and filaments prepared by the PD method, while no defects were visible at the end of the friability tests for either the mini-tablets or the filaments. However, 0.3% weight loss was observed for EC50 mini-tablets. The average crushing force is summarised in table 3. The EC50 HME mini-tablets were 35-fold more fragile than the PD mini-tablets, which is expected due to the lower printing accuracy and design integrity of the EC50 mini-tablets. Commercially available filaments (i.e. the hydrosupport filament used to prepare the PD Mini-tablets) resulted in better resolution prints with greater hardness.

Table 3: Friability and hardness of the PD formulation versus the EC50 HME formulation (n=3). Key; SD: standard deviation

Formulation	Physical form	Friability (% weight loss)	Hardness in Newton (± SD)
PD	Filaments	0.0	413.5 ± 0
	Mini-tablets	0.0	403.1 ± 14.37
EC50	Filaments	0.0	223.1 ± 0.11
	Mini-tablets	0.3 ± 0.08	11.4 ± 8.01

2.3. Content uniformity and drug loading

After PD optimisation, the highest achieved NFD loading was 4% compared to loadings of more than 50% achieved for the HME filaments. However, the homogeneity of the filaments and printed mini-tablets produced by PD was better (4.3 and 7.9% RSD respectively) than those obtained by HME (8.1 and 11.2% RSD respectively). The larger variability observed for HME filaments can be explained by several factors. It is well-known that reaggregation and de-mixing due to in melt viscosity differences and intrinsic changes in flow dynamics can often occur in a single-screw extruder. Also, it is more difficult to achieve an accurate diameter for the filaments during HME, resulting in mini-tablets with greater weight and drug loading variability. HME manufactured filaments had a diameter ranging from 1.45-1.57 mm, while a diameter of 1.75 ± 0.05 mm is recommended for printing; this resulted in lower printing quality. Regarding the drug degradation during the printing process, a similar loss of NFD was observed for both methods (6.7-8.5%), which is attributed to the choice of printing temperature that was similar for both PD and HME loaded filaments (Table 4).

Table 4: Drug loading and content uniformity results for the different methods. Key: SD, standard deviation.

Composition	Drug loading (±SD)		Mean drug loss due to 3D printing
	Filaments	Mini-tablets	
PD	4.00 ± 0.17 %	3.66 ±0.29 %	8.50 ± 3.05 %
EC50	53.47 ± 4.31 %	49.86 ± 5.56 %	6.75 ± 3.79 %

2.4. Solid State characterisation

PXRD

PXRD analysis of the raw materials revealed that NFD and PEG 4000 were highly crystalline (Fig. 5A). The crystallinity of the physical mixtures can be attributed mainly to NFD and PEG 4000 and partially to ethylcellulose and magnesium stearate which also exhibited Bragg peaks but of lower intensity compared to NFD and PEG 4000 (Fig. 5B). The PD formulation did not exhibit any Bragg peaks, probably indicating that the NFD is in the amorphous state. However, we need to bear in mind the lower loading of NFD in PD filaments.

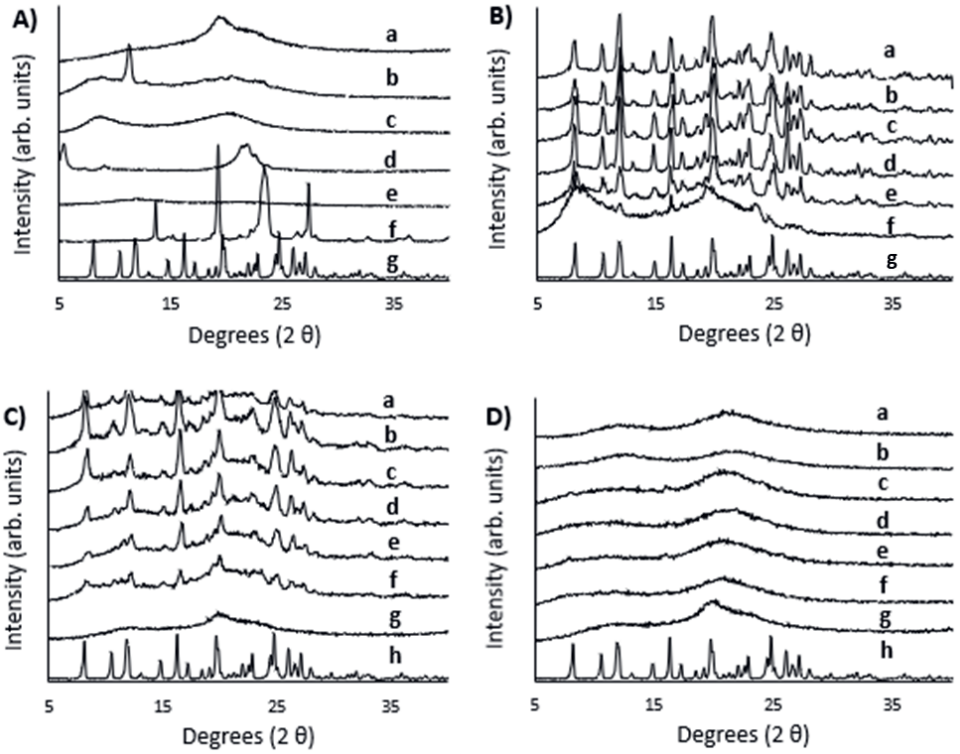


Figure 5. PXRD analysis. Key: A) Unprocessed materials; a) Hydrosupport filament b) Ethylcellulose, c) Hydroxypropyl cellulose, d) Magnesium stearate, e) Kollidon VA 64, f) Polyethylene glycol 4000 and g) NFD. B) Physical mixtures; a) KVA250 formulation, b) cpKVA150 formulation, c) EC60 formulation, d) EC50 formulation, e) EC40 formulation, f) EC30 formulation and g) NFD. C) Filaments: a) KVA250 , b) cpKVA150, c) EC60, d) EC50, e) EC40, f) EC30 and g) PD and h) NFD; D) 3D printed mini-tablets: a) KVA250 , b) cpKVA150, c) EC60, d) EC50, e) EC40, f) EC30 g) PD and h) NFD.

HME filaments demonstrate lower intensity Bragg peaks than the equivalent physical mixtures and this was more pronounced for filaments containing KVA64 compared to the EC based filaments (Fig. 5C). The lower Tg of KVA64 compared to EC allows for better interaction with NFD at the processing temperatures utilised, which explains the lower intensity peaks. The 3D printing process results in largely PXRD amorphous mini-tablets likely due to the higher temperatures used for printing, which are above the melting point of the NFD compared to the temperatures employed during HME (~ 60-80 °C less). Additionally, printing was performed at low speed to ensure higher resolution (Fig. 5D). Small Bragg peaks were found for EC60, EC50, and EC40 corresponding to NFD (indicating less than 5% crystallinity), but not for KV64-based formulations. NFD and KVA64 have more similar Hansen solubility parameters compared to NFD and EC, which explains the greater miscibility of NFD in the KVA64 polymeric matrices (Archer, 1991; Cerda et al., 2020; Kolter and Gryczke, 2012).

Differences in the PXRD diffractograms were observed between the surface and the inner core of the mini-tablets prepared with EC (Fig. S1, supplementary material). This is likely attributed to a phase separation

between NFD and polymer and hence, the higher susceptibility of NFD amorphous domains to moisture which triggers the crystallisation of the NFD localised in the outer domains of the mini-tablet. However, 3D printed materials are very dense with low porosity, which limits the permeability of water molecules to the inner core of the printed mini-tablets preventing the crystallisation of amorphous NFD. This observation is further supported with dynamic vapour soprtion (DVS) data (Section 4.7).

Thermogravimetric analysis

TGA analysis revealed that the physical mixtures, filaments, and mini-tablets were thermally stable up to 230 °C (Fig. 6). The temperatures selected during HME and 3D printing were below 230 °C to limit thermal degradation during manufacturing of 3D printed NFD dosage forms. In all the formulations, the residual water content was below 1.3%, which is necessary to ensure a longer shelf life of the formulations.

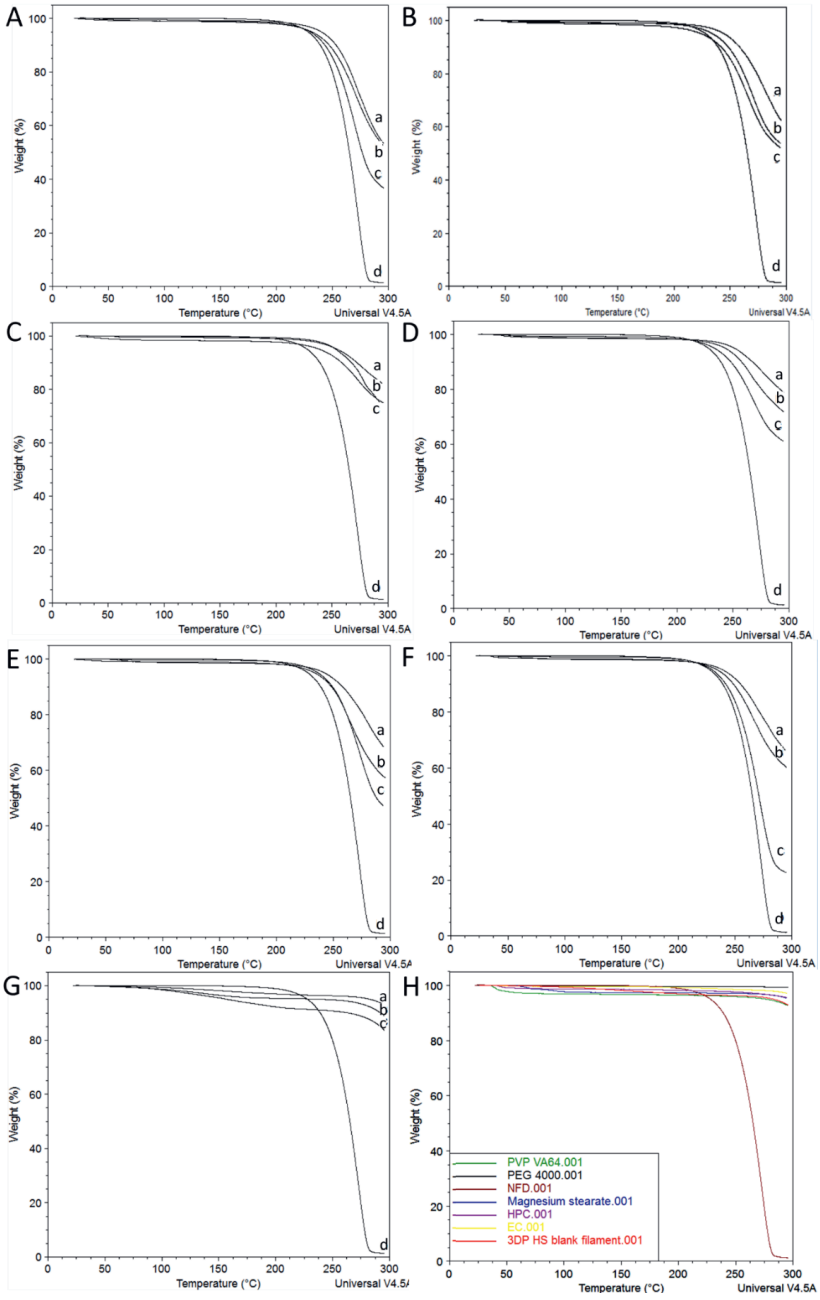


Figure 6. TGA curves for cpKVA150 (A): Mini-tablet (a), filament (b), PM (c), NFD (d). KVA250 (B): Mini-tablet (a), PM (b), filament (c), NFD (d). EC30 (C): PM (a), Mini-tablet (b), filament (c), NFD (d); EC40 (D): Mini-tablet (a), filament (b), PM (c), NFD (d); EC50 (E): Mini-tablet (a), filament (b), PM (c), NFD (d); EC60 (F): Mini-tablet (a), filament (b), PM (c), NFD (d); PD (G): HS blank filament (a), Mini-tablet (b), loaded filament (c), NFD (d). Unprocessed materials (H).

Differential scanning calorimetry

Unprocessed NFD showed a sharp endothermic event at 173.0 ± 1.0 °C corresponding to the melting of the drug with a heat of fusion of 112.5 ± 0.8 J/g, (Fig 7A-a). Unprocessed PEG 4000 also exhibited a sharp melting event at 60.0 ± 1.0 °C (Fig 7H-a). The Tg for the KVA64 and EC was 101 °C and 127 °C respectively, which is similar to previous reported values (Kolter and Gryczke, 2012; Lai et al., 2010). Bearing in mind the XRD results which indicated the largely amorphous nature of all printed mini-tablets, it is apparent that NFD recrystallises during the DSC heating ramp of the mini-tablets printed from HME filaments (Fig.7A-7F). Based on the heat of fusion of NFD and the theoretical total content of NFD within each mini-tablet formulation, the percentage of the drug that recrystallised during the DSC run was calculated. The amount of crystalline NFD in the PD formulation was below the quantification limit (Fig. 7H). In the other systems, the lowest percentage of crystalline NFD was found in the KVA250 formulation followed by $_{CP}$KVA150 (supplementary material, table S2). EC-based formulations exhibited a higher fraction of recrystallised NFD, ranging from 50-63%. The lower crystalline content in KVA formulations may be explained by the higher miscibility with the drug and the lower Tg of the PVPVA64 compared to EC based formulations.

Melting point depression of NFD occurred in all formulations indicating that NFD is partially solubilised within the excipient matrix. A single Tg was observed for all the mini-tablet formulations (supplementary data, table S3, Fig S2) which is close to the Tg of the amorphous NFD obtained by melt quench (data not shown). This indicates that a homogenous amorphous domain is formed when interacting with the polymeric excipients. However, the low value of the Tg indicates that it is not a highly stable amorphous formulation, which can explain the crystallisation upon exposure to high relative humidity (DVS data shown in section 4.7), or on heating in the DSC. This behaviour has been associated with miscible polymer systems that exhibit monotonic negative deviations from the predictions of the mass- and volume-additivity (Fox) rules (Kalogeras and Brostow, 2009). This behaviour is usually attributed to blends with prevailing conformational entropic effects, due to the weakening of the interactions between, in this case, NFD and the polymer chain segments (see FTIR section).

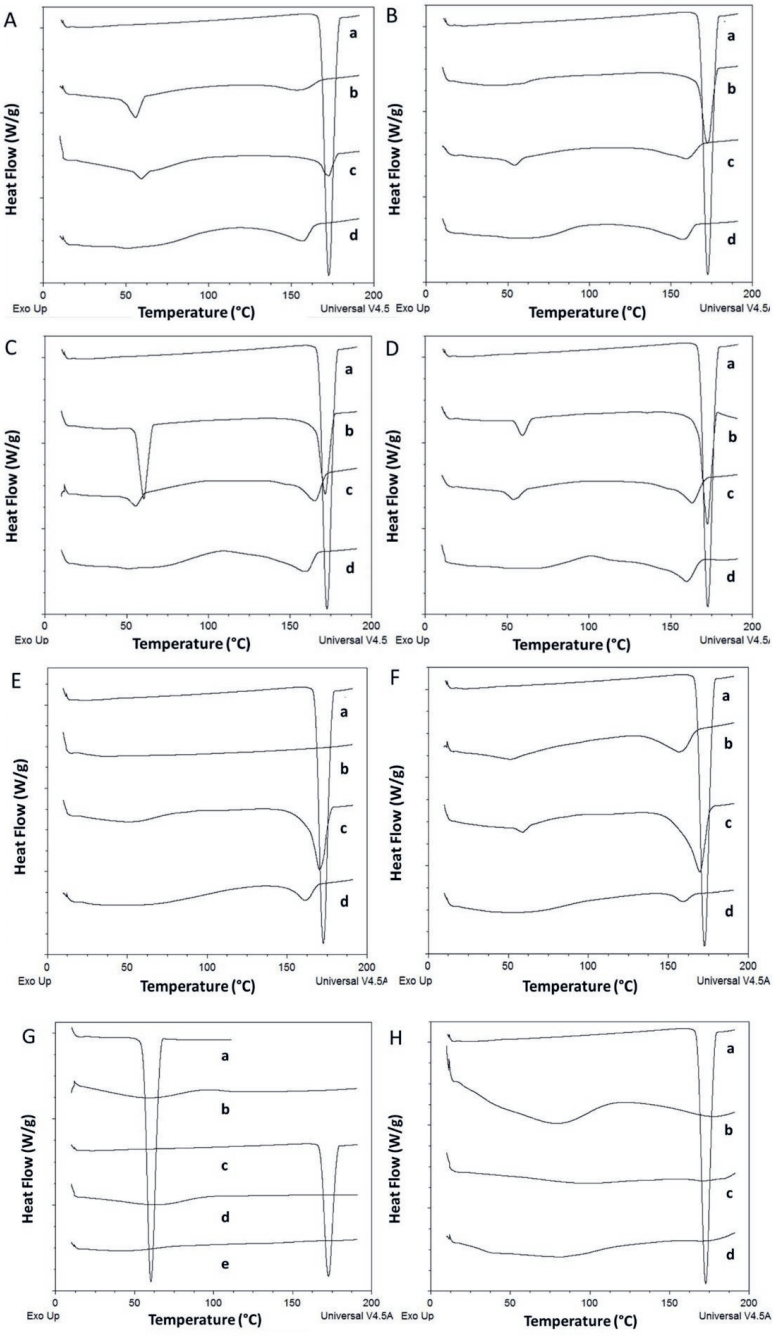


Figure 7. DSC thermograms of the unprocessed materials, physical mixtures (PM), filaments and 3D printed mini-tablets. Key: EC30 (A), EC40 (B), EC50 (C), EC60 (D), cpKVA150 (E), KVA250 (F), unprocessed materials (G) and PD (H). Within the graphs(A-F): NFD unprocessed material (a), PM (b), filament (c) and mini-tablet (d). For graph (G): PEG 4000 (a), KVA64 (b), NFD (c), HPC (d) and EC (e).

For graph (H); NFD unprocessed material (a), Hydrosupport filament (b), NFD loaded hydrosupport filament (c) and mini-tablet (d).

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra revealed H-bond interactions between NFD and the excipients (Fig. 8). Shifts were observed in the carbonyl (C=O stretching at 1679 cm^{-1}) and the C-O (1225 cm^{-1}) functional groups of NFD after co-processing by HME and after 3D printing. None of these shifts were present in the physical mixtures (PM). Shifts were more prominent in the KVA64-based formulations compared to the EC-based formulations indicating stronger API-polymer interactions and better miscibility. Similar shifts were observed in the KVA250 formulation compared to the $_{CP}$KVA150. Amongst the EC-based formulations, strongest shifts were observed in the EC30 formulation, for which the ratio of total excipients to NFD was the greatest. Finally, filaments and 3D printed mini-tablets showed broader bands, possibly due to the greater amorphous nature of the systems compared to the physical mixtures and unprocessed NFD.

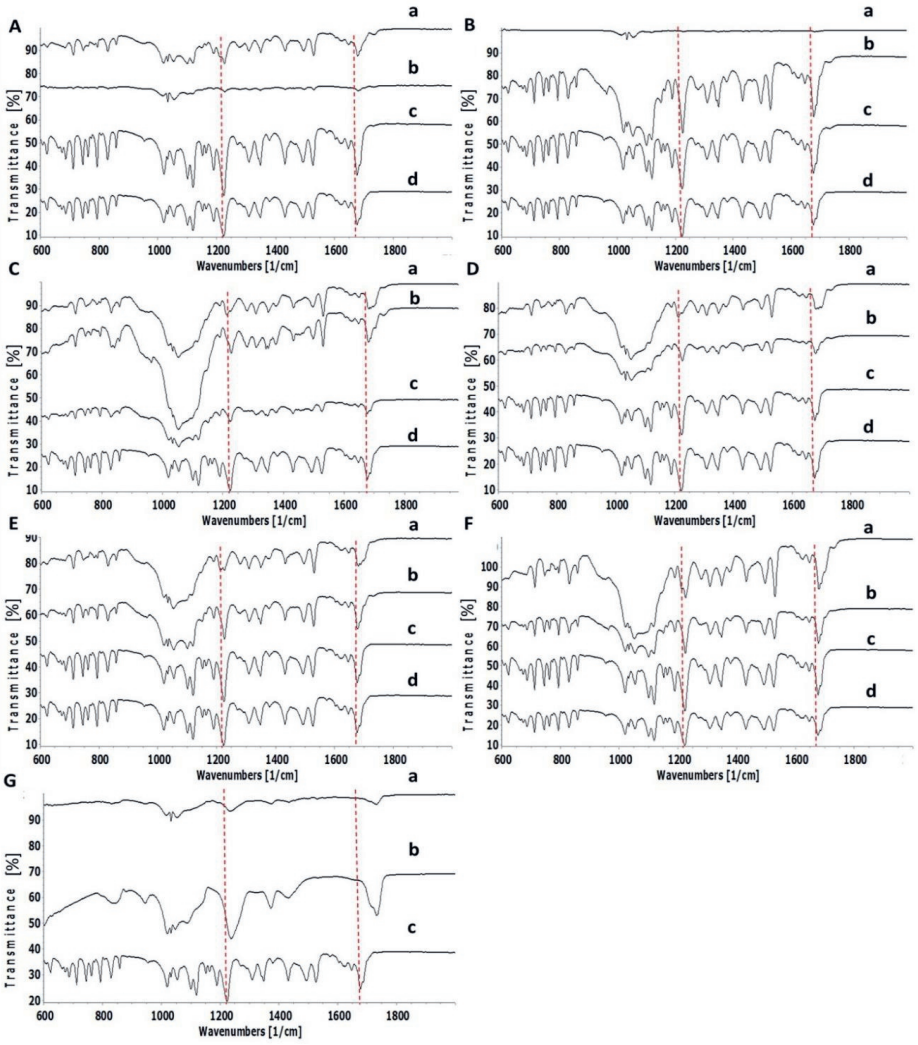


Figure 8. FTIR spectra of the physical mixtures, filaments, and 3D printed mini-tablets. Key: cpKVA150 (A), KVA250 (B), EC30 (C), EC40 (D), EC50 (E), EC60 (F), PD (G). Within the graphs (A-F): Mini-tablet (a), filament (b), PM (c) and unprocessed NFD (d). For graph (G); Mini-tablet (a), loaded HS filament (b) and unprocessed NFD (c).

2.5. Dissolution studies

As crystalline NFD has a low aqueous solubility, dissolution studies were performed in media containing sodium lauryl sulphate to ensure sink conditions. A markedly different dissolution profile was observed for the two commercially marketed NFD tablets (Fig. 9). Adalat Oros is an osmotic system consisting of a semi-impermeable barrier created mainly by cellulose acetate and a dual reservoir with sodium chloride and NFD amongst other excipients (Liu et al., 2003). The compartment with sodium chloride, upon wetting, increases the osmotic pressure of the system forcing the NFD contained in the other compartment to be slowly released across the pore located at the surface of the tablet. This behaviour results in a zero-order release (R^2= 0.9874) as clearly observed in figure 9. In contrast, Stada tablets (even though they are retard formulations) were rapidly disintegrated into smaller fragments from which the NFD was released. The 3D printed mini-tablets prepared using PD filaments showed a sustained release over 6 h and behaved like monolithic matrices from which the drug diffused into the liquid media matching the results obtained by other authors (Cerda et al., 2020). The best fitted dissolution kinetic model for Stada tablets and PD mini-tablets was Higuchi (R^2= 0.8859) and Korsmeyer-Peppas (R^2= 0.9878), respectively (Supplementary data, Table S4).

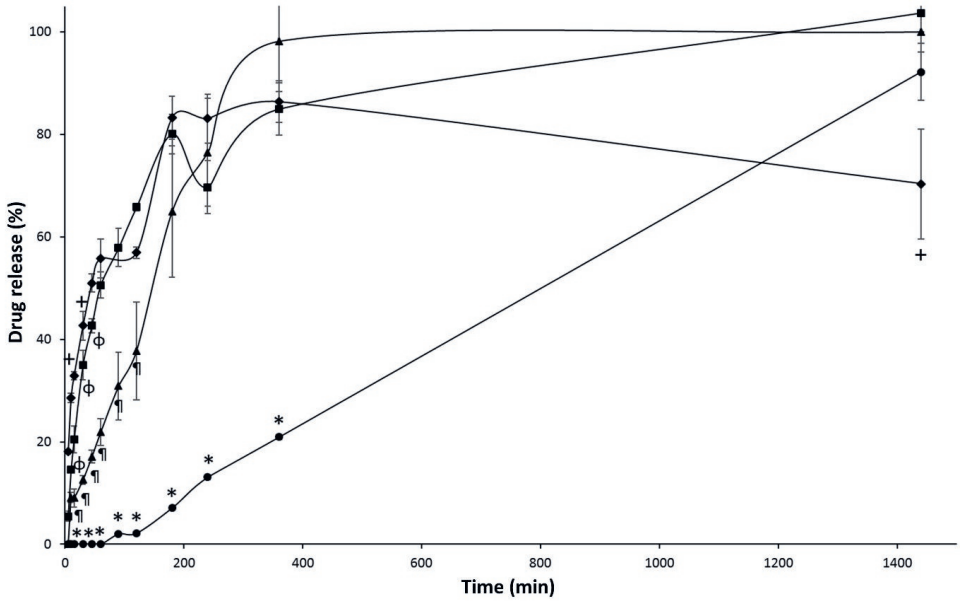


*Figure 9: Dissolution profile for the PD formulation (-▲-) compared to unprocessed NFD (-◆-) and commercially marketed NFD tablets: Adalat OROS 30 mg (-●-) and Nifedipine STADA retard 20 mg (-■-). Key: *p<0.05 Adalat OROS vs. all other formulations (incl. t=5 and t=10); ¶p<0.05 PD vs. all other formulations (incl. t=5 and t=10); +p<0.05 raw NFD vs. all other formulations (incl. t=5 to t=15) and Φp<0.05 STADA vs. all other formulations (incl. t=5 to t=15).*

A dissolution study was also performed for the HME-based mini-tablets (Fig. 10). In all cases, a biphasic release was observed, with two apparent zero-order release phases. The main excipient used in the formulation played a key role in the speed and extent of the NFD release. The dissolution profile of the KVA-based mini-tablets showed a faster drug-release profile than EC-based formulations. The channelled $_{cp}$KVA150 mini-tablets had the fastest and most complete drug-release from all formulations, which can be attributed to the greater surface area (1.6-fold greater than non-channelled mini-tablets of KVA) and the composition. The release profile of KVA formulations more closely mimicked the Adalat Oros profile, but with a greater burst release observed in SGF over the first two hours. The dissolution profile from the EC-based formulations was slow and incomplete. A higher percentage of NFD within the EC matrix did not result in a faster release and the EC60 formulation showed the poorest release profile. However, the EC50 formulation showed a slightly better dissolution performance compared to other EC-based formulations. No statistically significant differences were observed between the dissolution profiles of EC50 and cpEC50 formulations (Supplementary data, Fig S3). This demonstrates the importance of the suitable selection of the excipient over the geometry when designing sustained release solid dosage forms.

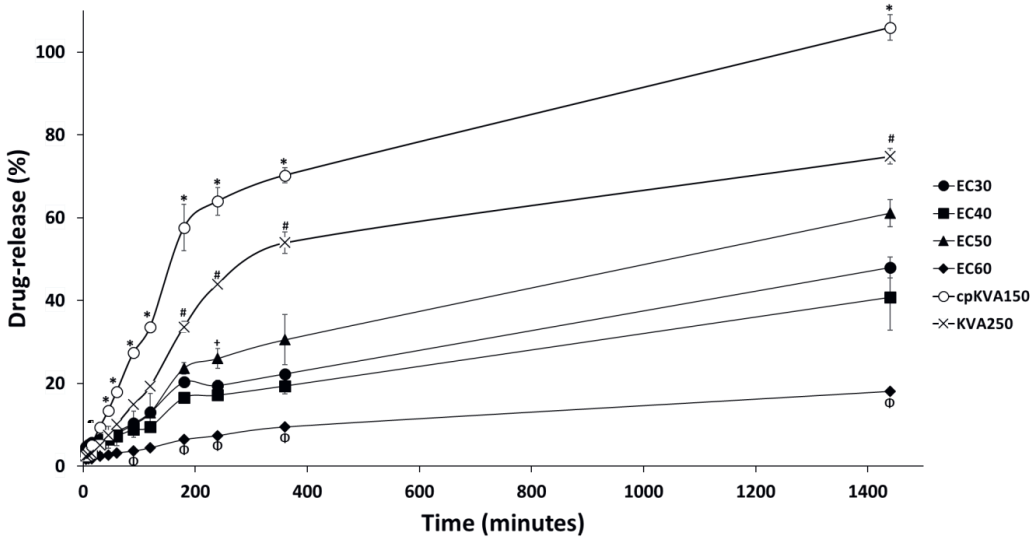


*Figure 10: Drug-release profiles for all HME formulations. Key: *: p<0.05 cpKVA150 vs. all other formulations; #: p<0.05 KVA250 vs. all other formulations; +: p<0.05 EC50 vs. all other formulations; Φ: p<0.05 EC60 vs. all other formulations (incl. t=5 to t=15) and ¶: p<0.05 EC30 vs. all other formulations (t=5, t=10).*

2.6. Multivariate analysis of the effect of excipients on the dissolution profile

To optimize the drug release profile, the impact of NFD and the three key excipients employed in the manufacturing of the HME-based tablets (EC, KVA64, HPC) on the percentage of drug released at 6 hours was evaluated (Fig. 5). PCA analysis showed an inverse correlation between EC and KVA64 content on the NFD drug

release. The same correlation was observed by multi linear regression (MLR) analysis, corroborating that fact that KVA64 had a statistically significant positive effect on the NFD release (p=0.0015), while EC had a statistically significant negative impact (p=0.0181).

The percentage of HPC and NFD did not show a statistically significant correlation with the NFD release (p>0.05). This explains why EC-based mini-tablets with a wide range of NFD content (30-60%) did not show any correlation in terms of NFD release. Even though a limited number of formulations was used to feed the model, a good PLS correlation (high R^2> 0.99 and a low Mean Square Root Error <0.8) was found between the type and percentage of excipient with the NFD released at 6 h (Supplementary material, Fig. S4).

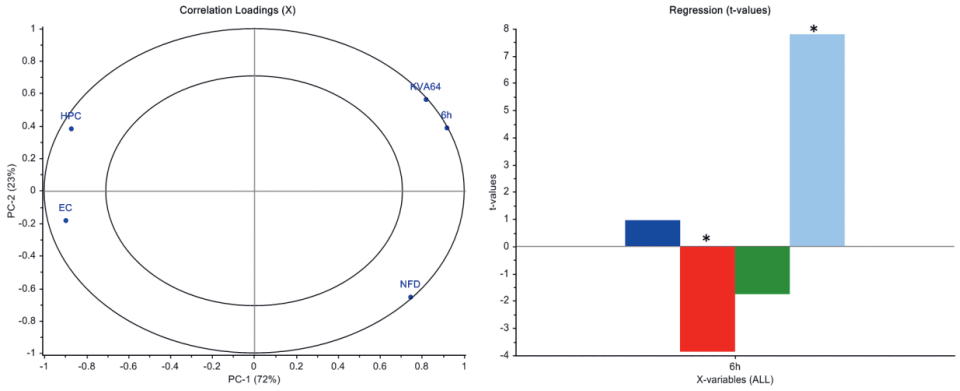


Figure 11: Principal component analysis represented by the correlation loading plot (left) and MLR analysis represented as T-values (right). Key: NFD (dark blue), EC (red), HPC (green), KVA64 (light blue). Statistically significant differences are depicted as *p<0.05.

2.7. Dynamic vapour sorption (DVS)

DVS analysis was performed to compare the adsorption moisture profile of the 3D printed mini-tablets (with 50% NFD) that contained either EC or KVA64 in their matrix. Moisture sorption isotherms showed a similar profile for both formulations up to 60% RH (Fig. 12). There is a gradual increase in water uptake (~2%) for both formulations. However, markedly different behaviour in the sorption profile was observed above 70% RH. The KVA64 mini-tablet showed a gradual increase in water uptake until 90% RH, while the EC50 mini-tablet showed a decrease in mass at 70-80 % RH associated with drug crystallisation. PXRD analysis was performed after DVS and confirmed the crystallisation of the NFD under high RH conditions in the mini-tablet with EC (data not shown). Regarding the desorption cycle, a large hysteresis was observed in the KVA64 mini-tablet, which can be linked to the formation of small cavities and pores during the cooling of the extrudates, where water can condense, slowing down the desorption process. The combination of PXRD, DSC, TGA, and DVS data led to the

conclusion that the formulations containing KVA64 as polymeric matrix represent a more physically stable amorphous system compared with the EC-based formulations.

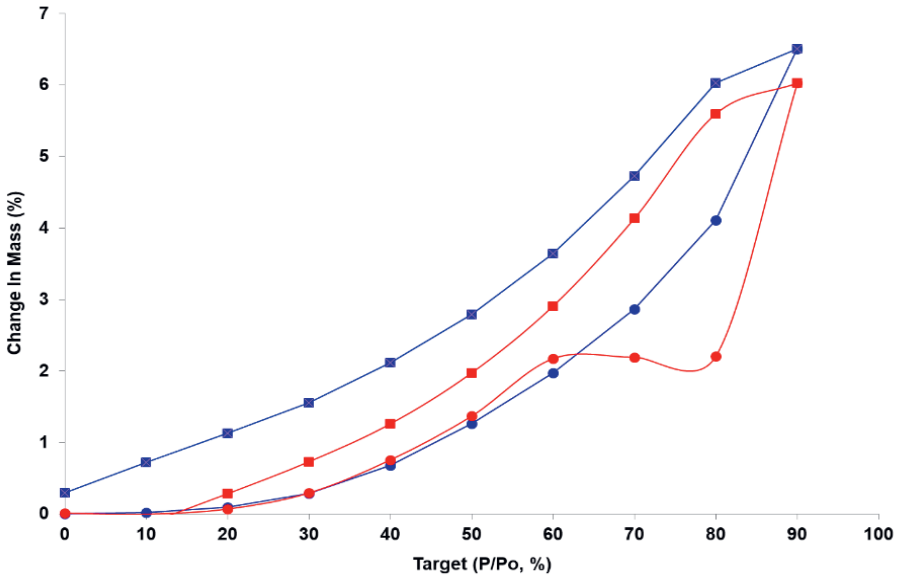


Figure 12: Moisture adsorption isotherms for KVA50 (blue line) and EC50 (red line) mini-tablets. Key: Circles represent the sorption cycle and squares represent the desorption cycle.

3. Discussion

In this work we have demonstrated that the release profile of a poorly water-soluble API (NFD) can be tailored using 3D printing with drug-loaded filaments produced by PD or HME and we demonstrated for the first time the manufacture of channelled mini-tablets with enhanced surface area. The major drawbacks of PD loaded filaments are that the maximum drug loading achieved was only 4% and the process is lengthy. HME-based filaments demonstrated more than 13-fold higher loading compared to PD filaments. Filaments loaded with up to 60% NFD were successfully manufactured by HME. However, HME is more complicated to implement in clinical practice within hospitals, for example, while passive diffusion, especially for potent drugs, could be more easily achieved. 3D printers with a direct powder extrusion module can be an alternative to avoid the need of creating a printable filament through HME. A closer collaboration between industry and hospitals will be required to enable the clinical translation of these 3D printed personalised solid dosage forms based on HME filaments.

A greater resolution of the printed mini-tablets was obtained when using PD loaded commercial filaments as HME filaments were more heterogeneous in diameter and were more porous due to the extrusion process. The latter issue can be easily overcome using high specification industrial hot melt extruders with twin co-

rotating screws and a ventilation unit to remove generated air during the mixing and the melting within the extruder. The use of a highly concentrated masterbatch use and intermediary products can be other approaches.

Loaded filaments were utilised to prepare 6 mm spherical mini-tablets. Currently, there is only a single report that has described the successful manufacture of 3D printed Mini-tablets as a novel controlled release platform technology (Awad et al., 2019). Mini-tablets are easier to combine within a capsule avoiding potential physicochemical interactions between different active pharmaceutical ingredients, while they also allow versatility in the administered dose. A size 0 capsule was selected as three mini-tablets can fit within it. This allows a greater versatility to manufacture tailored oral dosage forms either by increasing the dose of NFD per capsule or combining different APIs (fixed-dose combinations (Fernandez-Garcia et al., 2020)) within the same capsule to treat multiple pathologies such as hypertension, hypercholesterolemia and diabetes. However, mini-tablets are more challenging to 3D print considering the smaller dimensions compared to larger tablets especially when including additional intricate channels to increase surface area.

We were also able to determine which, between geometry and composition, seems the most important consideration for 3D printing these dosage forms. Initially, mini-tablets with different diameters were 3D printed. However, the increase in surface area was limited and the impact on dissolution was not statistically significant (data not shown). For this reason, a more complex geometry including seven internal channels was developed to increase the surface area of the mini-tablets by 1.6-fold. Several authors have shown that the geometry of the solid dosage form has a key impact on dissolution (Goyanes et al., 2015b; Sadia et al., 2018). Surprisingly, the change in geometry and the enhancement in the surface area only led to a significantly faster dissolution profile in those formulations containing KVA64, but not in those with EC. This shows that the dissolution of NFD was governed first by the composition of the mini-tablet and secondly by the geometry. EC-based formulations showed an overall hampered dissolution profile compared to the KVA-based ones. The enhancement in the surface area of the EC-based mini-tablets was not sufficient to trigger an improvement in the dissolution rate. This can be related with the formation of a gel-like layer around the mini-tablet limiting dissolution and inhibiting the effect of the greater surface area. However, those solid mini-tablets containing KVA64 show a faster dissolution rate and more complete dissolution profile, and hence, the additional increase in surface area was translated into amplified release. Based on the Hansen solubility parameters, KVA64 has better miscibility than EC with NFD. This can explain the better amorphization of the NFD within the excipient matrix, and the more stable amorphous system upon exposure to high RH leading to a single Tg composite observed by DSC. Nevertheless, a fraction of crystalline NFD remained after the 3D printing process in both types of HME formulations indicating that the manufacturing of filaments with a lower percentage of NFD will be more suitable to ensure stability over prolonged periods.

The dissolution profile of the NFD mini-tablets can be tailored when a successful geometry and composition are combined. NFD is a poorly soluble BCS Class II drug. Slow and incomplete dissolution profiles have been

previously reported for 3D printed solid dosage forms, especially when high levels of hydroxypropyl methyl cellulose were used (Khaled et al., 2015). Mini-tablets prepared from PD filaments demonstrated a faster release profile matching that of NFD commercial tablets (Stada). HME mini-tablets showed a biphasic release with two zero-order phases, more closely mimicking the commercial Adalat Oros profile, especially those mini-tablets containing KVA, as the EC-based mini-tablets, resulted in an incomplete release with a slow rate. This is possibly due to the formation of a diffusion and erosion-resistant gel layer that hinders release of NFD, also limiting effects from the higher surface area conferred by the pores. Zero-order release is clinically suitable for antihypertensives as immediate release formulations can elicit serious adverse effects, such as orthostatic hypotension, whereas a 24 h sustained release can provide the required pharmacological effect over a whole day, consequently enhancing patient compliance as only a single dose is required.

4. Conclusions

3D printing is a versatile technology providing the possibility to manufacture solid dosage forms within complex geometries, such as channelled mini-tablets, potentially with high drug-loading (up to 60%). In this work, we have shown that appropriately combining the solid dosage form composition and geometry allows us to tailor drug-release profiles according to the patient's needs. The composition of the extruded filaments has a more significant impact on dissolution than geometry. KVA-based mini-tablets exhibited a faster and more complete release than EC-based formulations showing a similar release profile to other commercially available formulations and may be easily translated into clinical practice.

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Supplementary material

Table S1. Characteristics of the in-house manufactured filaments and mini-tablets.

Formulations	Average mini-tablet weight (mg)	SD	Average filament diameter (mm)	SD	Drug-release in 24 hours (%)
PD	386.20	8.76	1.75	0.05	100
EC30	64.65	1.34	1.51	0.02	47.97
EC40	63.75	0.21	1.45	0.02	40.80
EC50	64.30	1.84	1.46	0.06	61.08
$_{CP}$EC50	69.533	2.81	1.46	0.06	48.53
EC60	86.70	1.99	1.45	0.03	18.14
$_{CP}$KVA150	81.90	1.27	1.53	0.03	108.93
KVA250	110.20	0.28	1.57	0.02	74.85

Table S2. The fraction of crystalline NFD within the mini-tablets derived from the heat of fusion taking into account the amount of NFD within the formulation. BQL: below the quantification limit.

Raw NFD and mini-tablet formulations	Heat fusion (J/g)	Amount of NFD in the formulation (%)	Fraction of crystalline NFD (%)
Raw NFD	112.5	100	100
$_{CP}$KVA150	13.57	50	24.1
KVA250	5.00	50	8.8
EC30	21.34	30	63.2
EC40	22.12	40	49.2
EC50	32.16	50	57.17
EC60	37.54	60	55.5
PD	-	4	BQL

Table S3. Glass transition temperatures for raw KV64, raw EC and 3D printed mini-tablets calculated from the reversed heat flow DSC thermograms.

Formulation (mini-tablets)	T_g (°C)
Raw KVA64	101.90 ±1.2
Raw EC	122.64 ±2.3
$_{CP}$KVA150	47.23 ± 0.8
KVA250	43.98 ± 0.7
EC30	47.6 ± 1.2
EC40	49.46 ± 1.1
EC50	48.54 ± 0.9
EC60	46.79 ± 0.8
PD	43.98 ± 0.8

Table S4. Dissolution modelling data

	Formulation	First order (R^2)	Zero order (R^2)	Hixson–Crowell (R^2)	Korsmeyer–Peppas (R^2)	Higuchi (R^2)
HME	**EC30**	0.9287	**0.9954 (0-120 min)** **0.9943 (180-1440 min)**	0.9160	0.9840	0.9840
	EC40	0.9439	**0.9698 (0-120 min)** **0.9993 (180-1440 min)**	0.9333	0.9869	0.9867
	EC50	0.9851	**0.9938 (0-120 min)** **0.9982 (180-1440 min)**	0.9843	0.9790	0.9669
	EC60	0.9592	**0.9913 (0-120 min)** **0.9663 (180-1440 min)**	0.9400	0.9854	0.9827
	$_{CP}$EC50	-2,2255	**0,9926 (0-120 min)** **0,9895 (180-1440 min)**	0,9797	0,9819	0,9752

	$_{CP}$KVA150	-1.015	**0,9925 (0-180 min)** **0,9973 (240-1440 min)**	0.9511	0.4445	0.9221
	KVA250	0.9855	**0,9935 (0-180 min)** **0,9989 (240-1440 min)**	0.9536	-0.0786	0.9056
PD	**6 mm mini-tablets**	0.9595	0.9653	0.9806	**0.9878**	0.8856
Comme-rcialsed formulations	**STADA**	0.8588	0.1845	0.7621	0.8659	**0.8859**
	ADALAT OROS	0.8913	**0.9874**	0.9307	0.7646	0.7000

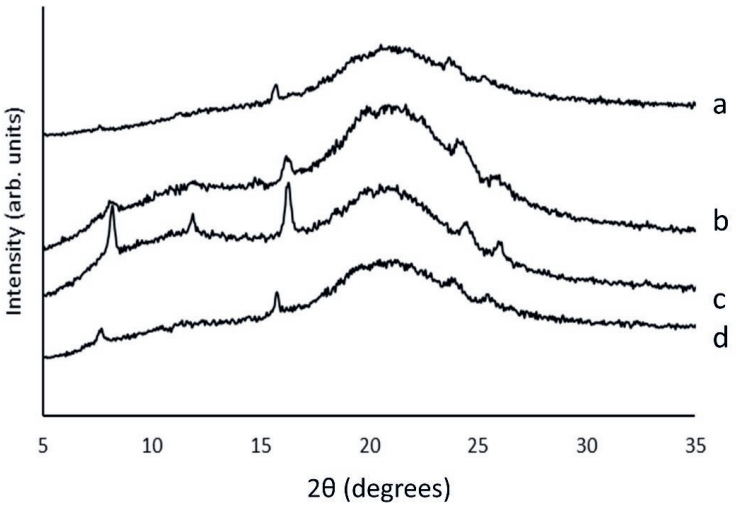


Figure S1. PXRD analysis of the surface of the EC-based mini-tablets: EC60 (a), EC50 (b), EC40 (c) and EC30 (d).

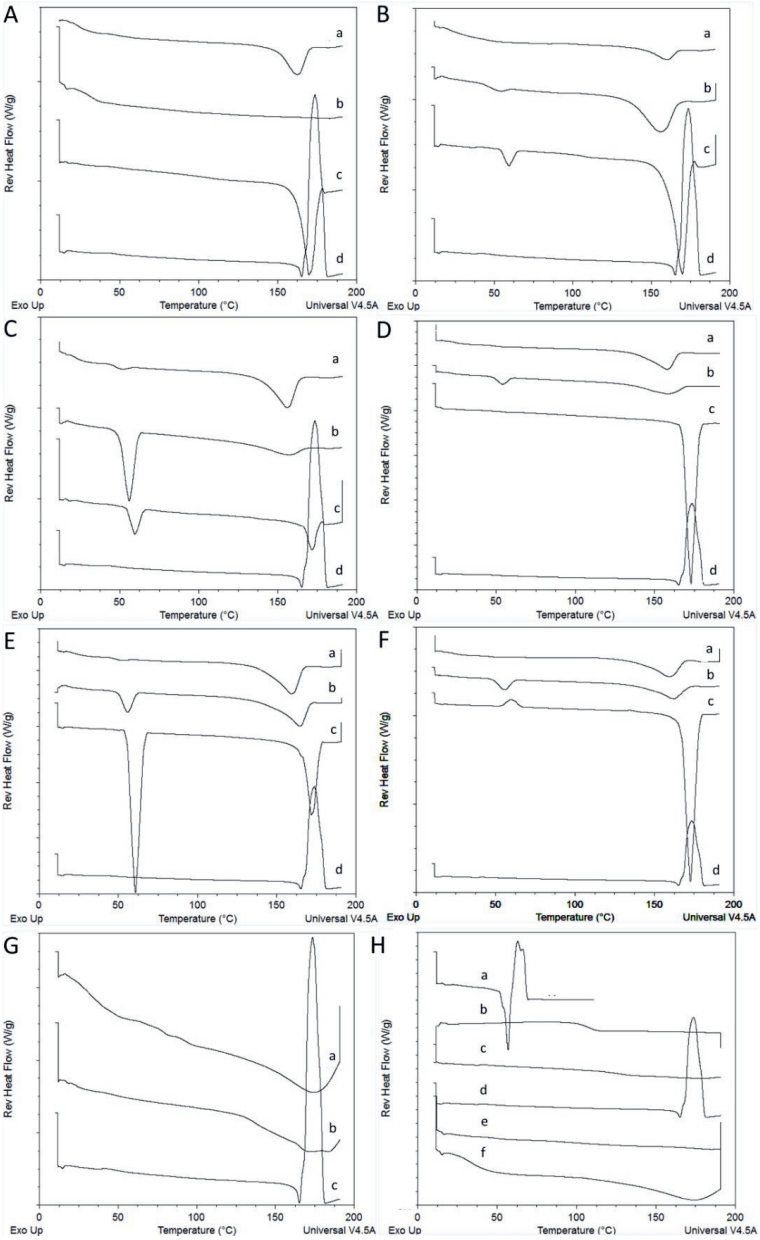


Figure S2. DSC reverse heat flow thermograms of the raw materials, physical mixtures, filaments and 3D printed mini-tablets. Key: $_{CP}$KVA150 (A), KVA250 (B), EC30 (C), EC40 (D), EC50 (E), NC60 (F), PD (G) and for all raw material (H). Within the graphs (A-F): mini-tablet (a), filament (b), PM (c) and raw NFD (d). For graph (G); mini-tablet (a), loaded HS filament (b) and raw NFD (c). For graph (H); PEG4000 (a), KVA64 (b), EC (c), NFD (d), HPC (e) and HS (f).

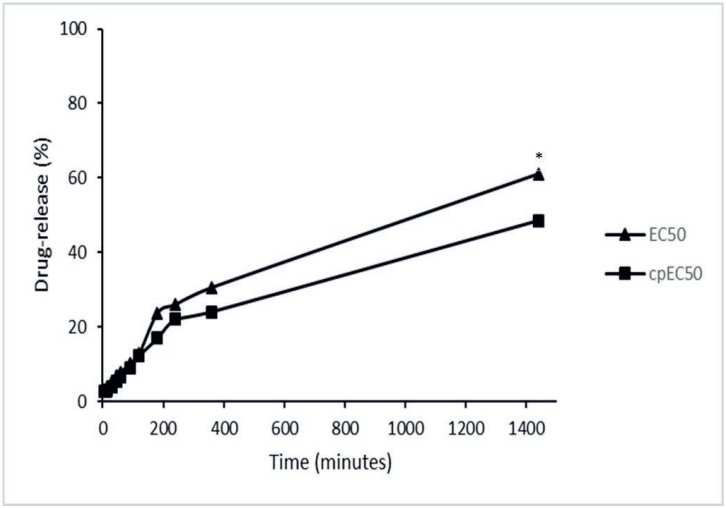


Figure S3. Drug-release profiles for the EC50 and cpEC50 formulations. Key: statistically significant differences are depicted with *p<0.05.

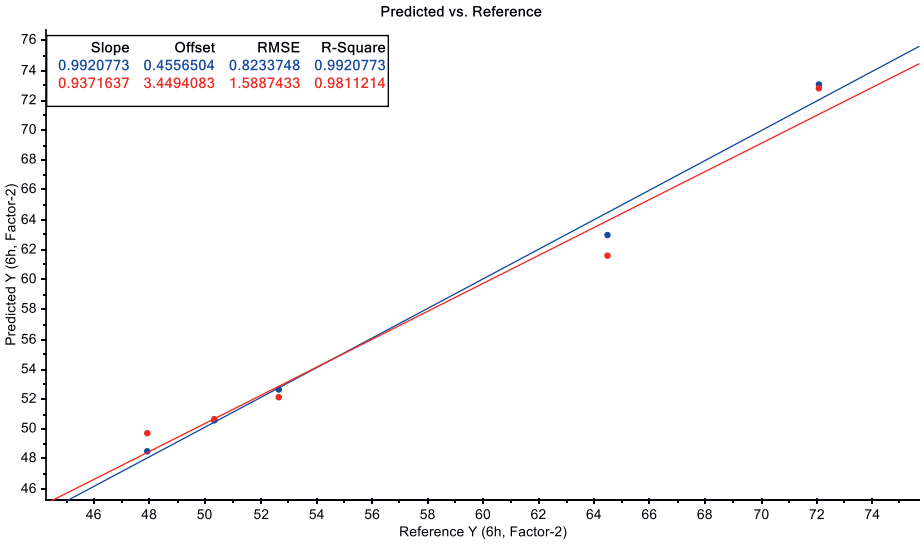


Figure S4. PLS prediction model of NFD release.

3

Chapter 3

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

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Abstract

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 24h 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 24h 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 (1). 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 (2, 3). 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 (4). 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 (3). 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 (5-7). A dual release (DR) HC formulation, Plenadren®, has been developed and marketed in an effort to optimize the treatment (8). 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 (8). 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 (3). 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 (2).

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 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 (9). There are several 3DP techniques of which fused deposition modelling (FDM) is the most extensively researched in medicine (10-13). In FDM, drug loaded polymeric filaments are fed into the printer where they are melted at a specific temperature (Fig. 1) (10, 14). 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 (15). 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 (10).

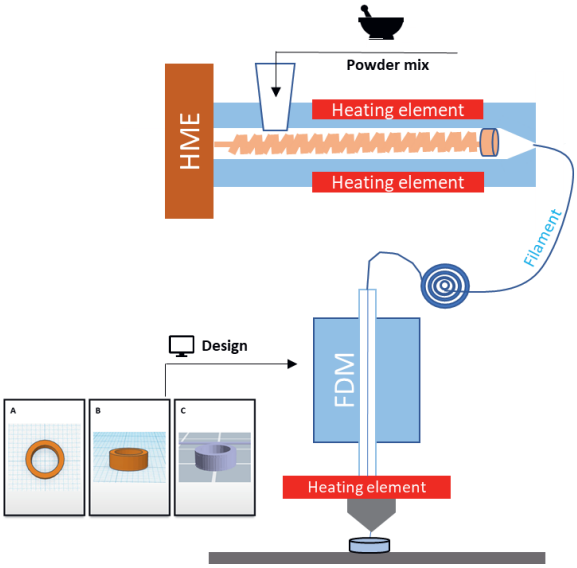


Figure 1. Hot melt extrusion coupled with fused deposition modelling 3D printing.

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 (1) to demonstrate that dose adaption is straightforward with this technique, (2) to test the final formulation against European Pharmacopeia (Ph. Eur.) requirements and (3) 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.

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 (16). Analytical reagents were used without further purification.

2.2 Methods

2.2.1 Hot melt extrusion

Four formulations were developed (Tab. 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 (Tab. 1) and HC, PEO, HPC, MgS and RL (Tab. 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 minutes after which the mixture was sieved through a 1.6 mm screen prior to extrusion at barrel temperatures of 110 °C and 150 °C.

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

2.2.2 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.

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 (Tab. 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.

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

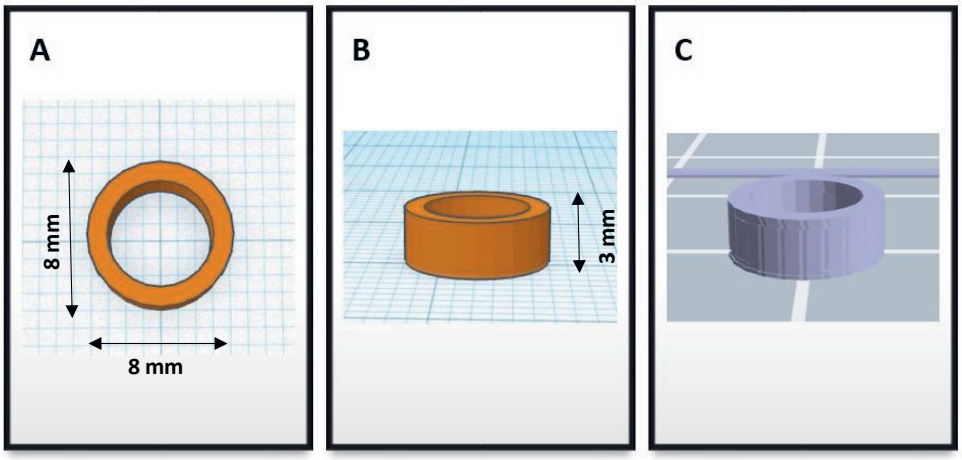


Figure 2. CAD designs for formulation F3 and F4: tinkercad top view (A), tinkercad side-view (B) and sliced design (C).

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: 1M 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 (100x4.6mm, 3.5µm). 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 nanometers. 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.

Table 3. 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

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) (17). 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 (17). 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 grams 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 grams 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.

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) (17). 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-1000N 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 hours. SIF (400 ml) was added and kept for the remaining 22 hours. Media were maintained at 37 ± 0.5 °C and 4M 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 minutes, and 1, 2, 3, 4, 6, 7, 21, 22, 23 and 24 hours. 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 (18). f2 was calculated by the mathematical software DDsolver (China Pharmaceutical University, Nanjing, China) (19).

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 minutes 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 (20). 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 (Tab. 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.

Table 5: Hydrocortisone contents at different processing temperatures for F1.

Temperature (°C)		HC content (%) ± SD
Extrusion	3D printing	
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

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. Figure 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 (21).

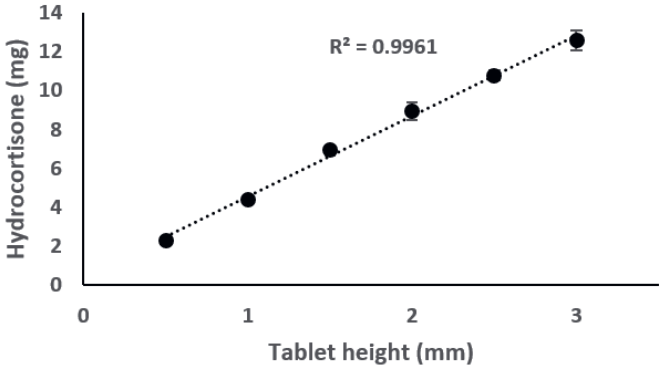


Figure 3. F2 tablet height and tablet content correlation.

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.

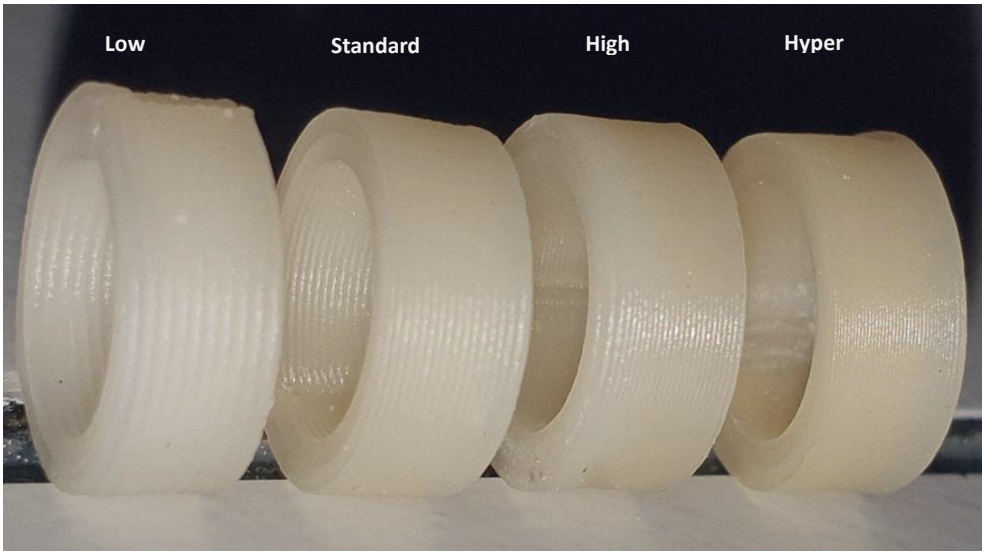


Figure 4. F4 tablets printed with low, standard, high and hyper resolution setting (left to right). Difference in layer-height is clearly visible with more layers at higher resolution.

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 (22). 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. Full data is provided in the supplementary material, Appendix B.

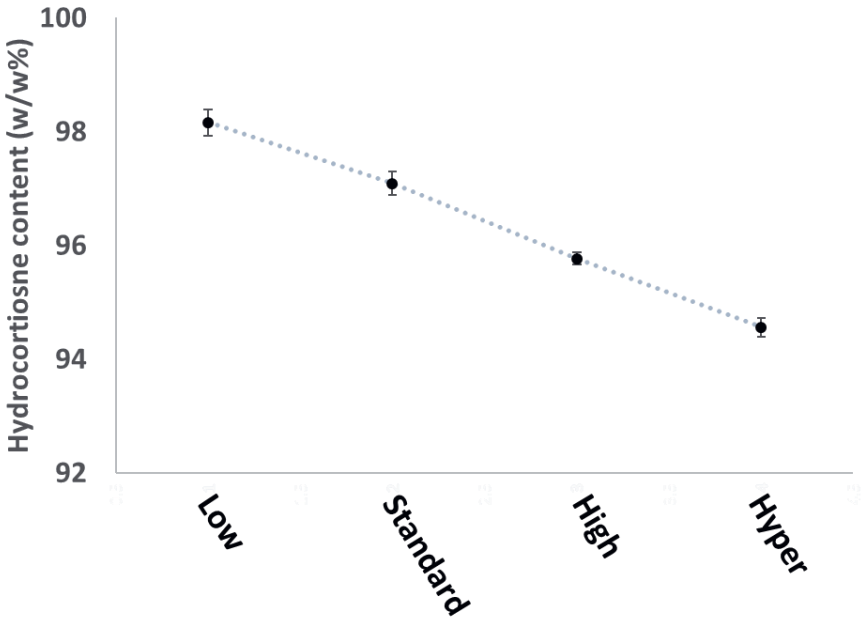


Figure 5. Hydrocortisone content at different resolution settings for F4 tablets.

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 (23). 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' (24). 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.

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 24h 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.

3.2 Physical properties

The friability of the tablets met the Ph. Eur. requirement of <1.0% mass loss (Tab. 6). Some tablets adhered to the drum wall during testing. According to Ph. Eur., a sample of tablets corresponding to 6.5 grams 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 grams 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 (25).

The results for tablet hardness (Tab. 6) suggest that tablet mechanical strength is comparable to other HME-FDM based tablets (26, 27). 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).

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

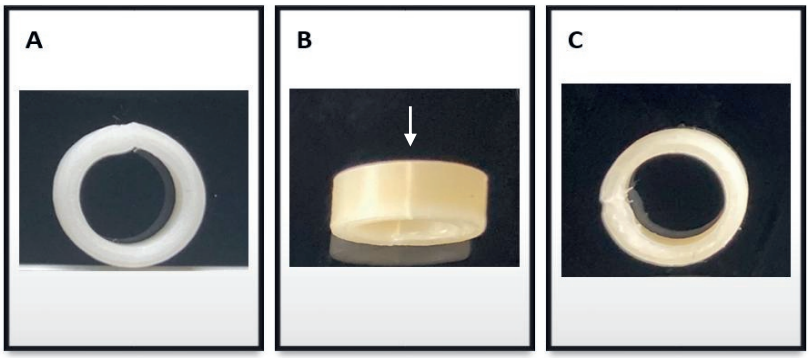


Figure 66. 3D printed tablets before hardness test (A) and after hardness test (B, C).

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 (Tab. 8). 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.

Table 8. 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

Twin screw filaments had a higher variation in filament diameter compared to single screw filaments. Average filament diameter was between 1.74 mm – 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 (28).

3.3 Dissolution

F4 single-screw and twin-screw tablets comply to the Ph. Eur. recommendation of >80% drug release within 24h (Fig. 6A). Drug release data (Fig. 6B) show a low intra-batch variability at 24h (<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 24h 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. 6A) 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 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 (29).

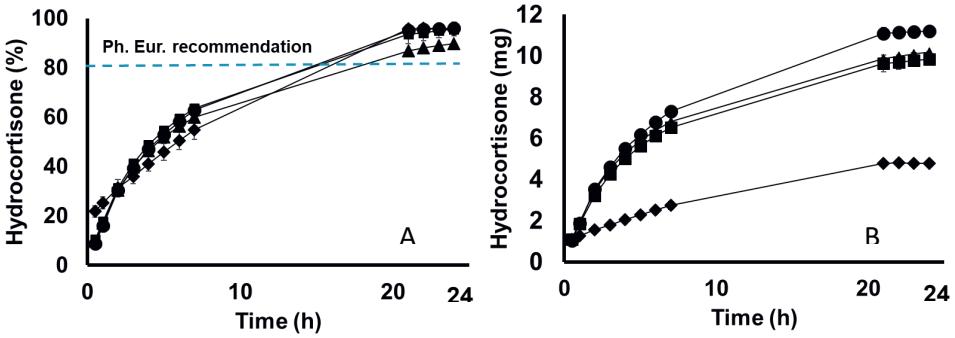


Figure 6. Drug release profiles in mg (A) and in % (B) of three single screw extrusion F4 batches (● ■ ▲) and Plenadren® 5 mg (◆).

3.4 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 (30). 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 minutes (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 (31, 32). 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.

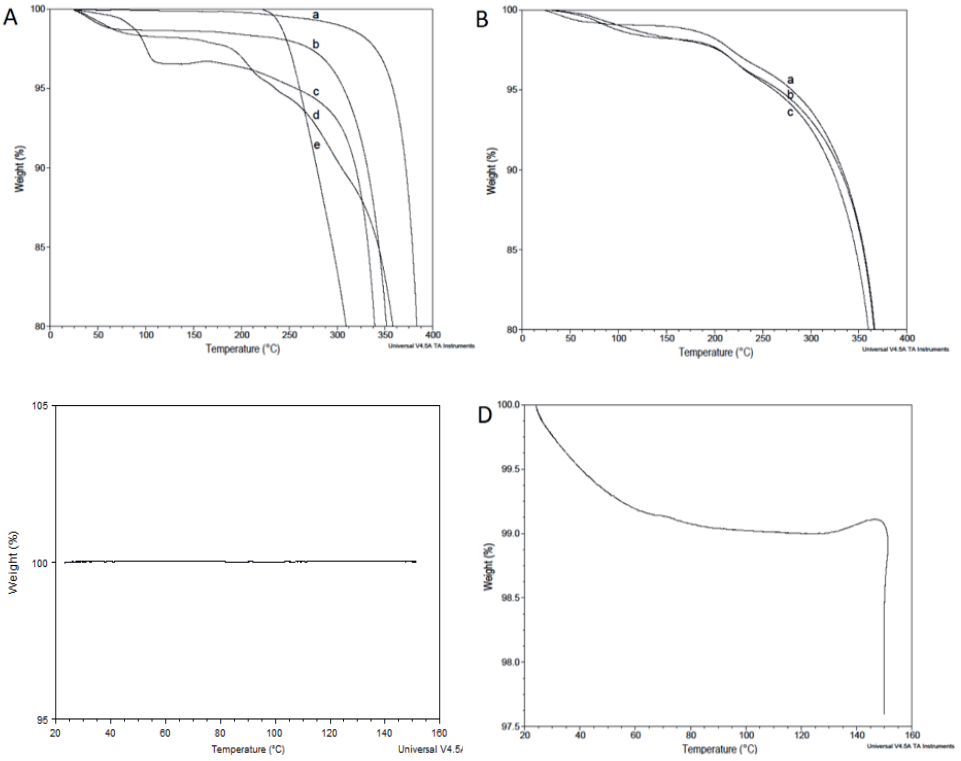


Figure 8. TGA curves for A: PEO (a), HPC (b), MgS (c), RL (d) , hydrocortisone (e); B: powder mixture (a), F4 tablet (b) and the drug-loaded F4 filament (c); C: heat-and-hold hydrocortisone; D: heat-and-hold powder mixture.

3.5 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) (33).

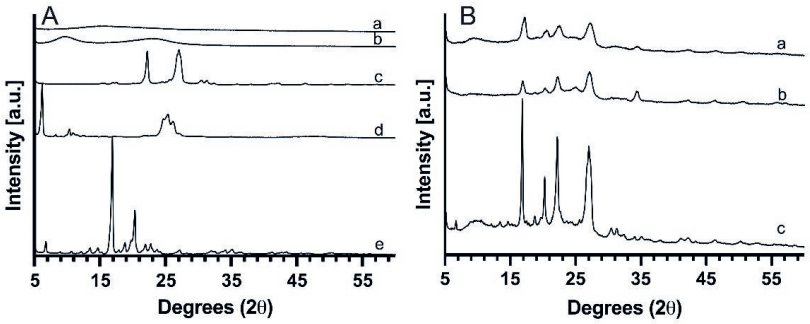


Figure 97. XRPD diffractograms of A) the raw materials; a) Eudragit RL PO, b) HPC, c) PEO, d) MgS, e) hydrocortisone and of B) processed samples; a) 3D printed F4 tablet, b) filament F4 and c) powder mixture F4.

3.6 DSC

The DSC thermographs of the F4 powder mixture, filament and tablet show an endothermic event at 60.7 ± 1.0 °C (Fig. 10), corresponding to the melting behavior of PEO (34). 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 (30). The endothermic HC peak is absent in the F4 powder mixture, filament and tablet which, especially for the powder mixture, is 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 (35, 36). Both polymers seem to have a high amorphous content as no endothermic events are observed.

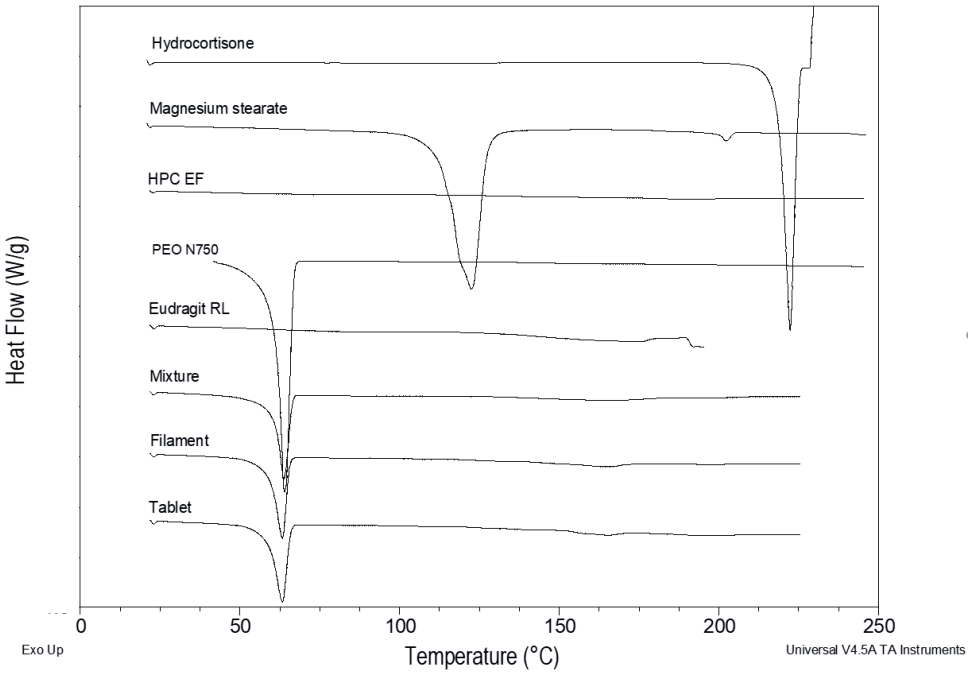


Figure 10. DSC thermographs of hydrocortisone, magnesium stearate, PEO N750, Eudragit RL, HPC, mixture, F4 filament and 3D printed F4 tablet.

3.7 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).

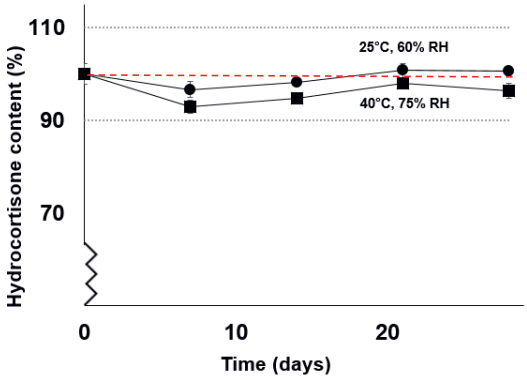


Figure 11. Stability data of F4 tablets tested over four weeks at 25°C 60% RH (●) and 40°C, 75% RH (■).

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).

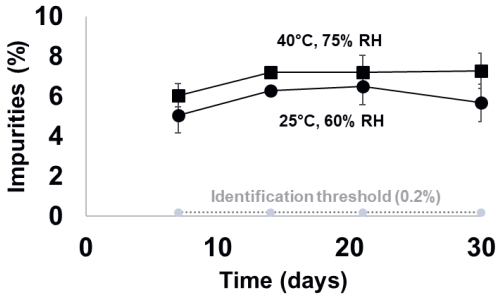


Figure 12. Average amount of total impurities observed over four weeks at 25°C 60% RH (●) and 40°C, 75% RH (■).

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.

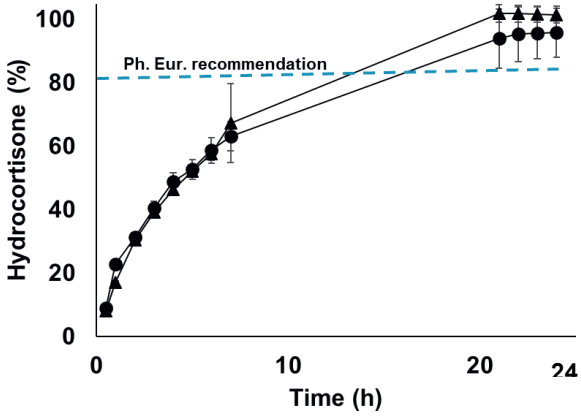


Figure 13. Dissolution profile of F4 tablets stored at 25°C, 60% RH after o days (▲) and 28 days (●).

3.8 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.

3.8.1 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 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.

3.8.2 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.

3.8.3 Drug release profile

Twin screw drug release profiles also comply to Ph. Eur. recommendation of >80% drug release within 24h (Fig. 13A). Intra-batch 24h release variability is <2.62% which is comparable to the single screw variability (<2.78%). The inter-batch variability is ± 0.42 mg after 24h 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. 13B). 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.

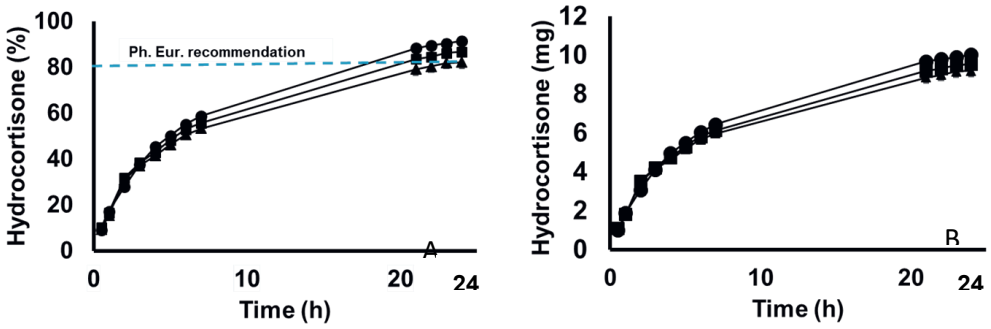


Figure 12. Drug release profiles in % (A) and in mg (B) of three twin screw extrusion batches

(●■▲)

3.8.4 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 (37-40). 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 (41).

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 24h. 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 (42). 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 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 (43).

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 (44).

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 (45). 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 (26, 46). 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 (47). 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 (22, 41, 48). FDM-HME tablet hardness is influenced by infill-density, choice of excipients, structural geometry, layer-height and layer-to-layer adhesion (26, 49).

F4 tablets demonstrated a stable 24h 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 (21). Dose individualization is not only specifically useful in adrenal insufficiency, where the 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 fully 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 minutes, 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 hours of storage at 60 °C (50). 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 (51-54). 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 (55, 56). 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 (57). Furthermore, removing kneading zones may also aid in reducing degradation due to a higher local residence time (32). 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 (58). 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 (59). 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 (60). 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 (1) operator qualification, (2) printing resolution, and (3) 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.

6. Literature

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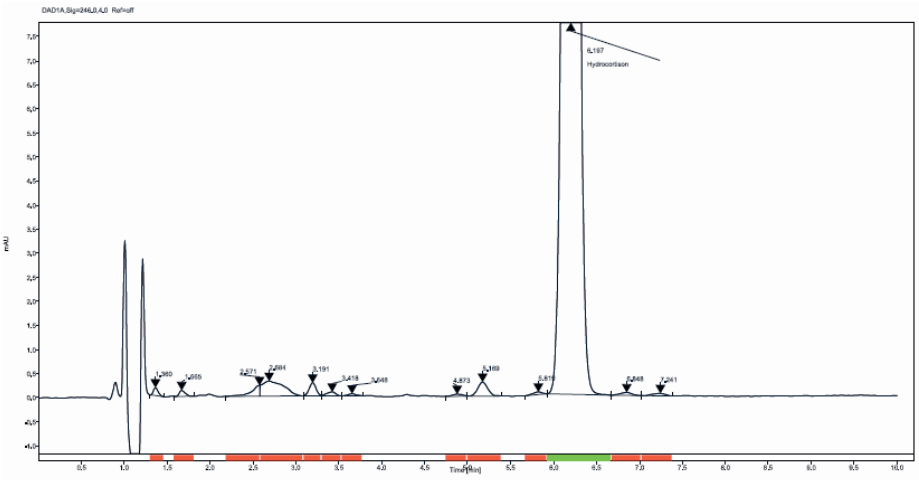
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Supplementary material

A. Observed impurities

Examples of observed impurities in HPLC graphs.

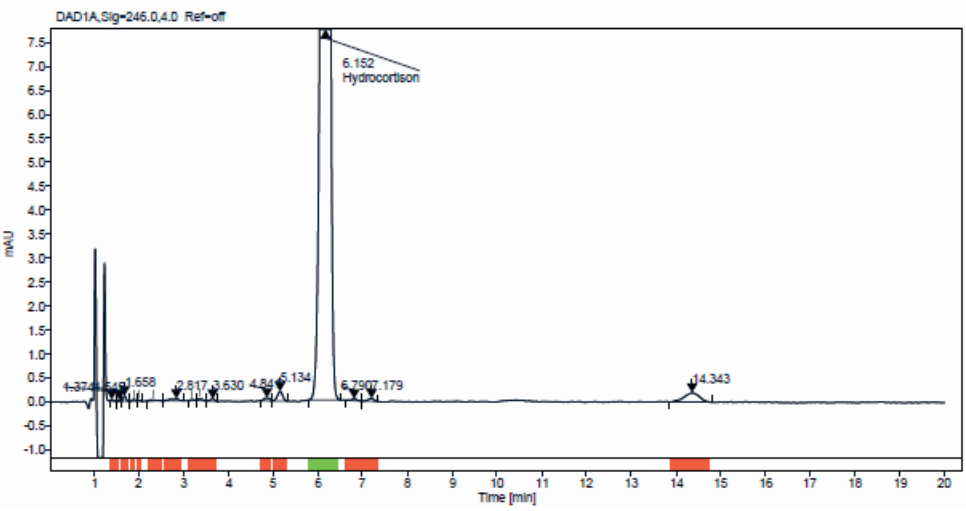
B8-G-2



Signal: DAD1A,Sig=246.0,4.0 Ref=off - 3/16/2022 12:35:46 PM

RT [min]	Name	Bijpiek tov API	Type	Breedte	Symmetrie	Area	Hoogte	Library	Purity	Amount
1,360		0,14	MM m	0,168	0,684	0,63	0,2		781	
1,665		0,12	MM m	0,241	0,594	0,57	0,1		437	
2,571		0,32	MM m	0,402	17,086	1,51	0,2		144	
2,684		1,15	MM m	0,507	0,438	5,43	0,3		963	
3,191		0,32	MM m	0,209	0,977	1,49	0,3		768	
3,418		0,12	MM m	0,231	1,569	0,57	0,1		771	
3,648		0,06	MM m	0,247	0,843	0,29	0,0		564	
4,873		0,08	MM m	0,256	0,817	0,36	0,0		674	
5,169		0,50	MM m	0,399	0,930	2,34	0,3		534	
5,819		0,09	MM m	0,260	1,528	0,41	0,1		710	
6,197	Hydrocortison	50,00	BB	0,753	0,987	466,39	48,9	1000	1000	4,668

Figure A. 1. HPLC graph of a tablet (F4) with impurities. The column 'bijpiek tov API' states impurity:API ratio in %. Impurities exceeding identification threshold (>0.2%) are marked in red.



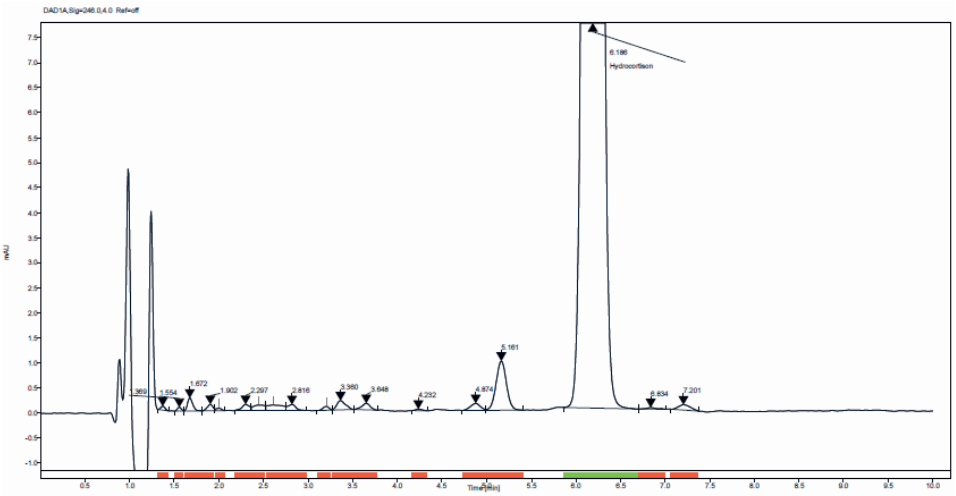
Signal: DAD1A,Sig=246.0,4.0 Ref=off - 6/13/2022 5:12:55 PM

RT [min]	Name	Bijpiek tov API	Type	Breedte	Symmetrie	Area	Hoogte	Library	Purity	Amount
1.374		0.02	MM m	0.156	0.608	0.11	0.0		474	
1.545		0.02	MM m	0.107	1.037	0.10	0.0		577	
1.658		0.11	MM m	0.200	0.897	0.52	0.1		601	
1.865		0.04	MM m	0.156	0.804	0.19	0.0		462	
1.985		0.02	MM m	0.112	1.046	0.09	0.0		591	
2.294		0.06	MM m	0.371	0.748	0.28	0.0		685	
2.817		0.12	MM m	0.444	2.254	0.58	0.0		988	
3.170		0.02	MM m	0.176	0.962	0.12	0.0		555	
3.337		0.05	MM m	0.215	0.535	0.26	0.0		546	
3.630		0.06	MM m	0.259	1.335	0.30	0.0		397	
4.841		0.12	MM m	0.278	0.987	0.58	0.1		655	
5.134		0.34	MM m	0.342	1.021	1.65	0.2		665	
6.152	Hydrocortison	50.00	BB	0.713	1.094	482.85	47.9	1000	1000	4.550
6.790		0.06	MM m	0.342	1.071	0.31	0.0		345	
7.179		0.12	MM m	0.381	1.221	0.57	0.1		634	
14.343		0.94	MM m	0.935	1.077	4.57	0.2		687	

Figure A. 2. HPLC graph of a Twin screw extrusion based tablet with impurities. The column 'bijpiek tov API' states impurity:API ratio in %. Impurities exceeding identification threshold (>0.2%) are marked in red.

Impurities at a lower extrusion temperature (140 °C) and similar printing temperature (150 °C) .

ex140p150s1



Signal: DAD1A,Sig=246.0,4.0 Ref=off - 3/30/2022 9:42:58 PM

RT [min]	Name	Bijpiek tov API	Type	Breedte	Symmetrie	Area	Hoogte	Library	Purity	Amount
1.369		0.03	MM m	0.126	0.831	0.26	0.1		699	
1.554		0.03	BV	0.107	0.932	0.24	0.1		770	
1.672		0.12	VB	0.205	0.723	1.07	0.3		560	
1.902		0.07	BM m	0.140	1.200	0.56	0.1		683	
1.996		0.02	MB m	0.114	1.028	0.21	0.0		970	
2.297		0.09	BM m	0.186	1.017	0.73	0.1		822	
2.438		0.11	MM m	0.164	0.758	0.96	0.1		994	
2.605		0.16	MM m	0.224	0.581	1.34	0.1		739	
2.816		0.09	MM m	0.233	1.053	0.78	0.1		978	
3.201		0.04	BV	0.170	1.226	0.37	0.1		664	
3.360		0.15	VB	0.242	0.705	1.25	0.2		720	
3.648		0.10	BB	0.267	1.125	0.86	0.1		796	
4.232		0.02	MM m	0.177	0.765	0.14	0.0		600	
4.874		0.13	BV	0.270	1.102	1.09	0.1		762	
5.161		0.92	VB	0.420	0.993	7.95	1.0		814	
6.186	Hydrocortison	50.00	BB	0.840	0.991	854.88	90.4	1000	1000	8.168
6.834		0.03	MM m	0.303	0.651	0.24	0.0		703	
7.201		0.12	MM m	0.315	0.679	1.00	0.1		820	

Figure A. 3. HPLC graph of a Noztek based F3 tablet produced with a lower extrusion temperature (140 °C). The column 'bijpiek tov API' states impurity:API ratio in %. Impurities exceeding identification threshold (>0.2%) are marked in red.

B. Observed impurities

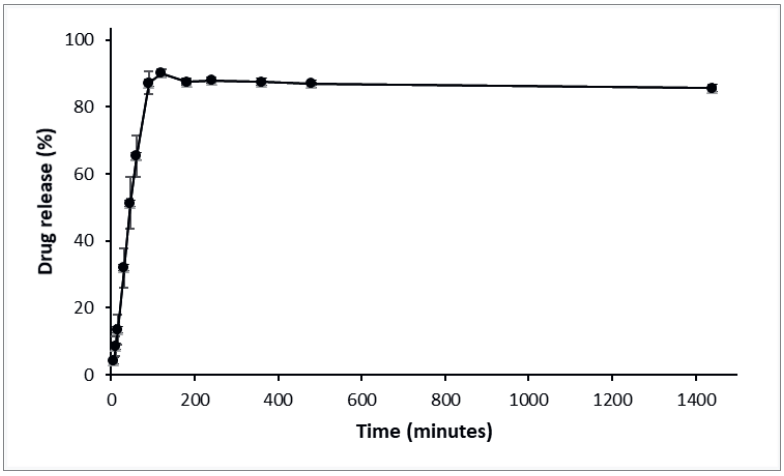


Figure B. 1. Dissolution study of F1 (n=3). This formulation does not have the desired sustained release effect and was therefore not further researched..

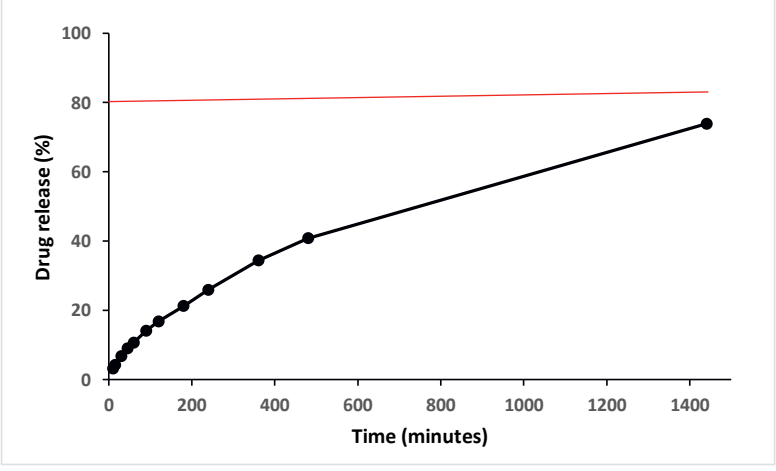


Figure B. 2. Drug release profile of F2 (n=1). This formulation did not comply to the ph. eur. recommendation of >80% drug release within 24 h and was therefore not further researched

C. Content uniformity data

Table C. 1. Tablet weight and content of F4 single screw tablets used for content uniformity assessment.

Unit	Tablet weight (mg)	Hydrocortisone content (mg)	Hydrocortisone content as a % of Target value (=12 mg)
1	85.44	11.93	99.40
2	85.17	11.93	99.45
3	85.91	12.03	100.24
4	87.71	12.26	102.15
1	85.88	12.23	101.92
2	85.12	12.11	100.88
3	86.11	12.28	102.37
4	85.08	12.05	100.45
1	86.42	12.41	103.43
2	86.48	12.42	103.48
3	87.17	12.51	104.28
4	84.98	12.23	101.88
Average		**12.20**	**101.66**
SD		**0.19**	**1.60**

Table C. 2. Tablet weight and content of F4 twin screw tablets used for content uniformity assessment.

Unit	Tablet weight (mg)	Hydrocortisone content (mg)	Hydrocortisone content as a % of Target value (=11 mg)
1	89.62	11.38	103.4
2	77.71	10.03	91.2
3	93.23	12.10	110.0
4	88.08	11.23	102.0
1	86.84	11.24	102.1
2	86.71	11.06	100.5
3	80.48	10.32	93.8
4	89.36	11.39	103.5
1	85.43	10.93	99.4
2	91.85	11.81	107.4
3	83.04	10.62	96.5
4	82.13	10.46	95.1
Average		**11.05**	**101.41**
SD		**0.61**	**5.54**

Table C. 3. Tablet weight and content for resolution study samples.

No.	Weight (mg)	Hydrocortisone content (%)	Average content (%) ± SD
	Low resolution		
1	76.40	98.2	
2	76.60	98.1	98.16 ± 0.23
3	76.44	98.4	
4	77.16	97.9	
	Standard resolution		
1	81.39	97.2	
2	82.27	97.3	97.09 ± 0.21
3	81.58	97.1	
4	82.66	96.8	
	High resolution		
1	86.42	95.7	
2	86.48	95.7	95.77 ± 0.10
3	87.17	95.7	
4	84.98	95.9	
	Hyper resolution		
1	82.44	94.7	94.56 ± 0.16
2	82.24	94.4	
3	84.05	94.5	
4	83.14	94.6	

D. Mechanical properties

Table D. 1. Filament diameter of single screw extrusion batches and twin screw extrusion batches.

Filament diameter (mm)					
Single screw extr.			Twin screw extr.		
Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3
1.7	1.8	1.8	1.7	1.7	1.6
1.8	1.8	1.8	1.8	1.8	1.7
1.8	1.8	1.7	1.8	1.9	1.8
1.8	1.8	1.7	1.8	1.7	1.9
1.8	1.7	1.7	1.8	2.0	1.7
1.9	1.7	1.7	1.9	1.9	1.8
1.8	1.8	1.8	1.7	1.7	1.7
1.8	1.8	1.7	1.7	1.9	1.8
1.8	1.8	1.8	1.9	1.7	1.9
1.8	1.8	1.9	1.9	1.5	1.5

Table D. 2. Other mechanical properties of single screw batches and twin screw batches.

Batch	Maximum force (N)	Maximum bending stress at max force (mPa)	Elongation after max force (mm)
single screw extrusion filaments			
1	6.28	66.57	4.31
2	6.10	61.40	4.17
3	5.62	68.52	4.87
Twin screw extrusion filaments			
1	6.64	74.97	4.91
2	6.61	78.59	3.88
3	5.70	67.72	4..66

E.Dissolution study

Table E. 1. Tablet weight of tablets (F4) used in dissolution studies.

	Single screw batch 1 (mg)	Single screw batch 2 (mg)	Single screw batch 3 (mg)	Twin screw batch 1 (mg)	Twin screw batch 2 (mg)	Twin screw batch 3 (mg)
1	82.66	82.61	86.04	81.94	87.24	89.81
2	82.95	82.3	84.83	85.3	88.03	90.57
3	82.23	81.59	84.53	88.04	88.29	93.59

F. stability study

Table F. 1. Tablet weights for tablets used in stability study.

Tablet weight (mg)		
Sample	25°C 60% RH	40°C, 75% RH
T=0		
1	87.32	87.32
2	84.66	84.66
3	79.73	79.73
T=7		
1	95.88	94.61
2	94.46	89.88
3	90.35	94.49
T=14		
1	94.53	88.84
2	92.30	92.32
3	88.63	93.92
T=21		
1	92.49	91.79
2	86.85	94.53
3	87.05	89.92
T=28		
1	92.75	98.05
2	94.78	95.79
3	90.45	95.85
Average	91.71	91.45
SD	3.05	4.85

Table F.2. % of impurities found during stability study.

	Total content of impurities (%) ± SD	
Time (days)	**25°C, 60% RH**	**40°C, 75% RH**
7	5.07 ± 0.88	6.05 ± 0.58
14	6.29 ± 0.23	7.20 ± 0.05
21	6.51 ± 0.93	7.22 ± 0.83
28	5.68 ± 0.93	7.27 ± 0.88
Av	5.90 ± 0.90	6.90 ± 0.78

4

Chapter 4

The Quest for Child-Friendly Carrier Materials Used in the 3D Semi-Solid Extrusion Printing of Medicines

Eveline E. M. van Kampen, **Sejad Ayyoubi**, Luc Willemsteijn, Kjeld J. C. van Bommel, Elisabeth J. Ruijgrok

Pharmaceutics. 2022;15(1):28

Abstract

This work gives a brief overview of carrier materials currently used in pharmaceutical studies on the three-dimensional (3D) semi-solid extrusion (SSE) printing of medicines for pediatrics. The suitability of using these carrier materials in pediatric formulations, concerning safety and toxicity, was reviewed by consulting the 'Safety & Toxicity of Excipients for Pediatrics' (STEP) database and the Food and Drug Administration (FDA) regulations. In the second part of this work, carrier materials were tested on their ability to form a semi-solid mixture with lactose by dual asymmetric centrifugation (DAC) and printing by SSE. With the combination of theoretical and experimental studies, this work will guide research toward grounded decision-making when it comes to carrier material selection for pharmaceutical pediatric 3D SSE printing formulations.

1. Introduction

Administering the correct dose of medication to children is a complex task. Children, compared to adults, need lower doses and a flexible dosage form as they experience physical growth and their organ functions mature [1]. Consequently, many dose corrections are performed through splitting, crushing and dissolving tablets or administering intravenous liquids orally. Cross-contamination, inaccurate dosing and altered absorption are associated risks with these manipulations [2]. In the quest for better medication for children, 3D printing can provide a good option. With 3D printing, dose-flexible and age-appropriate solid oral dosage forms can be manufactured [3]. By pharmaceutical printing, the active pharmaceutical ingredient (API) is added to a mixture of the carrier material, forming the base of the formulation and excipients, enhancing properties such as stand-up or dissolution profiles. After mixing all compounds, an object created by computer-aided design (CAD) software is printed layer-by-layer [4]. The field of printing child-friendly, dose-flexible solid oral dosage forms is evolving as multiple 3D printing techniques are studied [3].

Extrusion-based 3D printing is a frequently used method in the 3D printing of drugs. With fused deposition modeling (FDM), API-loaded filaments are pushed through a heated nozzle, where they are melted and extruded. Examples of FDM-printed child-friendly drugs are chewable candy-like formulations with indomethacin [5], minitablets with baclofen [6] and nifedipine [7]. With semi-solid extrusion (SSE), a syringe is filled with a molten or semi-solid formulation, after which the material is pressed through a nozzle by a piston or back pressure. SSE operates at lower temperatures than FDM and therefore is suitable for thermally sensitive APIs. Proof-of-concept studies showed successful printing of different chocolate-based formulations with ibuprofen or paracetamol for pediatric use [8]. Other studies report the production of 3D-printed gummies with ranitidine and lamotrigine, low-dose furosemide, and sildenafil tablets for children [9]. As sildenafil was tested in a clinical setting, this gives insight into the excellent feasibility of using SSE printing in a hospital pharmacy as small-scale manufacturing.

For the development of a pediatric formulation, carrier material and excipients should be considered carefully. When it comes to patient safety, and more specifically pediatric patient safety, the materials should be well tolerated by children [10]. As their physiological systems are still developing, certain compounds (e.g., propylene glycol or ethanol) cannot be metabolized by children as they can by adults [11]. So even compounds generally regarded as safe (GRAS) by the FDA might not be tolerated. The STEP database, set up by the European Pediatric Formulation Initiative (EuPFI), covers excipient safety data on pediatric use from peer-reviewed scientific journals, government reports and databases. Besides patient safety, material properties are critical for developing a pediatric formulation. The most relevant material property in 3D SSE printing is the melting temperature of the carrier material, as the processing temperature should remain below the degradation temperature of the API. Degradation of API could also occur when the API is exposed for a longer period to elevated temperatures even when they remain below the degradation temperature.

The objective of this work is to give an overview of carrier materials used in SSE 3D printing research for pediatric use and to evaluate their theoretical suitability and experimental extrudability. We describe the selection of a suitable carrier material(s) to print child-friendly mini-tablets using the SSE 3D print method. First, suitable carriers were identified by a literature search, then their safe application in children was assessed theoretically, and finally, their extrudability was determined in practical experiments.

2. Materials and Methods

2.1. Carrier Material Selection from Literature

Suitable carrier materials were selected by performing a Pubmed literature search (Appendix A) and screening the 'Handbook of Pharmaceutical Excipients' [12]. The literature search focused on materials used for pharmaceutical SSE 3D printing of medication for pediatrics. Carrier materials were selected if reported as 3D printed or extruded for pediatric purposes and had a melting temperature or glass-transition temperature between 30 °C and 80 °C.

2.2. Assessment of Suitability for Pediatric Use

The selected carrier materials were assessed on their suitability for pediatric use by screening the STEP and US FDA Inactive Ingredients databases for each carrier material [13,14]. Materials were included as appropriate if the FDA currently approved their oral use. The STEP database was also consulted, as the FDA approval for oral use does not explicitly specify safe for pediatric use. The STEP database includes an up-to-date overview of the literature on the safety and toxicity of carrier materials used in children. Available data on the acceptable daily intake (ADI) in children described in this database was noted in the results.

2.3. Extrudability Screening

From the 27 carrier materials found, we assessed the extrudability of ten available carrier materials by one preparation and extrusion process for equal comparison. For this selection, the available information on pediatric safety or FDA approval for in-human-use was not used to create specific inclusion and exclusion criteria. Gelling agents were excluded from the experiments as preparing tablets based on gelling agents would result in an additional drying step unincorporated in our process.

Ten materials were evaluated using an experimental setup of the dual axial centrifuge (DAC) and SSE 3D printing. DAC is preferred over mixing by mortar and pestle to increase the reproducibility of the process. First, the materials were mixed and melted by DAC (Section 2.3.2), second, the syringe was filled (Section 2.3.3), and third, the mixture was extruded by our SSE 3D printer (Section 2.3.4). Each step is described in detail below. There was an evaluation step if the process was successful or unsuccessful, visualized in a decision tree in Figure 1.

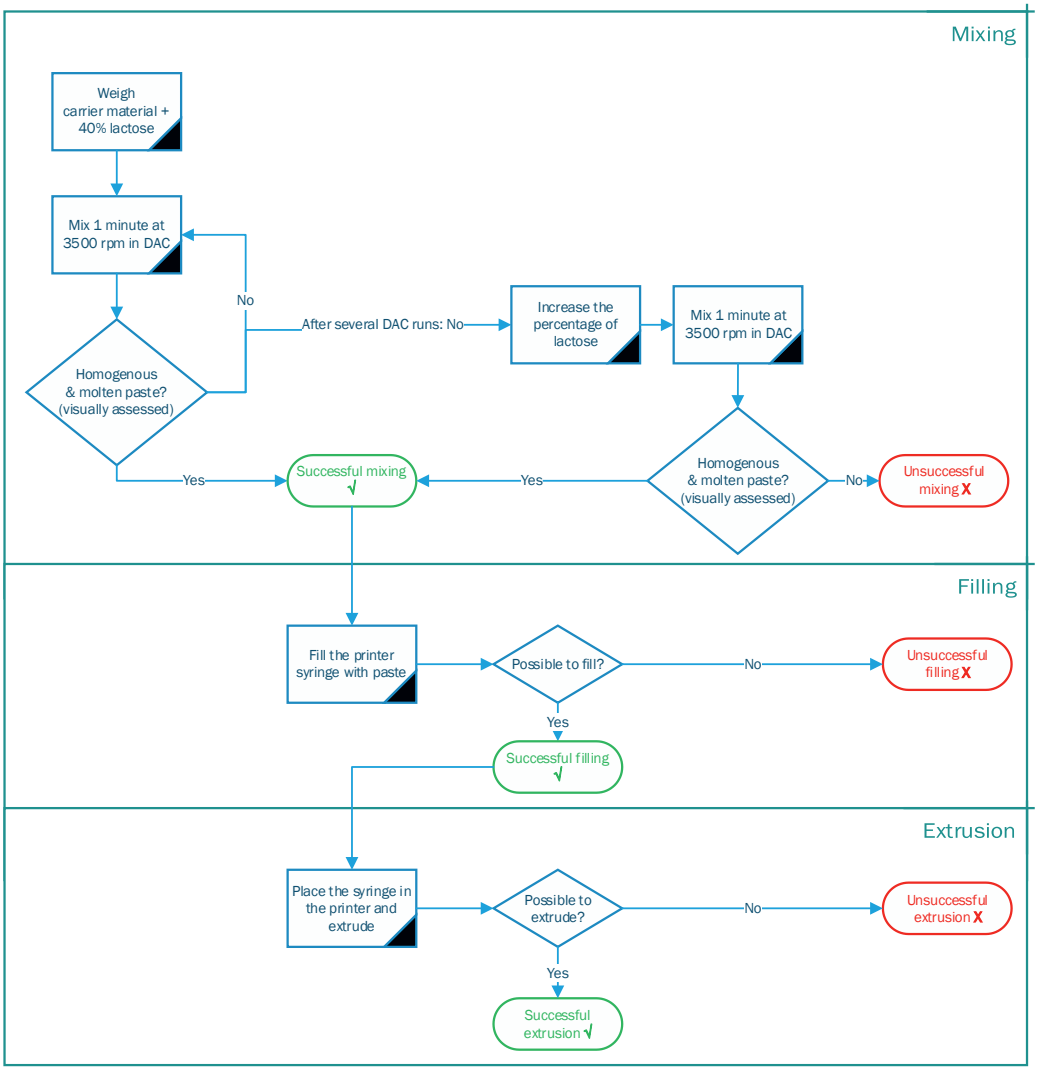


Figure 1. Decision tree of different processing steps for SSE 3D printing.

2.3.1. Materials

Methacrylate-Copolymers (Eudragit E PO) were obtained by Evonik. Poloxamer 407 (Kolliphor® P407) was kindly donated by BASF (Ludwigshafen, Germany). Polyethylene glycol 4000 (PEG 4000) (EMPROVE® ESSENTIAL Ph Eur) and Polyethylene oxide (PEO) were purchased from Sigma-Aldrich (Zwijndrecht, The Netherlands). Adeps solidus (Witepsol® H15) was obtained from BÜFA. White beeswax (Cera Alba) was purchased from Fagron (Capelle aan den Ijssel, The Netherlands). Glycerol dibehenate (Compritol® 888 ATO), glycerol distearate (type I) (Precirol® ATO 5), glycerol monostearate 40–55 (Type I) (Geleol™ mono and diglyceridedes NF) and stearoyl polyoxyl-32 glycerides (Gelucire® 50/13) were kindly donated by Gattefossé (Saint-Priest, France). Lactose (SorboLac® 400) was kindly donated by MEGGLE Group (Wasserburg am Inn, Germany).

2.3.2. Mixing and Melting

The carrier material and lactose (40:60 *w*/*w*) were weighed to a total of 55 g and placed in a disposable plastic Speedmixer™ cup (185 mL). Subsequently, the cup was placed in a SpeedMixer™ (DAC 150.1 FVZ-K) and mixed by DAC at 3500 rpm for 1 min. Afterward, the temperature of the semi-solid mixture was measured. In DAC, the Speedmixer™ cup rotates around two axes causing a particle flow that generates friction between the individual particles. This friction generates enough heat to melt the carrying material. Adding an excipient with a high melting temperature (Tm), in this case, lactose (Tm = 140 °C) enhances the particle friction during DAC, resulting in heat development. The DAC step was repeated until a visually homogenous mixture with a constant temperature was obtained.

The mixture was transferred to the pre-heated stainless-steel syringe of the SSE 3D printer once it visually appeared homogeneous, and the temperature was constant above the melting point of the carrier material. If the mixture was not molten or the temperature was not above the melting point, the mixing and melting in the DAC continued for an extra minute at 3500 rpm. If this repetition was unsuccessful, the percentage of lactose was increased stepwise. The adjusted formulation was mixed until the desired consistency and temperature, resulting in successful mixing. If neither the prolonged DAC mixing nor the increased amount of lactose led to an enhanced texture, mixing was declared unsuccessful.

2.3.3. Syringe Filling

Heating the stainless-steel syringe to the melting temperature of the carrier material before filling prevented the material from hardening while filling the syringe. The pre-heated syringe was placed on a plastic holder. This holder was the size of the Speedmixer™ cup with an opening in the middle, matching the diameter of the syringe. The holder with the syringe was placed on top of the molten formulation in the Speedmixer™ cup. By pressing the holder downwards with a SpeedPress™, the molten formulation was pushed upwards filling the syringe [15].

2.3.4. Melt-Extrusion 3D Printing

Figure 2 illustrates the setup of the SSE 3D printer used to determine the extrusion of the mixture. First, the syringe (A) loaded with the molten formulation was placed in the syringe heater (B). The heater was adjusted to the melting temperature of the carrier material. Second, a metal nozzle (C) with a diameter of 0.4 mm was attached to the syringe. The nozzle was heated by a separate heating block (D) to the melting temperature of the carrier material, to prevent solidification of the material in the nozzle. Third, a mechanically controlled piston (E) was attached. With the piston, the material was extruded through the nozzle and the applied force was logged. The maximum force of this printer setup was 400 N. Finally, the printer head, controlled by a computer (F), moved in three dimensions (*x*-, *y*-, and *z*-axis). If the printed formulation did not adhere to the printing platform (G), as the formulation cools too quickly, the platform could be heated with a separate heating bed (H). On the contrary, if the formulations did not solidify due to residence heat, air cooling (I) could be applied to enhance the solidification of the tablet.



Figure 2. Used printer setup; syringe (A), the heating element of the syringe (B), nozzle (C), the heating element of the nozzle (D), piston (E), computer with Pronterface (F), printing platform (G), heating bed (H), and cooling (I).

In the experimental part of this study, the formulations were extruded onto a glass plate or a piece of baking paper. Instead of printing a specific shape, the software Pronterface monitored and sent commands to the 3D printer. In this experimental stage, the command to extrude was given manually and not by running any G-code.

3. Results

3.1. Carrier Material Selection from Literature

From our literature search, 27 carrier materials were found that complied with the selection criteria of being 3D printed or extruded with a melting or glass temperature in the range of 30–80 °C (Table 1). All 27 materials were printable below a temperature of 80 °C using SSE. To structure the different materials, we organized them into four categories: polymers (e.g., polyethylene glycol), fats (e.g., beeswax), gelling agents (e.g., hydroxypropyl methylcellulose), and others.

The carrier materials show a wide range of melting and glass transition temperatures, ranging from 30 °C (Tm of adeps solidus) to above 80 °C (glass transition temperature (Tg) of polyvinylpyrrolidone K12 (PVP)). Formulations based on different carrier materials not only differed in processing temperature but also in release profile. Use of highly water-soluble PEG resulted in tablets with a fast and complete release profile. Tablets made from highly lipophilic and water-insoluble fats tended to show a more sustained release,

depending on the API. Most of the 27 carrier materials were printed with different types of API at different concentrations, ranging from nearly 1% (*w*/*w*) of ibuprofen and acetaminophen [8] to 50% (*w*/*w*) of praziquantel [16].

There was also a variety of preparation methods of the semi-solid mixture. To compare the carrier materials equally, we selected ten available carrier materials for the experimental part of this study.

3.2. Assessment of Suitability for Pediatric Use

In general, it can be stated that there is a limited amount of information on the safety of carrier materials for pediatric use. The expected concentration of carrier material is 30–70% in 3D-printed tablets weighing 50–250 mg. This amount should remain below the toxicity limits for children. From the selected of 27 carrier materials, 18 are approved by the FDA to use in food or drugs. Six carrier materials are present in the STEP database; poloxamer 407, polyethylene glycol (PEG) 4000, polyvinylpyrrolidone (PVP), carboxymethylcellulose (CMC), hydroxypropyl methylcellulose (HPMC), and glycerol dibehenate. For PEG 4000, HPMC and PVP, the ADI is indicated. Of the selected 27 carrier materials, only three are both present in the STEP database and FDA-approved: poloxamer 407, PEG 4000 and HPMC.

PEG is a commonly used excipient in pharmaceutical products. Small amounts of PEG are added to liquid formulations to adjust the viscosity of liquids or alter the solubility of APIs. Relatively large amounts of PEG are used in solid dosage forms such as tablets and suppositories to create a solid dispersion. Due to its laxative properties, PEG has a maximum ADI of 10 mg/kg body weight when used as an excipient for children. High doses of PEG 4000, up to 0.8 g/kg body weight, are used in children of one month and older when these laxative properties are intended.

PVP is the second carrier material for which an ADI is described. The World Health Organization (WHO) defined an ADI of 0–50 mg/kg body weight for PVP [13]. It is primarily used as a binder in oral dosage forms. Although there is information on ADI, there is limited information available regarding clinical data in the pediatric population [13].

Another suitable material is poloxamer 407. Although clinical data on oral administration and ADI is lacking, there is data focused on the parenteral administration in children with sickle-cell disease [17,18]. However, the absorption in the gastrointestinal tract should be studied in further detail before general use.

Table 1. Carrier material selection from the literature.

Carrier Material	Melting or Glass Transition Temperature (°C)	Pharmaceutical Considerations	Pediatric Toxicology—STEP-Database—FDA Approved	Relevant Extrusion and/or 3D Print Example(s) in Literature
Polymers				
Methacrylate-Copolymers (Eudragit)	54 (Tg) (Eudragit® EPO) 63 (Tg) (Eudragit RL®) 64 (Tg) (Eudragit RS®)	• Different release profiles (sustained release, enteric), based on grade. • Wide applicability in the pharmaceutical industry	• Not included in the STEP database [13] • FDA approved for oral use [14]	• Tablets Eudragit RS with 40% theophylline were printed using direct extrusion at a printing temperature of 80 °C [19] • Eudragit EPO: TEC: Theophylline (50: 3.25: 46.75) was extruded at 90 °C and printed using FDM at 145 °C [20]
Poloxamer 407	52–57 (Tm) [12]	• Used in soft capsules, tablets, and suspensions [21] • Complete drug release within 2 h [22]	• FDA-approved for oral use [14] • GRAS [13] • Included as an excipient for pediatric formulations by the WHO [13] • No data on acceptable daily intake [13]	• Tablets containing 5% (*w*/*w*) pantoprazole made with HME-FDM printed at 60 °C [22]
Polyethylene glycol (PEG) Mn 4000/6000	50–58 (Tm) [12]	• Complete and fast-release profile [23]	• ADI: 10 mg/kg body weight [13] • FDA-approved for oral use [14] • Used as laxative agent up to 20 g/day (Children aged 8–18 years) [24]	• Puerarin: PEG4000 (1:3–6) tablets made using melt extrusion 3D printing at 54–57 °C [23] • Tablets containing 10% (*w*/*w*) pantoprazole with PEG6000 were printed at 60 °C with HME-FDM [22,25]
Polyethylene-co-vinyl acetate	43 (Tm) (40% VA) 73 (Tm) (28% VA)	• Slow and incomplete release profile [26] • Non-degradable [27]	• Not included in the STEP database [13] • Not FDA-approved for oral use [14]	• Extrudes with 10–50% (*w*/*w*) metoprolol produced via hot-melt extrusion at 60 °C (VA content 28% and 40%) [26] • 50% (*w*/*w*) metoprolol extrudes with EVA (VA content 9–40%) were extruded with HME between 70–110 °C [28]
Poly(lactic-co-glycolic acid)	30–60 (Tg) [29]	• Widely used in pharma applications • Biocompatible/biodegradable	• Not included in the STEP database [13] • FDA-approved for oral use [14]	• Drug delivery patch with PLGA 3D printed at 140 °C [30].
Polycaprolactone	50–60 (Tm) [31]	• Slow and incomplete release profile [32] • Biodegradable [31] • Water insoluble [31]	• Not included in the STEP database [13] • Not FDA-approved for oral use [14]	• Tablets containing 10–20% (*w*/*w*) ciprofloxacin produced with HME-FDM at 130–170 °C [32] • Coating with polycaprolactone printed at 58 °C [33]
Polyethylene oxide (PEO) 100,000	65 (Tm) [34]	• Non-ionic, hydrophilic and uncross-linked polymer [35]	• Not included in the STEP database [13] • FDA-approved for oral use [14]	• Syringe-based 3D printing and piston-based extrusion. Drug/PEO ratio (50/50 and 80/20) at 60 °C and 80 °C [36]
Polylactic acid	50–80 (Tg) [37]	• Biodegradable, thermoplastic polymer [38]	• Not included in the STEP database [13] • GRAS • FDA-approved for oral use (Lactic acid) [14]	• Only printed with relatively high temperatures so far (e.g., ≥135 °C) [39]
Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®)	70 (Tg) [40]	• Enhancement of bioavailability [40]	• Exposure of 114 mg/kg is regarded as safe [40] • Not FDA-approved for oral use [14] • Not included in the STEP database [13]	• Tablets containing dutasteride, Lutrol® F68, and Soluplus® (1:10:89) were printed at 160 °C using a hot-melt pneumatic dispenser [41]
Polyvinylpyrrolidone (PVP) K12	108 (Tg) [42]	• Water-soluble • Immediate release (100% within 15 min) [22]	• ADI: 0 to 50 mg/kg body weight [13] • Clinical trials in the pediatric population [13] • Not FDA-approved for oral use [14]	• Printed at 79–87 °C 10–30% pantoprazole and 10–25% TEC with HME-FDM [22]
Fats				
Adeps solidus (Witepsol®)	30–45 (Tm) [12]	• Low melting point (storage conditions) • Used in suppositories	• Not FDA-approved for oral use [14] • Not included in STEP database [13]	• N/A
Beeswax, white	60–67 (Tm) [12]	• Slow and incomplete release profile [43]	• Not FDA-approved for oral use [14] • Used as an excipient in tablets and capsules	• Tablets containing 5% (*w*/*w*) fenofibrate with different infills made with a piezoelectric inkjet printer at 90 °C [43]

			• Not included in the STEP database [13]	
Glycerol dibehenate (Compritol®)	65–77 (Tm) [12]	• Slow and incomplete release profile • Dissolution profile alters over time [16]	• FDA-approved for oral use [14] • Only clinical data on topical use [13] • No data on acceptable daily intake [13]	• Extrudes containing 50% (*w*/*w*) praziquantel and 1% SiO_2 produced with HME at a temperature just below the melting point [16]
Glycerol distearate (Precirol® AT05)	50–60 (Tm) [44]	• Slow and incomplete release profile	• Not included in STEP database [13] • Not FDA-approved for oral use [14]	• Extrudes containing 15–20% (*w*/*w*) phenylpropanolamine made with HME at 60 °C [45]
Glycerol monostearate (Geleol™)	54–64 (Tm) [46] 55–60 (Tm) [12]	• Slow and incomplete release profile [16] • Dissolution profile alters over time [16]	• Not included in STEP database [13] • FDA approved for oral use as an inactive ingredient [14]	• Extrudes containing 50% (*w*/*w*) praziquantel produced with HME at a temperature just below the melting point [16]
Glycerol tripalmitate	66–67 (Tm) [16]	• Slow and incomplete release profile [16] • Dissolution profile alters over time due to unstable modifications [16]	• Not included in STEP database [13] • Not FDA-approved for oral use [14]	• Extrudes containing 50% (*w*/*w*) praziquantel produced with HME at a temperature just below the melting point [16]
Paraffin (solid)	50–61 (Tm) [12]	• Slow and incomplete release profile [16]	• Not included in STEP database [13] • FDA approved for oral use as an inactive ingredient [14]	• Extrudes containing 50% (*w*/*w*) praziquantel produced with HME at a temperature just below the melting point [16]
Gelling agents				
Carboxymethylcellulose (CMC)	60–80 (solid-gel) [47]	• Water-soluble, anionic cellulose-derivative [48] • Biocompatible	• FDA approved for oral use as an inactive ingredient [14] • No ADI available [13] • Widely used in pharmaceutical products	• Tablets containing levetiracetam printed and processed at ambient temperature using semi-solid extrusion 3D printing [49]
Carrageenan	40–60 (solid-gel conversion) [50]	• High molecular weight polysaccharide [51]	• Not included in STEP database [13] • Widely used in the food industry as a gelling, thickening, emulsifying and stabilizing agent. • FDA-approved for oral use [14]	• Printed at temperatures below 80°C with a liquid feed 3D printer [52]
Gelatin	22–26 (solid-gel conversion) [53]	• Biocompatible polymer [54] • Thermo-reversible gelation	• Not included in STEP database [13] • Widely used in food and pharma • FDA-approved for oral use [14]	• Printed at ambient temperature with a bioprinter [55]
Hydroxypropyl methylcellulose (Hypromellose, (HPMC))	55–77 (solid-gel) [56]	• Safe biopolymer [57] • Sustained release profile [58] • Thermo-reversible gelation [57]	• ADI: 0 to 25 mg/kg body weight as a food additive (sum of total modified celluloses) [13] • GRAS [13] • FDA approved for oral use as an inactive ingredient [13] • Widely used in pharmaceutical products [57]	• Semi-solid extrusion of tablets containing naftopidil after processing at 90 °C [25,59] • Tablets with HPMC were made after processing at room temperature and cooling in the refrigerator at 4 °C [60] • Semi-solid extrusion of tablets containing theophylline after processing at 80 °C [58] • Gastro-floating tablets with dipyridamole prepared and printed at room temperature [61] • Syringe loaded at 80 °C and printed with extrusion-based syringe printing at ambient temperature [62]
Methylcellulose (MC) A4M	60–80 (gelation)	• Biocompatible • Sustained release profile [63]	• Widely used in food and pharma [64] • Not included in STEP database [13] • FDA approved for oral use as an inactive ingredient [14]	• Semi-solid extrusion of tablets containing theophylline at ambient temperature after processing at 70 °C [63]
Pectin	15–50 (gelation) [65]	• Biocompatible, gelling properties [66]	• FDA approved for oral use as an inactive ingredient [14]	• Hydrogel printed at 25 °C after processing at 65 °C [67]

			• Widely used in food and pharma • Not included in STEP database [14]	
Starch (e.g., corn starch, waxy maize starch, potato starch)	75 (gelatinization) [68]	• Safe biopolymer • Drug release dependent on the starch type [69]	• Widely used in pharmaceutical products [70] • FDA approved for oral use as an inactive ingredient [14] • Not included in STEP database [13]	• Tablets containing ibuprofen printed using syringe-based 3D printing at ambient temperature after processing at 90 °C [69]
Xanthan gum	60 (HME processing temperature) [71]	• Non-toxic, biodegradable polymer [72] • Stable over a broad pH range	• Not included in STEP database [13] • Used in several commercial products • FDA-approved for oral use [14]	• Xanthan gum in combination with ethyl cellulose at an extrusion temperature of 60 °C [71]
Other				
Chocolate	29–30 (Tm)	• Ethical and safety issues because of 'candy-like formulation' • Good palatability • Low melting point (storage conditions)	• Food product • High in sugars and saturated fat	• Different attractive shapes with paracetamol and ibuprofen (different formulations) printed with an extrusion printer at 45 °C [8,73]
Lauroyl Polyoxyl-32 glycerides (Gelucire® 44/14)	42.5–47.5 (Tm)	• High Hydrophilic-Lipophilic Balance (HLB) • Enhances the solubility of hydrophobic APIs [74] • Tablets can be considered conventional-release tablets [9]	• Not included in STEP database [13] • Polyoxyl stearates are listed in the US FDA Inactive Ingredients database for several administration routes and dosage forms [14]	• S-SMEDDS formulations (Gelucire® 44/14, Gelucire® 48/16, and Kolliphor® P 188) loaded with fenofibrate or cinnarizine were printed at 65 °C [75] • Suppositories with Gelucire® 44/14, coconut oil, and tacrolimus were printed with SSE at 42 °C [76]
Polyoxyl-32 stearate (type I) NF (Gelucire® 48/16)	46–50 (Tm)			• Tablets with furosemide (2/10 mg) and sildenafil (4 mg) were printed using SSE at 44 °C [9] • Suppositories with Gelucire® 48/14, coconut oil, and tacrolimus were printed with SSE at 48 °C [76]
Stearoyl polyoxyl-32 glycerides (Gelucire® 50/13)	46–51(Tm)			• Tablets with ricobendazole were printed using SSE at 49 °C [74]

3.3. Extrudability Screening

Ten available carrier materials, from the 27 carrier materials found in the literature, were assessed on their extrudability with our printing process. Gelling agents were excluded from the experiments as their preparation method needed an additional drying step unincorporated in our process. Following the decision tree, it was determined for each of the 10 materials if a process step could be executed successfully or not. Table 2 shows the outcome of this decision tree, where a green √ indicates a successful result, an orange ~ indicates it was partly possible and a red × indicates an unsuccessful outcome. The following sections describe the principal findings for each process step.

Table 2. Outcomes of extrudability screening per formulation of carrier material and lactose. (√ means successful, ~ means suboptimal and × means unable to process).

Carrier Material	Lactose (% *w*/*w*)	Mixing	Filling	Extrusion	Measured Temperature after DAC (°C)	Minutes DAC	The Temperature of the Syringe and Nozzle (°C)
Polymers							
Methacrylate-Copolymers (Eudragit® E PO)	40	×	n/a.	n/a.	40	1	n/a.
Poloxamer 407	42	√	√	√	>70	2	57
Polyethylene glycol (PEG) Mn 4000	55	√	√	√	67	4	75
Polyethylene oxide (PEO) 100,000	40	×	n/a.	n/a.	>100	2–3	n/a.
Fats							
Adeps solidus (Witepsol®)	60	√	√	√	44	2	35
Beeswax, white	70	√	~	√	80	3	63
Glycerol dibehenate (Compritol®)	70	√	√	√	70	1	70
Glycerol distearate (Precirol® AT05)	55	√	√	√	58	2	57
Glycerol monostearate (Geleol™)	70	√	~	√	84	3	64
Others							
Gelucire® 50/13	40	√	√	√	46	3	46

3.3.1. Mixing and Melting

All formulations containing a carrier material plus lactose reached a temperature above the melting temperature or glass transition temperature of the carrier material after DAC. Nearly all formulations (PEG 4000, poloxamer 407, beeswax, adeps solidus, glycerol dibehenate, glycerol distearate, glycerol monostearate and stearoyl polyoxyl-32 glycerides) formed a semi-solid mixture after DAC. Exceptions were the formulation with PEO 100,000 remaining too viscous to fill the syringe and Eudragit® E PO resulting in hard round lumps which created cracks in the Speedmixer™ cup after DAC. As these formulations containing PEO and Eudragit® E PO did not form an adequate semi-solid mixture, they were considered unsuitable for SSE in combination with DAC.

In general, we observed that fat-based formulations needed a higher percentage (*w*/*w*) of lactose (55–70%) compared to polymer-based formulations (40–55%) to reach a temperature above the melting or glass transition temperature.

3.3.2. Syringe Filling

Filling the syringe using the Speedpress™ is the following tested process step once a semi-solid mixture of carrier material and lactose was obtained after DAC. It was successful for PEG 4000, poloxamer 407, adeps solidus, glycerol dibehenate, glycerol distearate, and Stearoyl polyoxyl-32 glycerides. Fats with a relatively high melting point (e.g., glycerol monostearate) were challenging to process as they hardened quickly at room temperature. While being centrifuged with DAC, the material is pushed upwards along the sides of the Speedmixer™ cup. As the material solidified fast, a thin layer of solid material was formed, so the holder of the Speedpress™ rested on the remaining material. Accordingly, the holder could not be pushed down, and the syringe not filled. In contrast, the white beeswax formulation was so liquid that it leaked from all sides of the holder without filling the syringe.

3.3.3. Melt-Extrusion 3D Printing

Successfully filled syringes were placed in the printer. To retain a semi-solid mixture, the stainless-steel syringe and nozzle head were both (pre-)heated to the melting or glass transition temperature of the carrier material. Experiments showed that each material that could be loaded into the syringe was suitable for extrusion using the 3D printing setup. Suitable extrusion was assessed by qualified operators and was defined by adequate flow of semi-solid material coming out of the printer below the force limit of 400 N.

4. Discussion

This study aimed to identify suitable carrier material(s) to print child-friendly tablets with SSE 3D printing. In the literature, we found 27 different carrier materials used in previous studies on the 3D printing of pediatric drugs. When formulating child-friendly oral medication, safety should be one of the main considerations. Of the 27 materials found, only six were described in the STEP database [13], of which the acceptable daily intake was reported for PEG 4000, PVP and HPMC. The lack of knowledge on the remaining carriers does not exclude their use in pediatric formulations, but currently their toxicity is not fully assessed. These knowledge gaps must be addressed further when considering these materials for future use [10]. The STEP database is a usable resource but far from complete.

Several questions on the use of carrier materials for the production of pediatric drugs remain. Information on the safety and toxicity aspects of carrier materials is limited, as stated by Quodbach et al. [77]. Even if the information is available, it might not cover its use for the 3D-printed medicines. In most cases, the safety evaluation is based on small amounts of material used as coatings and not in large amounts as carrier materials in 3D printing. Side effects become more important in the latter case. For example, using PEG up to 20 g/day is considered safe for children between 8 and 18 years. However, its laxative effects might be unfavorable in combination with specific APIs [24]. Besides the addressed constraints of the available literature, it becomes clear that the limited amount of information could hamper the development of safe 3D-printed pediatric formulations. This limitation emphasizes the need to extend a validated database, such as the STEP database, listing information on the safety and toxicity of excipients for pediatrics.

We created four categories to streamline the decision-making of child-friendly carrier materials; polymers, fats, gelling agents and others. The found studies used different techniques to prepare a semi-solid mixture, so we selected ten available carrier materials to evaluate in the experimental part of this study. We did not examine gelling agents in the experimental part as they need to be mixed with water, and some need to dry to solidify. In the case of ad hoc production in a hospital setting, using gelling agents in 3D-printed formulations might be too complicated as it is time-consuming. Some authors describe the use of chocolate as a carrier material. Out of ethical considerations, we do not consider this a realistic option used in daily clinical practice. The association of chocolate with candies might lead to an extensive intake of the final pharmaceutical product with the risk of overdosing children. Four polymers, five fats and one type of glyceride (Stearoyl polyoxyl-32 glycerides, Gelucire®) were evaluated by our SSE process.

The ten selected materials differed in their DAC processing requirements. For instance, fats needed more lactose to create enough particle friction to reach their melting temperature than polymers. The uniform shape of the saturated fatty acids might result in a tight packing and a crystalline-like structure, making it harder to transform the material into a semi-solid mixture. This transition can be enhanced with higher friction caused by increasing the amount of lactose. Most of the tested mixtures of carrier material and lactose could be processed by DAC in combination with SSE below 80 °C.

For two of the tested materials, it was impossible to create a semi-solid mixture by DAC either the mixture became too viscous (PEO) or too solid (Eudragit®). Picco et al. successfully mixed their formulation of PEO with olanzapine by using DAC, but they dissolved PEO in water to mix [36]. Eudragit® was successfully printed by Kuźmińska et al., but they lowered the viscosity of their formulation by adding plasticizers such as triethyl citrate. Nevertheless, the process temperature remained above our set criteria of 80 °C [19]. Therefore, it seems that Eudragit® is more suitable to process at higher temperatures [20]. From the four polymers tested in the experimental part, PEG 4000 and poloxamer 407 could be extruded by the SSE 3D printer. The success of printing PEG 4000 is consistent with the work of Li and others, even though the mixing and melting steps differ [23]. Instead of using DAC, they mixed in a pestle and mortar for 10 min and heated and stirred the mixture at 70 °C on a heating plate before SSE. Several studies report this method of mixing and melting by hand [22,23]. We prefer DAC to create a homogenous semi-solid mixture in a reproducible way. Poloxamer 407 is described in the production of thermo-sensitive drugs, shown by Kempin et al., which suggests its suitability in SSE.

Mixing by DAC and the extrudability was visually assessed by qualified operators. Although this is a qualitative assessment, this way of determining if the SSE mixture was molten, resulted in successful semi-solid mixtures for SSE. The temperature of the semi-solid mixture was measured quantitative. Furthermore, the force was measured during extrusion and did not exceed the limitations of the printer.

The majority of the selected fats could be processed successfully in the experimental phase. Exceptions were beeswax and glycerol monostearate, as filling the syringe was challenging with these formulations. White beeswax was too liquid, and glycerol monostearate solidified too quickly. Kyobula et al. used white beeswax to print different geometries to tune drug release and dissolution profiles when printing with a piezoelectric inkjet printer [43]. Their work suggested white beeswax as a suitable carrier material. On the contrary, the mixture of lactose and white beeswax did not solidify after SSE in our experiments and could not be clarified. A similar result was observed when extruding adeps solidus. By remaining soft at room temperature, the stability of the end product might be at risk. Adding other excipients to overcome this issue was not part of this study.

Here, we describe the first step in selecting child-friendly carrier materials for SSE printing. By adding more compounds to the mixture, e.g., API, the mixing and melting behavior of the powder mix in the Speedmixer™ might change or lead to different kinds of semi-solid mixtures, influencing the extrusion behavior. Formulating a final product containing API might lead to a different outcome than described here, as particle size and compatibility of the carrier material and API may influence the process. Each combination and addition of API should be further studied.

5. Conclusions

In this study, we aimed to provide a guide on the selection of carrier materials for manufacturing 3D-printed pediatric drugs. We have described 27 different carrier materials which might be suitable for SSE printing between 30 °C and 80 °C. We have assessed their available safety and toxicity data. The STEP database is useful but contains limited information. Furthermore, we have evaluated the extrudability of ten selected materials to assess consistency with the literature using DAC and our SSE 3D printing process. The results showed that studies should be critically reviewed, depending on the preparation method of the semi-solid mixture. Both

PEG 4000 and poloxamer 407 performed well in the extrudability experiments, and their use is generally considered safe in children. Six other carrier materials were successfully printed. A toxicity assessment should be conducted before using them in pharmaceutical 3D printing for pediatric use. Although future studies are needed, this study supports implementing SSE printing of child-friendly drugs.

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Appendix A

PubMed search terms used August 2022.

((((“printing, three dimensional” [MeSH Terms] OR (“printing” [All Fields] AND “three dimensional” [All Fields]) OR “three-dimensional printing” [All Fields] OR (“3d” [All Fields] AND “printing” [All Fields]) OR “3d printing” [All Fields]) AND (“tablet s” [All Fields] OR “tabletability” [All Fields] OR “tableted” [All Fields] OR “tablets” [MeSH Terms] OR “tablets” [All Fields] OR “tablet” [All Fields] OR “tableting” [All Fields] OR “tabletted” [All Fields] OR “tabletting” [All Fields]) AND (“paediatrics” [All Fields] OR “pediatrics” [MeSH Terms] OR “pediatrics” [All Fields] OR “pediatric” [All Fields] OR “pediatric” [All Fields])) OR ((“printing, three dimensional” [MeSH Terms] OR (“printing” [All Fields] AND “three dimensional” [All Fields]) OR “three-dimensional printing” [All Fields] OR (“3d” [All Fields] AND “printing” [All Fields]) OR “3d printing” [All Fields]) AND “drug” [All Fields] AND (“paediatrics” [All Fields] OR “pediatrics” [MeSH Terms] OR “pediatrics” [All Fields] OR “pediatric” [All Fields] OR “pediatric” [All Fields])) OR ((“printing, three dimensional” [MeSH Terms] OR (“printing” [All Fields] AND “three dimensional” [All Fields]) OR “three-dimensional printing” [All Fields] OR (“3d” [All Fields] AND “printing” [All Fields]) OR “3d printing” [All Fields]) AND (“biopharmaceutics” [MeSH Terms] OR “biopharmaceutics” [All Fields] OR “pharmaceutic” [All Fields] OR “pharmaceutics” [All Fields] OR “pharmaceutical preparations” [MeSH Terms] OR (“pharmaceutical” [All Fields] AND “preparations” [All Fields]) OR “pharmaceutical preparations” [All Fields] OR “pharmaceutical” [All Fields] OR “pharmaceuticals” [All Fields] OR “pharmaceutical s” [All Fields] OR “pharmaceutically” [All Fields]) AND (“paediatrics” [All Fields] OR “pediatrics” [MeSH Terms] OR “pediatrics” [All Fields] OR “pediatric” [All Fields] OR “pediatric” [All Fields])) OR ((“printing, three dimensional” [MeSH Terms] OR (“printing” [All Fields] AND “three dimensional” [All Fields]) OR 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Chapter 5

What does pharmaceutical 3D printing cost? A framework and case-study with hydrocortisone for adrenal insufficiency.

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Abstract

Background

Pharmaceutical three-dimensional printing (3DP) technology offers an automated platform which can be utilized to manufacture personalized medicine, improving pharmacotherapy. Although 3D printed products have entered clinical trials, no costing studies have been performed yet. Cost insights can aid researchers and industry in making informed decisions about the feasibility and scalability of 3DP.

Objective

The aim of this research was therefore to develop a framework which can be utilized to estimate the manufacturing cost of one 3D tablet in a hospital pharmacy setting.

Methods

To develop the costing framework, general manufacturing phases were identified, consisting of i) pre-printing, ii) printing, and iii) post-printing. For each phase, cost categories were defined, including, personnel, materials, equipment, facility and quality assurance. The three phases combined with the categories formed the base of the costing framework. An earlier developed 3D printed hydrocortisone formulation (M3DICORT) was used as a case-study. Costs were expressed in 2022 euros (€). The framework was applied to M3DICORT in four scenarios: a base case scenario, worst-case scenario, best-case scenario and a scaling scenario. In the scaling scenario, we assumed that 3D inks were mass produced.

Results

Costs of manufacturing a single M3DICORT tablet were €1.97 - €3.11 (best-case – worst-case) and €1.58 - €2.26 for the scaling scenario.

Conclusion

Manufacturing costs of 3D printed pharmaceuticals were thus far unknown. The framework is translated into an open-access costing tool to facilitate adoption by other parties; and is also applicable for other pharmaceutical 3DP techniques.

Introduction

Pharmaceutical products are often manufactured in bulk and generally effective for most patients. However, some individuals require personalized pharmaceutical products. Therefore, the emergence of three-dimensional printing (3DP) in pharmaceutical manufacturing has attracted significant attention in recent years (1, 2). 3DP has been mainly used in academic research to manufacture personalized oral dosage forms, such as tablets. Several studies have shown that this technology has the potential to improve pharmacotherapy by personalizing the drug dose, release profile, and even adapting taste, appearance, or shape (3-5). The major advantage of 3DP is allowing for personalization of drug dose and release profiles, compared to conventional manufacturing of pharmaceuticals (2). Currently in (hospital) pharmacies, drug formulations are compounded by using manual capsule filling machines or by manipulating existing dosage forms. Both approaches come with safety and quality concerns as these practices may lead to dosing errors, putting patients at risk (6-9). In contrast, studies on 3DP have demonstrated the feasibility of printing personalized medication with varying dose ranges and with high quality (10, 11). For instance, Pietrzak et al. (2015) demonstrated that the tablet dose can be personalized by adjusted the 3D printed tablet size (12). Additionally, Macedo et al. (2022) demonstrated that 3D-printed tablets have intra-batch mass and drug content variabilities are within pharmacopeial limits, indicating high quality (13).Although several studies have been published demonstrating the role of 3DP in drug manufacturing, no formal costing studies have been performed in this field yet (2, 14, 15). However, to successfully move from proof-of-concept to more widespread implementation, insights into economic aspects related to manufacturing process of 3D printed pharmaceuticals are needed, particularly as the first of such products have already entered clinical trials (11, 16). Insight in economic aspects such as resource use and major cost drivers can help researchers and the industry make informed decisions about the feasibility and scalability of 3DP for drug manufacturing. Only with a thorough understanding of all cost items, can the most cost-effective strategies for manufacturing and distribution be identified to facilitate patient access. Cost insights may also be useful for health technology assessment bodies in case of a reimbursement decision, as well as for clinicians, pharmacists, investors, and for policymakers to include economic considerations during guideline development (17, 18). Therefore, the aim of this study was to develop a costing framework to assess manufacturing costs of pharmaceutical 3DP in a small-scale hospital pharmacy setting. The development of the framework, including the manufacturing process of 3D printed products are stated in the methods. The methodology underlying the costing framework is demonstrated through a case study of 3D printed sustained release hydrocortisone for patients with adrenal insufficiency (M3DICORT) (10).

Methods

Framework development.

To develop the costing framework, we first identified the different phases of the 3DP process. The 3DP manufacturing phases were based on our previous experience in pharmaceutical 3DP and reflect the general manufacturing phases. Subsequently, we used the costing framework for a micro-costing study with several scenarios on M3DICORT. The formulation of M3DICORT was developed in previous research using fused deposition modelling (FDM) 3DP, and is described in detail elsewhere (10). The study was conducted at the academic hospital pharmacy of the Erasmus Medical Center (MC), which has a total surface area of 2,654 m^2, 230 full time equivalent (FTE) personnel, and is hence the largest academic hospital pharmacy in the Netherlands.

The costing framework includes three main phases in the 3DP process: i) pre-printing, ii) printing, and iii) post-printing. For each phase, cost categories were identified including personnel, materials, equipment, facility, and quality assurance (QA). These cost categories are based on an existing manufacturing framework for Advanced Therapy Medicinal Products (19).

3D printing process

In phase 1, in the pre-printing phase, a digital 3D model is designed and converted to a readable file for the 3D printer to produce the desired shape. 3D models are designed using generic computer-aided design (CAD) software. These models can be directly accessed through ready-to-use digital designs, available for download in the .stl file format. Once obtained, an .stl file is converted into a geometric-code (g-code) by specialised 3DP software. This g-code entails the precise movements required by the printer, guiding it to accurately reproduce the 3D model layer by layer. The design of the final product is a crucial step in pharmaceutical 3DP as it influences the release profile and supports the manufacturing of specific formulation dosages (5, 10, 20, 21). The detailed manufacturing steps, including the design of the M3DICORT used in this study are described elsewhere (10). Once designed, the g-code can be used over and over.

During the pre-printing phase, drug loaded filaments, which serve as the ink for the 3D printer, are manufactured. To this end, raw pharmaceutical powders are mixed and melted by means of hot melt extrusion, resulting in a printable drug loaded filament. Currently, drug-loaded filaments are not commercially available and have to be manufactured in-house.

In phase 2, the printing phase, the drug loaded filament is manually fed into the 3D printer, after which the tablets are printed layer-by-layer until the final products are formed.

Finally, in phase 3, the post-printing phase, the printed tablets undergo rigorous quality checks and packaging. In pharmaceutical manufacturing lines, quality control (QC) and quality assurance (QA) systems play a crucial

role to guarantee and maintain high quality standards. In terms of QC, both pharmaceutical manufacturing lines, raw pharmaceutical products and final products need to be validated to ensure consistent quality. Typically, this is realized by analysing drug contents, stability, uniformity, homogeneity, and mechanical properties of the final product. Before distribution, batches need to be formally released by a qualified person. Also, during this phase, any used equipment is cleaned, and the printed tablets are packaged, labelled, and stored before transportation. QA involves an active quality management system which proactively prevents product defects and deviations. For instance, by conducting risk assessments, developing standard operating procedures, and comprehensive documentation to ensure that final products meet with predefined quality parameters. As hospital pharmacies generally have QA systems in place, this study limits QA costs to costs related to QA personnel only.

Costing definitions and allocation

For each of the three printing phases, the framework further distinguishes between fixed and variable costs within the following five cost categories:, personnel, materials, equipment, facility, and QA. Fixed costs are defined as all costs that are not correlated with a change in the number of printed products or services, while variable costs are costs that change in proportion to manufacturing output.

To quantify manufacturing costs per identified phase and category, we applied the costing framework following an activity-based costing methodology with which costs were estimated as a function of volume and price per volume (22). We assumed a manufacturer perspective, meaning that only costs incurred by the developer, in this study the Erasmus MC hospital pharmacy, were considered. Consequently, costs for diagnosis, medical interventions and logistics were not included (23).

Fixed costs are defined as the sum of the costs per year divided by the amount of tablets produced annually. For variable costs, we took an opportunity cost approach, to allocate variable cost items. Hence, we valued all time and resources that were spent manufacturing the product of interest and therefore could not be used for other purposes. Historic prices or costs were converted and adjusted for inflation in adherence to the guideline of the Dutch National Healthcare institute (Zorginstituut Nederland; ZIN) on economic evaluations studies (24). All costs stated here are expressed in 2022 Euros (€).

All expenses associated with materials were identified as variable costs and included raw pharmaceutical ingredients, disposable items (such as face masks and gloves), packaging, and labelling materials. Resource use frequencies for these items were based on the M3DICORT development study, with detailed quantities used for this case study provided in the supplementary appendix (10). All these items were valued using retail prices, derived from quotations received by the hospital pharmacy.

All expenses associated with equipment were identified as fixed costs. Equipment needed to manufacture M3DICORT includes an FDM 3D printer, a hot melt extruder to produce filaments, a scale for weighing, a rotor

stator mixer for mixing, and a label printer. Costs for these items were based on their initial acquisition price and an annual depreciation. This depreciation was calculated by dividing the purchase price by an annuity factor that incorporated the lifespan of the respective equipment. The latter was uniformly assumed to be ten years for all equipment items (25). In addition, a standard interest rate of 4.2%, and an annual maintenance markup of 5% of the purchase price was considered for all equipment (19). The annual expenditure for each device was further adjusted based on the printing time per tablet.

For the case study, we assumed that manufacturing is performed by a pharmacy technician and batch release by a qualified person (QP). It is a legal requirement for pharmaceutical manufacturers in the Netherlands to have a QP (26). This QP is responsible for certifying the release of every batch of a pharmaceutical product. By releasing a batch, a QP ensures that the batch complies to applicable laws, requirements of the marketing authorization, and with good manufacturing practices. QP's are typically pharmacists, with additional training on quality of pharmaceutical products. Time needed for weighing, mixing, extruding, printing, cleaning, labelling, and packaging was recorded with a stop-watch. Time for batch-release were based on expert opinion and experience, as 3D printed medication is not formally released yet. Batch release is a quality check performed by a qualified pharmacist after production. If the batch is formally signed and released by the qualified person, it can be distributed, and the batch is then 'released'. Assumed working hours for personnel were 1,558 hours per year, based on a 36 hour workweek, including holidays (27). Personnel times were either valued with their respective salaries gathered from the collective labour agreement from The Dutch Federation of University Medical Centres (Nederlandse Federatie van Universitair Medische Centra; NFU) 2022-2023 for pharmacy staff or with references prices from the Dutch costing manual (28). A correction of 39% was applied to salaries which included holiday payments and social funds (29). Personnel costs related to cleaning, loading ink and QA were considered fixed costs, as they are not influenced by the manufacturing output. Other personnel costs were considered variable. Total FTEs of the 3DP team at our site consist of 3.04% compared to the total pharmacy's FTEs. CAD software is available license-free and 3DP software are usually delivered together with a 3D printer. Simple shapes, such as tablet designs are typically generated for pharmaceutical 3DP. We have not applied costs for designing since the final design is identified during formulation development. Revision control of modelling and slicing software were not considered. Once dimensions and slicing parameters are established and logged, they can be generated easily with other modelling and slicing software.

For facility costs, estimates of surface areas needed for pre-printing, printing and post-printing rooms were made, including non-production rooms. Internal financial data demonstrate general costs of production rooms of €1,467.87 per m^2/year, and for non-production rooms at €698.40 m^2/year. Production room costs were classified as variable costs, and non-production rooms as fixed. For the facility, we assumed that a total of 26 m^2 was needed for manufacturing and storage and 7.6 m^2 for offices, based on internal pharmacy area data.

Based on the 3.04% FTE, the share in m^2 for the non-manufacturing areas (e.g., office, hallway, bathrooms) of the 3D facility was assumed to be the same value in relation to the whole facility.

In the base-case analysis we assumed a manufacturing output of an arbitrary 75% but varied this in scenario analyses to acknowledge variability in manufacturing output. For a precise analysis, we employed a "follow the technician" approach to monitor the duration of all activities across the three phases. More specifically, we measured start and stop time of all activities using a stopwatch, following an experienced technician. The production of 250 cm filament, which can be used to print 164 tablets, took 105 minutes. This includes weighing, mixing and extruding. Hot melt extrusion, used to produce the filaments, is also known as continuous manufacturing (30). In theory, by continuously adding powder to the extruder, an endless length of filament can be produced, enabling tablet printing until the filament is exhausted. Once produced, the filament is fed to the printer, which becomes the production rate-limiting step of the production process with a rate limited to 120 tablets per hour. Assuming a facility run time per year is equal to personnel working hours, (i.e., 1,558 hours per year), a maximum manufacturing output of 186,960 tablets per year could potentially be realised.

Cost of quality management software is not included as all hospital and compounding pharmacies already have a quality management system in place. QC is a component of QA and its incurred fixed costs were considered for validating the manufacturing process, starting material analysis, and mandatory pharmacopeial tests for oral dosage forms. The latter encompass assessments of content uniformity, dissolution, friability, hardness, impurity testing and a stability test (31). The FTE of the QA department reflect the QA department of the Erasmus MC hospital pharmacy.

Per category, QA costs were categorised based on their association either with ink manufacturing or 3D printing the final product. QA expenses specific to ink production were allocated to ink costs, while other attributes were attributed to 3DP. For costs that were related to both categories (i.e., ink production and 3DP), such as some facility expenses, a 50/50% allocation was applied.

Several input parameters for the M3DICORT case study are summarised in Table 1, and more detailed costs of personnel, materials, equipment, facility, and QA are provided in the supplementary material for all scenarios.

Table 1. General input parameters.

Input parameters	Quantity
Working hours personnel and facility run time	1,558 per year
Manufacturing output facility and equipment	186,960 tablets per year
One batch of filament	250 cm
Filament batch manufacturing time	105 minutes
Amount of filament for 1 tablet	1.52 cm
Filament manufacturing time for 1 tablet	0.64 minute
One batch of tablets	50 tablets
Maximum tablet printing rate	120 tablets per hour
FTE QA department/total FTE pharmacy	5-10%
Total personnel costs pharmacy	€17,464,000
Yearly maintenance equipment	5%
Yearly interest rate	4.2%
Total surface area pharmacy	2,654 m^2
Overhead facility	29%
Production room cost	€1,468 per m^2
Non-production room costs	€699 per m^2

Scenario analysis

In three scenario analyses we assessed how different assumption on the operational factors from the base-case would affect M3DICORT manufacturing costs. We specifically varied loss of materials during printing, manufacturing output, batch size, and QA share dedicated to M3DICORT quality.

The worst-case scenario was conceptualised to reflect the challenging operational environment. Here, the material loss during the printing process was highest, set at 20%, indicating significant inefficiencies. The manufacturing output was set at 50%, reflecting potential constraints in demand or operational limitations. This scenario also assumed that the printer would be dedicated to a single product, highlighting limited resource adaptability. Moreover, the QA department's engagement was extensive, with 10% of the total full-time staff focused on M3DICORT tablet testing.

Conversely, the best-case scenario assumed an ideal setting where operational processes are optimized for maximum efficiency. Material loss was reduced to just 1%, indicating highly effective resource use. The primary cause of material loss is residue in the extruder, but this is mitigated with better process control, leading to reduced waste. With higher production output, the relative material loss becomes negligible, supporting the assumption of a 1% loss rate. Manufacturing output was therefore set at 100% of the maximum printing capacity, assuming full utilization of the facility. As a result, 186,960 tablets can be produced annually. This scenario allowed for the printer to be used for two different products, showcasing an efficient allocation of equipment. In all but the best-case scenario, there is an excess capacity available on the 3D printing recourse, allowing for more products to be printed. However, in the best-case scenario, the equipment is fully utilized at 100%, which maximizes output. Consequently, fixed costs are spread across a larger number of units, reducing the per-tablet cost. Additionally, in a typical manufacturing setup, facilities are shared for the production of multiple products. By increasing the variety of products produced, economies of scale are achieved, further reducing costs per unit. In this best-case scenario, we assumed a 50% reduction in the cost per tablet for equipment, facility, and QA expenses. Furthermore, the involvement of the QA department was set at 5% of the total staff, implying a streamlined and effective quality assurance process. The total costs to produce a single M3DICORT tablet for each scenario, except the scaling scenario, was calculated by adding the costs of manufacturing the ink to the costs of 3D printing the M3DICORT tablets.

Finally, in the scaling scenario we calculated manufacturing costs under the assumption that ready-to-use pharmaceutical ink becomes commercially available. The aim was to mirror a realistic, balanced operational model with strategic procurement of filaments that fulfill quality standards and can thus directly be used for printing. We maintained the material loss during printing at 0% to 20%. The manufacturing output was 75%, relative to the maximum printing rate of 120 tablets per hour. This increased output was driven by the assumption that pharmacies would purchase ready-to-use pharmaceutical inks, instead of manufacturing the

filament materials in-house. By acquiring these pre-filled inks, pharmacists could save considerable time. Since purchased filaments would already fulfill certain quality criteria, the QA department's involvement in this scenario was set at 5%, similar to the best-case scenario assumption. Here, we assumed that the manufacturing site is shared by 2-4 products, translating to a 50-75% reduction in costs per product in categories of QA, facility and equipment. We assumed that due to volume discount, materials costs are reduced by 30%. When producing larger amounts of ink, weighing and mixing cost more time, while extruding and cleaning times remain fixed. We therefore assumed that due to scaling effects, personnel costs are reduced by 50%, compared to the base case scenario. The total costs for a 3D printed tablet in this scenario were calculated by adding the ink manufacturing costs to the costs of printing one tablet of the worst-case and best-case scenario.

Results

Based on the developed framework, the pharmaceutical 3DP process is divided into the three phases (i.e., pre-printing, printing, and post-printing) and represented in Figure 1. Within these phases, more intricate processing steps, such as filament manufacturing, are included. The framework is translated into a tool, which is included in the online appendix of this research. In the appendix, both an unpopulated and a populated version of the framework are provided. The unpopulated framework serves as a template for developers to conduct their own cost analyses of 3DP in a hospital pharmacy setting.

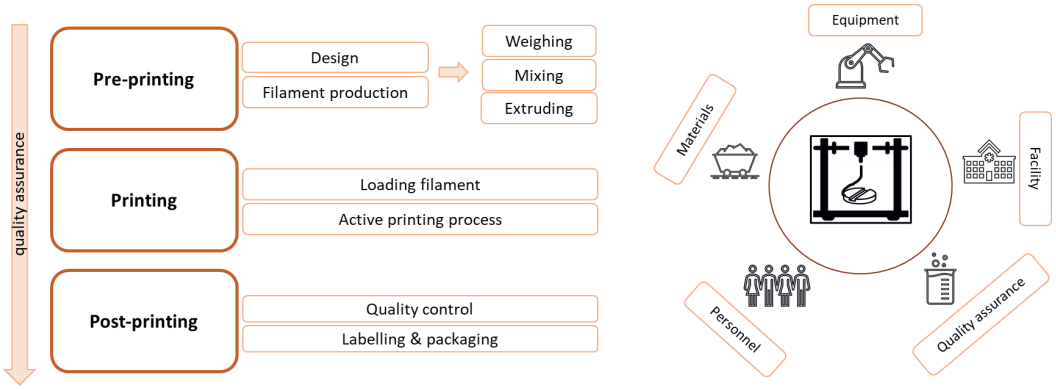


Figure 1 – schematic visual of the framework, including the pharmaceutical 3DP process (left) and cost categories (right).

Based on the framework, input parameters, and assumption, the total cost for manufacturing one 3DP M3DICORT tablet was estimated to be €2.34 in the base-case scenario, €3.11 in the worst-case scenario, €1.97 in the best-case scenario, and between €1.58 to €2.26 in the scaling scenario (Table 2).

Table 2. Assumptions, cost per category and total cost to produce one 3D printed tablet, split in ink manufacturing costs and 3D printing costs, for all scenarios.

Base case scenario			Worst-case scenario		Best-case scenario		Scaling scenario	
• 75% manufacturing output • 10% QA department • 10% material loss • Dedicated facility and equipment			• 50% manufacturing output • 10% QA department • 20% material loss • Dedicated facility and equipment		• 100% manufacturing output • 5% QA department • 1% material loss • Facility and equipment shared by 2 products		• 75% manufacturing output • 5% QA department • 0%-20% material loss • 50% lower personnel costs due to scaling • Shared facility and equipment by 2-4 products	
Category	Ink (€)	Printing (€)	Ink (€)	Printing (€)	Ink (€)	Printing (€)	Ink (€)	Printing (€)
Personnel	0.760	0.593	1.071	0.904	0.721	0.554	0.534	0.554 – 0.904
Materials	0.141	-	0.154	-	0.130	-	0.091 – 0.154	-
Equipment	0.169	0.147	0.110	0.147	0.055	0.073	0.035 – 0.073	0.073 – 0.147
Facility	0.211	0.243	0.297	0.314	0.169	0.209	0.026 – 0.051	0.209 – 0.314
QA	0.037	0.037	0.055	0.055	0.028	0.028	0.028	0.028 – 0.055
Total	1.32	1.02	1.69	1.42	1.10	0.86	0.71 – 0.84	0.86 – 1.42

Discussion

The aim of this research was to provide more insights in manufacturing costs associated with pharmaceutical 3DP. A framework, containing costing categories including personnel, materials, equipment, facility, and QA was therefore established and used to calculate the costs of a 3D printed sustained release hydrocortisone product (M3DICORT) (10). Following this framework and using price and cost estimates in 2022 Euros in the Netherlands, the total cost of one 3DP SR hydrocortisone tablet was estimated to be between €1.58 and €3.11, depending on the scenario. In a setting where a third party manufactures ink in high volumes, cost estimates of the final products can be lower. The ink manufacturing costs in this scenario are between €0.71 and €0.84, which is lower compared to the ink manufacturing costs of all other scenarios. The order of magnitude of the manufacturing costs for 3D printed pharmaceuticals were unknown until now. This study demonstrates that the manufacturing costs of one 3D printed sustained release hydrocortisone tablet is several Euros, which may also be the case for other generic, off-patent drugs. However, costs per tablet as an outcome measure do not reflect reality, as it is unlikely that the process will be conducted to produce just one tablet. Here it rather served as a simple outcome measure which can be used for comparison purposes. Cost per prescription for

e.g., 30 or 90 tablets can be easily calculated based on the costs per tablet. The developed costing framework can also facilitate a cost estimation for other products and 3DP techniques intended for manufacturing by 3DP. The pre-printing, printing and post-printing process applies to all 3D printing techniques and the hydrocortisone can be replaced by other active pharmaceutical substances.

The application of 3DP in fabricating personalized medicine has been researched extensively in the past years. It is a promising technology which allows for personalization of medicines in terms of drug dosage, release profile, drug combinations, shape, and taste (5, 10, 11, 32). The first 3D printed medicines have already been tested in clinical trials (11, 16). This study focused on the manufacturing costs of M3DICORT. A 3D printed sustained release, personalizable hydrocortisone tablet. It was developed for patients with adrenal insufficiency, where the hydrocortisone need differs from patient to patient (10). Currently, there are no sustained release alternatives on the market, of which the dose can be personalized to the need of an individual patient. 3D printing seems a feasible method to make personalized sustained release hydrocortisone available for patients that cannot maintain disease control with alternative hydrocortisone formulations. The prevalence of primary adrenal insufficiency is estimated at between 82–144/million, translating to 1476 – 2592 cases in the Netherlands (33), which is a chronic disease. A total of 2,592 patients treated with once daily hydrocortisone, translates to 946,080 tablets administered per year in the Netherlands. It is unknown which percentage of patients do not have stable disease control and would need a personalized 3D treatment. But the facility described in this study can produce enough for more than 19% of the patient population per year. Production costs per prescription per month, assuming 30 tablets, are €70 per patient in the base case scenario.

It seems very likely that academic university hospital pharmacies and/or large compounding pharmacies adopt 3DP technology first (34). We therefore gathered data from the Erasmus MC hospital pharmacy for the general input parameters. If demand increases, pharmaceutical ink manufacturers may be willing to enter the market. Pharmacies could then purchase ready-to-print inks for manufacturing. Our scaling scenario presents a practical and feasible model for the manufacturing of 3D printed SR hydrocortisone tablets when filaments are commercially available. It illustrates how the strategic procurement of materials, coupled with optimized resource allocation, can lead to efficient printing. Ink manufacturers may be able to offer inks against lower prices due to high volume manufacturing and scaling effects.

The food and drug administration (FDA) has published a proposed rule containing drug products that are difficult to compound, among them are drug products produced using hot melt extrusion (35). This is based on formulation complexity and for instance, compounding process complexity. It is very unlikely that small community pharmacies will use hot melt extrusion to produce filaments which can be printed subsequently. The equipment costs are very high and operating and validating an extruder requires significant training. Rather, large GMP compliant compounding pharmacies that extrude the filaments on a wider scale is a more

realistic scenario. Centralized larger compounding facilities have the knowledge and facility to set up complex compounding methods. Furthermore, the framework applies to other 3DP methods as well, such as Semi Solid Extrusion (SSE). This is a simpler technique without use of a hot melt extruder.

In this study, we used a "follow the technician" approach to record the duration of all activities within the manufacturing process, to offer a detailed perspective on time allocation for each task. This method contributed to the precision of our analysis, highlighting opportunities for enhancing process efficiency. However, it is important to acknowledge the learning curve associated with 3DP technologies, suggesting that the time spent on specific activities can fluctuate based on the technician's and organizations experience. As such, the times measured in this may not be fully representative of those in other facilities with different levels of expertise. Costs for training personnel have not been included, which may also be a limitation of this study.

The main limitation of this study was that this framework only includes manufacturing cost. Of note, not all costing categories associated with the final retail price of a pharmaceutical product were included. These categories include, but are not limited to, Research & Development (R&D), regulatory, profit margins, taxes, marketing, and logistics (36). Especially, R&D costs can have a significant influence on costs and may vary depending on which printing technique is used. In our experience, developing a product with FDM takes much more R&D efforts, and brings therefore higher costs, compared SSE 3DP. This is due to the nature of the inks as the filaments manufactured for FDM printing are challenging to develop as they require a balance in strength, stiffness, hardness, flexibility and thermorheological properties (37). In the case of SSE, the development of the ink might take less time and may therefore be less costly compared to FDM, as the mechanical properties are not relevant with this technique (38). Raw materials are mixed, filled in a syringe and subsequently printed, which is simpler compared to FDM (38). The advantage of FDM compared to SSE is that it is likely easier to manufacture and store in bulk. When comparing this to the current standard of manufacturing magistral medication, which is manual capsule filling, the R&D costs of 3D printed medication may be higher. In manual capsule filling, raw powders are mixed and directly inserted in empty capsules, the R&D costs for this process are minimal (11). Nevertheless, 3DP continues to be researched thoroughly in pharmaceutics and there may be standardized bases for printable inks in the future, in which any drug could be integrated. This would reduce R&D time and costs for developing 3D printed medication.

Profit margins may only be relevant in case pharmaceutical inks are commercialized. The costs of procuring the pharmaceutical inks may in that case be higher than our estimations in this study. It would have been more realistic to add the costs of procuring pharmaceutical inks to the printing costs, instead of the manufacturing costs, in the scaling scenario. There are however no publications related to the procurement costs of pharmaceutical inks. We therefore chose to add the printing costs of the best-case and worst-case scenarios to the ink manufacturing costs of the scaling scenario. In the scaling scenario, costs for filing the pharmaceutical ink for regulatory approval has also not been included but is very relevant. These costs may also increase the price of pharmaceutical inks. Profit margins, mark-ups and marketing costs are less relevant in case 3D printed

magistral formulations are manufactured by hospital pharmacies, which are public entities with no scaling interest. Also, some assumptions, for instance, the 30% reduction of materials costs due to scaling effect, may not reflect reality. The largest driver of savings may after all be the operators time, instead of materials. The framework was developed to give third parties the freedom to insert inputs that better reflect reality to calculate more accurate manufacturing costs.

Another limitation is in the cost calculation of equipment, the calculation is based on the time personnel uses the equipment. This may lead to an underestimation of the fixed costs, the rest of the equipment costs are absorbed by the overhead when the equipment is not in use. Equipment costs can also be calculated by distributing the costs over the annually produced pills. In this case, the output in will greatly affect the unit cost where larger outputs lead to lower unit costs.

We assumed an excess capacity available of the 3D printing resource, allowing for multiple products to be printed using the same equipment, facility and QA. This is a limitation as it may lead to an underestimation of costs. Producing another product with the same equipment and facility may still need investments, for instance of personnel. Although inefficiencies may be introduced by switching to another product, the increased utilization of the equipment will reduce cost per tablet.

Since 3DP makes it possible to adapt the dose and release-profile to the individual patients' needs, there is also a potential in reduction of macro healthcare costs. Adapting the dose and release profile may lead to better therapy control, less side effects and therefore lower healthcare costs in adrenal insufficiency (39, 40). However, this hypothesis has not yet been substantiated. Therefore, further clinical research is needed to investigate pharmacokinetics, effectiveness, and safety of 3DP tablets of M3DICORT and other formulations. The impact on healthcare spending can be further investigated with cost-effectiveness analyses. This study focused on one specific dosage, while the strength of 3D printing lies in manufacturing personalized medicine. Further costing studies are needed to understand the impact of personalization on manufacturing costs.

Conclusion

This study provides a solid framework for estimating manufacturing costs of printing 3D medication in a small scale or hospital setting. It can be used by compounding facilities to understand and optimize the economic aspects of (personalized) 3DP of medication, which is crucial for the wider adoption and success of 3DP technology in pharmaceutical practice. Manufacturing costs of pharmaceutical 3DP was unknown thus far. The developed framework was applied to M3DICORT, where manufacturing costs were estimated to be between €1.58 and €3.11. It seems to be a financially feasible technology to manufacture personalized generic medicines. 3DP enables personalization of medicine, which may in turn lead to a better therapy control and less adverse effects and therefore lower societal costs. More research is needed to confirm this potential.

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Supplementary material

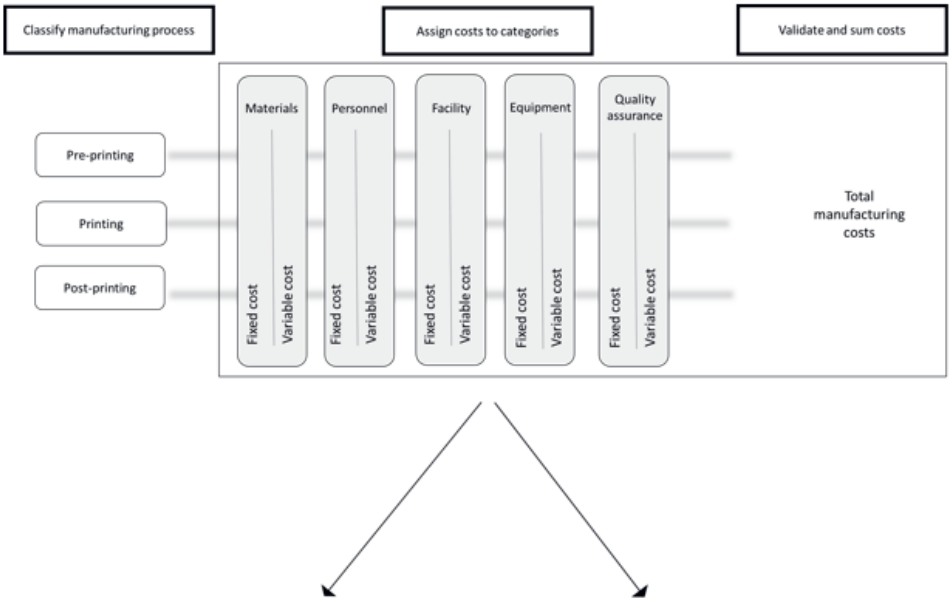
Empty framework

Pharmaceutical 3D printing costing template

Instructions

This template is designed as a tool to help pharmaceutical 3D printing developers to estimate product manufacturing cost.

A comprehensive explanation of use and interpretation of the costing framework and methodology reflected in this template is described in "Ayyoubi et al. 2024". We strongly advise to first read the detailed instructions before using this template.



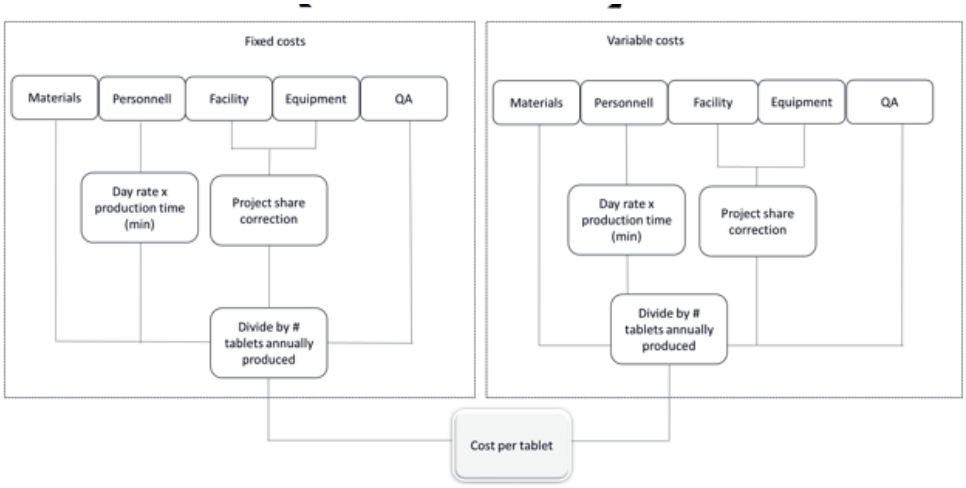


Figure 1: Framework (top) and costing methodology (bottom). Adapted from Ten Ham et al. (2020), with permission.

Waiver of Rights

The authors waive all responsibility and liability for use, application and maintenance of the provided costing template.

Version

Version 1.0. Last updated december, 2023.

	Scenario x		Scenario x		Scenario x		Scenario x		
	Value	Unit	Value	Unit	Value	Unit	Value	Unit	Source
Personnel									
Working hours per year		hours		hours		hours		hours	
Pharmacist assistant salary per year		Euro		Euro		Euro		Euro	
Pharmacist assistant salary holiday pay, social security contributions, benefits		percent		percent		percent		percent	
Pharmacist assistant cost per minute	#DIV/0!	Euro	#DIV/0!	Euro	#DIV/0!	Euro	#DIV/0!	Euro	
Quality Assurance (QA) department salary per year		Euro		Euro		Euro		Euro	
Estimated QA time dedicated to HC3DP		Percent		Percent		Percent		Percent	
QA cost per year	-		-		-		-		
QA cost per minute	#DIV/0!	Euro	#DIV/0!	Euro	#DIV/0!	Euro	#DIV/0!	Euro	
Qualified person costs per year incl holiday, social sec, benefits		Euro		Euro		Euro		Euro	
Qualified person cost per minute	-	Euro	-	Euro	-	Euro	-	Euro	
Materials									
Estimated material loss during production									
Volume discount	-		-				-		
Equipment									
Working hours per year		hours		hours		hours		hours	
Filament batch production time		minutes		minutes		minutes		minutes	
Amount of filament defined per filament batch		cm		cm		cm		cm	
Number of tablets per defined batch		tablets		tablets		tablets		tablets	
Filament use for defined tablet batch		cm		cm		cm		cm	
Filament use per tablet in defined batch	#DIV/0!	cm	#DIV/0!	cm	#DIV/0!	cm	#DIV/0!	cm	
Max tablet printing rate		tablets/hour		tablets/hour		tablets/hour		tablets/hour	
Manufacturing output		%		%		%		%	
Max batches production ouput per year	#DIV/0!		#DIV/0!		#DIV/0!		#DIV/0!		
Max tablets production output per year	0	tablets	0	tablets	0	tablets	0	tablets	
Developing final design		hours		hours		hours		hours	
Facility									
Office		euro/m2		euro/m2		euro/m2		euro/m2	
Laboratory		euro/m2		euro/m2		euro/m2		euro/m2	
Overhead		percent		percent		percent		percent	
Equipment and facility shared by amount of products:		products		products		products		product	
Quality									
Content uniformity		euro/tablet		euro/tablet		euro/tablet		euro/tablet	
Impurities		euro/tablet		euro/tablet		euro/tablet		euro/tablet	
Dissolution		euro/tablet		euro/tablet		euro/tablet		euro/tablet	
Hardness		euro/tablet		euro/tablet		euro/tablet		euro/tablet	
Friability		euro/tablet		euro/tablet		euro/tablet		euro/tablet	
Stability		euro/formulation		euro/formulation		euro/formulation		euro/formulation	
Raw material quality testing per package		euro		euro		euro		euro	

PERSONNEL

Pre-printing

Step	Staff	Cost per minute	Time per batch (250 cm) in minutes	Costs (WC)	Costs (BC)	Costs (SS)	costs (Base Case)	Fixed/variable	Comments
	Pharmacy assistant	#DIV/0!		#DIV/0!					
Weighing	Pharmacy assistant	#DIV/0!		#DIV/0!					
Mixing	Pharmacy assistant	#DIV/0!		#DIV/0!					
Extruding	Pharmacy assistant	#DIV/0!		#DIV/0!					
Cleaning	Pharmacy assistant	#DIV/0!		#DIV/0!					
Total per batch				#DIV/0!					
Total per tablet				#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		

Printing

Step	Staff	Cost per minute	Time (min)	Costs	Fixed/variable
Loading ink	Pharmacy assistant	#DIV/0!		#DIV/0!	
3D printing	Pharmacy assistant	#DIV/0!		#DIV/0!	
Total per batch				#DIV/0!	
Total per tablet				#DIV/0!	

Post-printing

Step	Staff	Cost per minute	Time (min)	Costs	Fixed/variable
Cleaning	Pharmacy assistant	#DIV/0!		#DIV/0!	
packaging/labell	Pharmacy assistant	#DIV/0!		#DIV/0!	
batch-release	Qualified pharmacist	-		-	
Total per batch				#DIV/0!	
Total per tablet				#DIV/0!	

Quality assurance

Scenario	Staff	cost per year	max amount of tablets per year	osts per tablet scenario	osts per tablet scenari	s per tablet scena	osts per tablet scenario	Fixed/variable
WC	**quality assurance**	10.00	0	#DIV/0!				
BC	**quality assurance**	10.00	0		#DIV/0!			
SS	**quality assurance**	10.00	0			#DIV/0!		
BaseC	**quality assurance**	10.00	0				#DIV/0!	

	Scenario x	Scenario x	Scenario x	Scenario x	Scenario x
TOTAL COSTS PERSONNEL	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	#DIV/0!	**#DIV/0!**
Ink	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
3D printing	#DIV/0!	#DIV/0!			#DIV/0!

MATERIALS

Pre-printing

Step	Type	Description	Supplier	Cost per gram/unit	Amount needed for 1 batch (=!	Costs	Source	Fixed/variable
Weighing						-		
Weighing						-		
Weighing						-		
Weighing						-		
Weighing						-		
Weighing						-		
Weighing						-		
Loading ink						-		
Total per batch						-		
Total per tablet						#DIV/0!		

Printing

Step	Type	description	supplier	cost per gram/unit	amount needed for 1 batch (=5	Costs	Source	Fixed/variable

post-printing

Step	Type	Description	Supplier	Cost per gram/unit	Amount needed for 1 batch (=!	Costs	Source	Fixed/variable
Packaging						-		
Packaging						-		
Packaging						-		
Labelling						-		
Total per batch						-		
Total per tablet						#DIV/0!		

	TOTAL COSTS MATERIA	#DIV/0!	Comments
Scenario x	ink	#DIV/0!	
Scenario x	ink	#DIV/0!	
Scenario x	ink	#DIV/0!	
Scenario x	ink	#DIV/0!	
Scenario x	ink	#DIV/0!	

FACILITY

Pre-printing

Room descripti	Comments	Type	Estimated m² needed	Cost per ge	Cost per	Batches	Batches prod	Batches produced per ge	Batches pro	Time use	Cost per batch (	Cost per	Cost per batc	Cost per	Source	Fixed/variable
Weighing/mixing				-	#DIV/0!					0.00	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		
Storage				-		#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		
Storage				-		#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		
Total per batch											#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		
Total per tablet											#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		

Printing

Step	Comments	Type	mated m² needed	Cost per ge	Cost per	Time use	Cost per batc	Source	Fixed/variable
Ink production				-	#DIV/0!	0.00	#DIV/0!		
Total per batch							#DIV/0!		
Total per tablet							#DIV/0!		

post-printing

Step	Comments	Type	mated m² needed	Cost per ge	Cost per	Batches	Time used (h	Cost per batch	Source	Fixed/variable
Labelling/packaging					#DIV/0!		0.00	#DIV/0!		
Storage				-		0.00		#DIV/0!		
Total per batch								#DIV/0!		
Total per tablet								#DIV/0!		

Non production rooms

Room descripti	Comments	Type	M2	ed share for	ost per ge	Cost per	Batches	Batches prod	Batches produced per ge	Batches pro	Cost per	Cost per batch (	Cost per	Cost per batc	Source	ed/variable
Hallways					-		#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		
Kitchen/coffee area					-		#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		
Sanitary area					-		#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		
Offices					-		#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		
Total per batch											#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		
Total per tablet											#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		

	TOTAL COST	#DIV/0!
Scenario x	Ink	#DIV/0!
	3D printing	#DIV/0!
		#DIV/0!
Scenario x	Ink	#DIV/0!
	3D printing	#DIV/0!
		#DIV/0!
Scenario x	Ink	#DIV/0!
Scenario x	Ink	#DIV/0!
		#DIV/0!
Scenario x	Ink	#DIV/0!
	3D printing	#DIV/0!

EQUIPMENT

pre-printing

Step	Description Supplier	Purchase price	Annual ma	Life expec	Cost per year incl	Share (%)	Cost per m	Time used	Costs scenario x	Costs scenario x	Costs scenario x	sts scenari	Costs scenario x	Source	Fixed/variable
							#DIV/0!	0.00	#DIV/0!						
Weighing							#DIV/0!	0.00	#DIV/0!						
Weighing							#DIV/0!	0.00	#DIV/0!						
mixing							#DIV/0!	0.00	#DIV/0!						
ink production							#DIV/0!	0.00	#DIV/0!						
Total per batch									#DIV/0!						
Total per tablet									#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		

Printing

Step	Description Supplier	Purchase price	Annual ma	Life expec	Cost per year incl	Share (%)	Cost per m	Time used	Costs scenario x	Costs scenario x	Costs scenario x	sts scenari	Costs scenario x	Source	Fixed/variable
printing							#DIV/0!	0.00	#DIV/0!						
Total per batch									#DIV/0!						
Total per tablet									#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		

post-printing

Step	Description Supplier	Purchase price	Annual ma	Life expec	Cost per year incl	Share (%)	Cost per m	Time used	Costs scenario x	Costs scenario x	Costs scenario x	sts scenari	Costs scenario x	Source	Fixed/variable
labelling							#DIV/0!	0.00	#DIV/0!						
Total per batch									#DIV/0!						
Total per tablet									#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!		

	TOTAL COSTS EQUIPMENT	**#DIV/0!**
Scenario x	Ink	#DIV/0!
	3D printing	#DIV/0!
		#DIV/0!
Scenario x	Ink	#DIV/0!
	3D printing	#DIV/0!
		#DIV/0!
Scenario x	Ink	#DIV/0!
Scenario x	Ink	**#DIV/0!**
		#DIV/0!
		#DIV/0!
Scenario x	Ink	#DIV/0!
	3D printing	#DIV/0!

Quality assurance

Quality control

Step	Description	Cost n=1	Amount needed for vali	Costs		Source		Fixed/variable	
Validation				€	-				
Validation				€	-				
Validation				€	-				
Validation				€	-				
Validation				€	-				
Validation				€	-				
QA raw materials				€	-				
					Scenario x		Scenario x		Scenario x	Scenario x
Total per batch					#DIV/0!		#DIV/0!		#DIV/0!	#DIV/0!
Total per tablet					#DIV/0!		#DIV/0!		#DIV/0!	#DIV/0!

		TOTAL COSTS QA	**#DIV/0!**
	Scenario x	Ink	#DIV/0!
		3D printing	#DIV/0!
			#DIV/0!
	Scenario x	Ink	#DIV/0!
		3D printing	#DIV/0!
			#DIV/0!
	Scenario x	Ink	#DIV/0!
			#DIV/0!
	Scenario x	Ink	#DIV/0!
		3D printing	#DIV/0!

RESULTS

Scenario	Assumptions	Cost per ink (for 1 tablet)	3D printing costs per tablet	Total per tablet
Scenario x		#DIV/0!	#DIV/0!	#DIV/0!
Scenario x		#DIV/0!	#DIV/0!	#DIV/0!
Scenario x		#DIV/0!	#DIV/0!	#DIV/0!
Scenario x		#DIV/0!	#DIV/0!	#DIV/0!
Scenario x		#DIV/0!	#DIV/0!	#DIV/0!

Lists

This sheet contains all the lists which are used in the drop down menus.

Dropdown menu

QA percentage time dedicated to HC 3DP	type of material	step in fase	type of facility
0%	Disposable	Weighing	Non-production
5%	Raw material	Storage	Production
10%	Container	Weighing/mixing	
	Label	Validation	
		Labelling/packaging	
		Mixing	
		Ink production/printing	
		Ink production	
		Loading ink	
		Printing	
		Packaging	
		Labelling	

Supplementary material

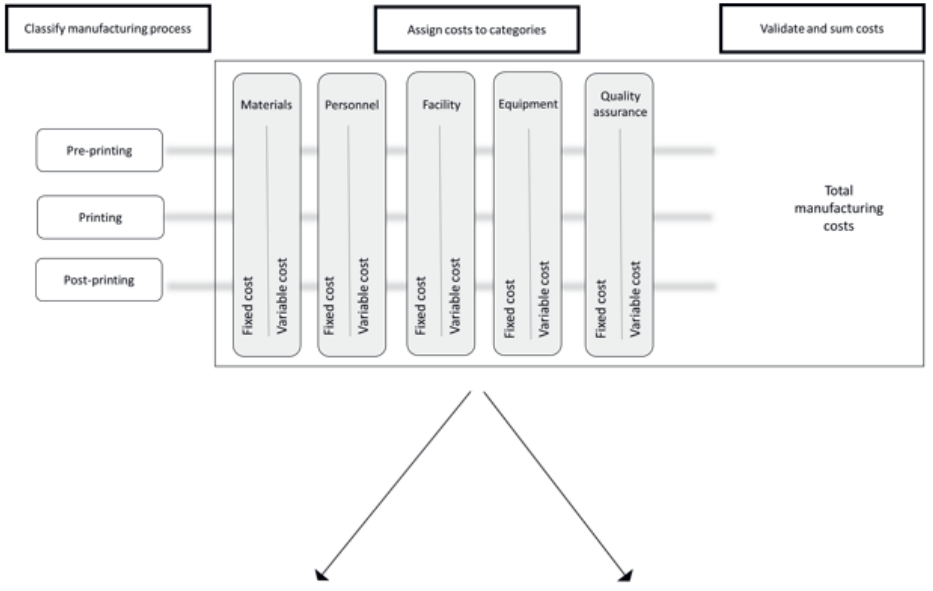
Populated framework for M3DICORT

Pharmaceutical 3D printing costing template

Instructions

This template is designed as a tool to help pharmaceutical 3D printing developers to estimate product manufacturing cost.

A comprehensive explanation of use and interpretation of the costing framework and methodology reflected in this template is described in "Ayyoubi et al. 2024". We strongly advise to first read the detailed instructions before using this template.



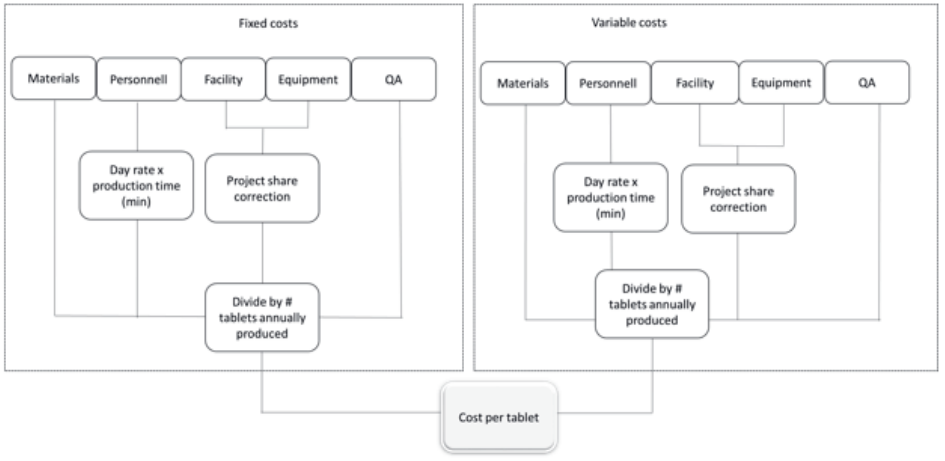


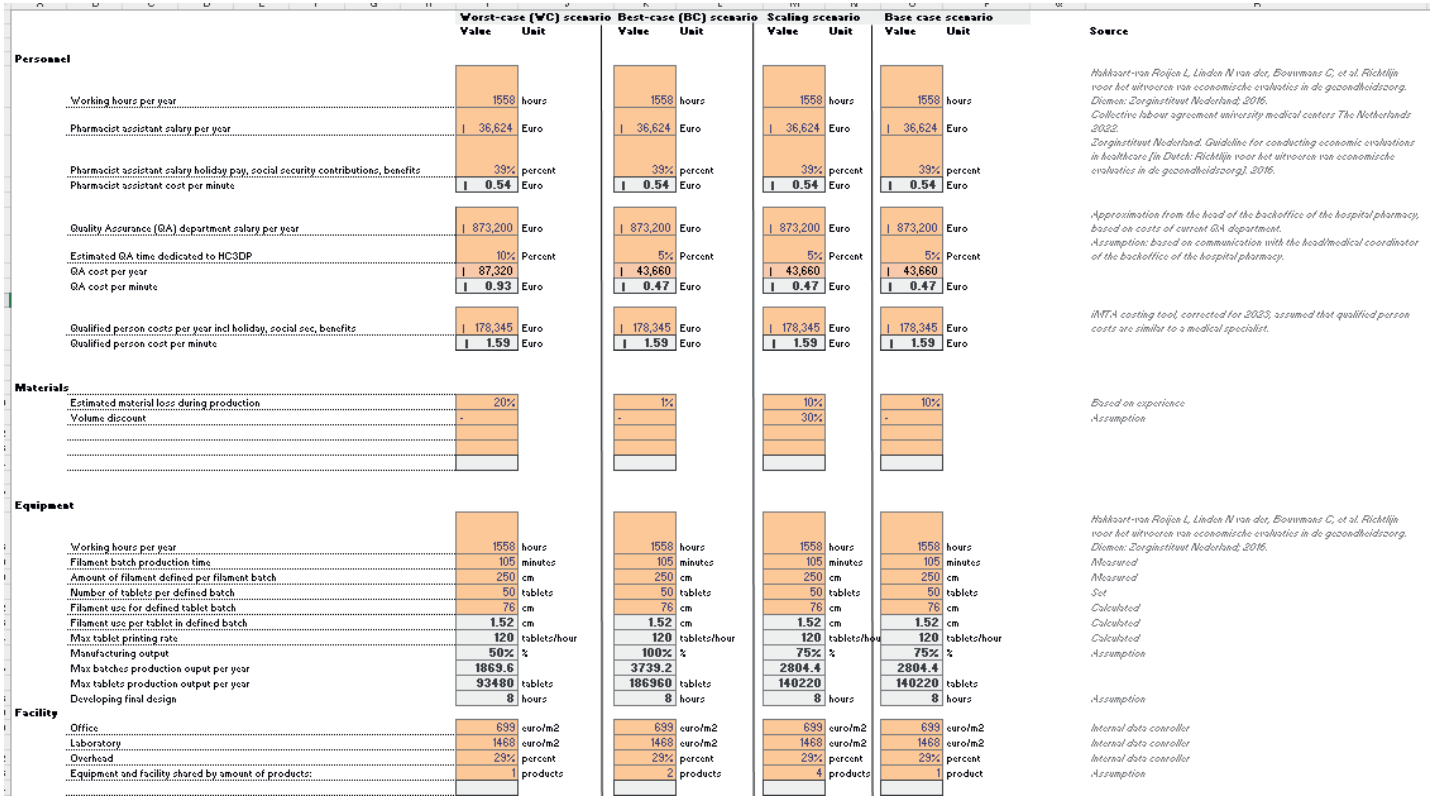
Figure 1: Framework (top) and costing methodology (bottom). Adapted from Ten Ham et al. (2020), with permission.

Waiver of Rights

The authors waive all responsibility and liability for use, application and maintenance of the provided costing template.

Version

Version 1.0. Last updated december, 2023.



	Worst-case (WC) scenario		Best-case (BC) scenario		Scaling scenario		Base case scenario		
	Value	Unit	Value	Unit	Value	Unit	Value	Unit	Source
Personnel									
Working hours per year	1558	hours	1558	hours	1558	hours	1558	hours	Hakkaart-van Roijen L, Linden N van der, Bouwmans C, et al. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. Diemen: Zorginstituut Nederland; 2016.
Pharmacist assistant salary per year	36,624	Euro	36,624	Euro	36,624	Euro	36,624	Euro	Collective labour agreement university medical centers The Netherlands 2022.
Pharmacist assistant salary holiday pay, social security contributions, benefits	39%	percent	39%	percent	39%	percent	39%	percent	Zorginstituut Nederland. Guideline for conducting economic evaluations in healthcare [in Dutch: Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg]. 2016.
Pharmacist assistant cost per minute	0.54	Euro	0.54	Euro	0.54	Euro	0.54	Euro	
Quality Assurance (QA) department salary per year	873,200	Euro	873,200	Euro	873,200	Euro	873,200	Euro	Approximation from the head of the backoffice of the hospital pharmacy, based on costs of current QA department.
Estimated QA time dedicated to HC3DP	10%	Percent	5%	Percent	5%	Percent	5%	Percent	Assumption: based on communication with the head/medical coordinator of the backoffice of the hospital pharmacy.
QA cost per year	87,320		43,660		43,660		43,660		
QA cost per minute	0.93	Euro	0.47	Euro	0.47	Euro	0.47	Euro	
Qualified person costs per year incl holiday, social sec, benefits	178,345	Euro	178,345	Euro	178,345	Euro	178,345	Euro	iMTA costing tool, corrected for 2023; assumed that qualified person costs are similar to a medical specialist.
Qualified person cost per minute	1.59	Euro	1.59	Euro	1.59	Euro	1.59	Euro	
Materials									
Estimated material loss during production	20%		1%		10%		10%		Based on experience
Volume discount	-		-		30%		-		Assumption
Equipment									
Working hours per year	1558	hours	1558	hours	1558	hours	1558	hours	Hakkaart-van Roijen L, Linden N van der, Bouwmans C, et al. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. Diemen: Zorginstituut Nederland; 2016.
Filament batch production time	105	minutes	105	minutes	105	minutes	105	minutes	Measured
Amount of filament defined per filament batch	250	cm	250	cm	250	cm	250	cm	Measured
Number of tablets per defined batch	50	tablets	50	tablets	50	tablets	50	tablets	Set
Filament use for defined tablet batch	76	cm	76	cm	76	cm	76	cm	Calculated
Filament use per tablet in defined batch	1.52	cm	1.52	cm	1.52	cm	1.52	cm	Calculated
Max tablet printing rate	120	tablets/hour	120	tablets/hour	120	tablets/hou	120	tablets/hour	Calculated
Manufacturing output	50%	%	100%	%	75%	%	75%	%	Assumption
Max batches production ouput per year	1869.6		3739.2		2804.4		2804.4		
Max tablets production output per year	93480	tablets	186960	tablets	140220		140220	tablets	
Developing final design	8	hours	8	hours	8	hours	8	hours	Assumption
Facility									
Office	699	euro/m2	699	euro/m2	699	euro/m2	699	euro/m2	Internal data controller
Laboratory	1468	euro/m2	1468	euro/m2	1468	euro/m2	1468	euro/m2	Internal data controller
Overhead	29%	percent	29%	percent	29%	percent	29%	percent	Internal data controller
Equipment and facility shared by amount of products:	1	products	2	products	4	products	1	product	Assumption

Quality

Content uniformity	48	euro/tablet	48	euro/tablet	48	euro/tablet	48	euro/tablet	Quote
Impurities	57	euro/tablet	57	euro/tablet	57	euro/tablet	57	euro/tablet	Quote
Dissolution	57	euro/tablet	57	euro/tablet	57	euro/tablet	57	euro/tablet	Quote
Hardness	0.39	euro/tablet	0.39	euro/tablet	0.39	euro/tablet	0.39	euro/tablet	Quote
Friability	**0.39**	euro/tablet	**0.39**	euro/tablet	**0.39**	euro/tablet	**0.39**	euro/tablet	*Assumed to be similar to hardness*
Stability	**1881**	euro/formulation	**1881**	euro/formulation	**1881**	euro/formu	**1881**	euro/formulation	Quote
Raw material quality testing per package	500	euro	500	euro	500	euro	500	euro	Quote

PERSONNEL

Pre-printing

Step	Staff	Cost per minute	Time per batch (250 cm) in minutes	Costs (WC)	Costs (BC)	Costs (SS)	costs (Base Case)	Fixed/variable	Comments
	Pharmacy assistant	I 0.54		I 4.36					
Weighing	Pharmacy assistant	I 0.54	25	I 13.61				V	
Mixing	Pharmacy assistant	I 0.54	5	I 2.72				V	
Extruding	Pharmacy assistant	I 0.54	15	I 8.17				V	
Cleaning	Pharmacy assistant	I 0.54	60	I 32.67				F	
Total per batch				I 61.54					SS:*0.5 due to scaling effect, producing more ink costs less time
Total per tablet				€ 0.37	€ 0.37	€ 0.19	€ 0.37		

Printing

Step	Staff	Cost per minute	Time (min)	Costs	Fixed/variable
Loading ink	Pharmacy assistant	I 0.54	1	I 0.54	F
3D printing	Pharmacy assistant	I 0.54	18	I 9.80	V
Total per batch				I 10.35	
Total per tablet				€ 0.21	

Post-printing

Step	Staff	Cost per minute	Time (min)	Costs	Fixed/variable
Cleaning	Pharmacy assistant	I 0.54	20	I 10.89	F
packaging/labell	Pharmacy assistant	I 0.54	15	I 8.17	V
batch-release	Qualified pharmacist	I 1.59	2.5	I 3.97	V
Total per batch				I 23.03	
Total per tablet				€ 0.46	

Quality assurance

Scenario	Staff	cost per year	max amount of tablets per year	Costs per tablet WC)	Costs per tablet (BC)	osts per tablet (S:	base case	Fixed/variable
WC	quality assurance	I 87,320.00	93480	I 0.93				F
BC	quality assurance	I 43,660.00	186960		I 0.23			F
SS	quality assurance	I 43,660.00	186960			I 0.23		F
BaseC	quality assurance	I 43,660.00	140220				I 0.31	F

	WC	BC	SS-BC	SS-WC	Base case
TOTAL COSTS PERSONNEL	**I 1.98**	**I 1.28**	**I 0.53**	0.53	**I 1.35**
Ink	I 1.071	I 0.721	I 0.534	I 0.534	I 0.760
3D printing	I 0.904	I 0.554			I 0.593

MATERIALS

Pre-printing

Step	Type	Description	Supplier		Cost per gram/unit	Amount needed for 1 batch (=50	Costs		Source	Fixed/variable
Weighing	Raw material	Hydrocortisone	Duchefa Pharma	€	3.39	1.29	€	4.37	Confidential	V
Weighing	Raw material	Eudragit RL (17,5%)	Evonik	€	0.09	0.75	€	0.07	Confidential	V
Weighing	Raw material	Polyethyene oxide n7!	Colorcon	€	0.03	1.18	€	0.04	Confidential	V
Weighing	Raw material	Magnesiumstearate (1	Duchefa	€	0.05	0.04	€	0.00	Confidential	V
Weighing	Raw material	Hydroxypropylcellulos	Ofipharma (Supplier w	€	0.43	0.71	€	0.31	Confidential	V
Weighing	Disposable	Face masks (FFP1, APF	RS components BV	€	2.48	1.00	€	2.48	Accessed on 2	V
Weighing	Disposable	Gloves nitrile, CL.10	VWR		0.23	2.00	€	0.46	Internal procur	V
Loading ink	Disposable	Gloves nitrile, CL.10	VWR		0.23	2.00	€	0.46	Internal procur	V
Total per batch							€	8.18		
Total per tablet							€	0.16		

Printing

Step	Type	description	supplier	cost per gram/unit	amount needed for 1 batch (=50	Costs		Source	Fixed/variable

post-printing

Step	Type	Description	Supplier		Cost per gram/unit	Amount needed for 1 batch (=50	Costs		Source	Fixed/variable
Packaging	Disposable	Gloves: detaching prin	VWR	€	0.23	2.00	€	0.46	Internal procur	V
Packaging	Container	Sealing bags for ink 10	Henry Schein medical	€	0.04	1.00	€	0.04	Accessed on 2	V
Packaging	Container	Tablet container	Spruyt Hillen	€	0.29	1.67	€	0.48	Confidential	V
Labelling	Label	Zebra PolyPro 3000T	Zebra	€	0.01	1.00	€	0.01	Confidential	V
Total per batch							€	0.99		
Total per tablet							€	0.02		

	TOTAL COSTS MATERIALS		0.13	Comments
Worst-case	ink	€	0.154	20% loss during manufacturing
Best-case	ink	€	0.130	1% loss
Scaling scenario-BC	ink	€	0.091	0% loss, 30% volume discount
Scaling scenario-WC	ink	€	0.154	20% loss during manufacturing
Base case	ink	€	0.141	10% loss

EQUIPMENT

pre-printing

Step	Description	Supplier	Purchase price	Annual ma	Life expec	Cost per year incl	Share (%)	Cost per m	Time used	Costs (WC)	Costs (BC)	Costs (CS-BC)	osts (CS-W	Base case	Source	Fixed/variable
	Fume hood	Interflow	9,490.00	320.00	10.00	1059.26	100.00	0.01	105.00	1.19					Confidential	F
Weighing	Analytical balance (x2)	Mettler toledo	20,000.00	1000.00	10.00	2557.97	100.00	0.03	25.00	0.68					Confidential	F
Weighing	Spoon	Pharma hygiene	9.00	0.45	10.00	1.15	100.00	0.00	25.00	0.00					Accesed on 29-08-2	F
mixing	Rotor stator mixer	IKA CM10 poedermixer	52,920.00	2646.00	10.00	4962.39	100.00	0.05	5.00	0.27					Confidential	F
ink production	Hot melt extr	Thermo Fisher	230,000.00	11500.00	10.00	29416.66	100.00	0.31	15.00	4.72					Confidential	F
Total per batch										6.86						
															CS-BC: equipment shared by 4 products	
Total per tablet										0.14	€ 0.07	€ 0.03	€ 0.07	€ 0.14	CS-WC: equipment	

Printing

Step	Description	Supplier	Purchase price	Annual ma	Life expec	Cost per year incl	Share (%)	Cost per m	Time used	Costs (WC)	Costs (BC)	Costs (CS-BC)	osts (CS-W	Base case	Source	Fixed/variable
printing	3D printer	-	150,000.00	7,500.00	10	30,863.55	100.00%	0.33	18.00	5.94					assumption	F
Total per batch										5.94						
Total per tablet										0.12	€ 0.06	€ 0.03	€ 0.06	€ 0.12		

post-printing

Step	Description	Supplier	Purchase price	Annual ma	Life expec	Cost per year incl	Share (%)	Cost per m	Time used	Costs (WC)	Costs (BC)	Costs (CS-BC)	osts (CS-W	Base case	Source	Fixed/variable
labelling	Label printer	zebra (x2) https://	2319.7	145.99	10.00	373.43	100.00	0.00	15.00	0.06					Accesed on 29-08-2	F
Total per batch										0.06						
Total per tablet										0.00	€ 0.00	€ 0.00	€ 0.00	€ 0.00		

	TOTAL COSTS EQUIPMENT	**0.26**
WC	Ink	0.110
	3D printing	0.147
		0.13
BC	Ink	0.055
	3D printing	0.073
		0.03
CS-BC	Ink	0.035
CS-WC	Ink	**0.07**
		0.069
		0.26
Base case	Ink	0.169
	3D printing	0.147

FACILITY

Pre-printing

Room descripti	Comments	Type	Estimated m² needed	Cost per yea	Cost per	Batches p	Batches prod	Batches produced per ye	Batches prod	Time used	Cost per batch (1	Cost per b	Cost per batch	Cost per	Source	Fixed/variable
Weighing/mixing	of raw materials	laboratory	2	2,936.00	1.88					1.75	3.30	3.30	3.30	3.30	formation	V
Storage	of raw materials	office	4	2,796.00		1869.60	3739.20	3739.20	2804.40		1.50	0.75	0.75	1.00	formation	F
Storage	equipment/tools	office	2	1,398.00		1869.60	3739.20	3739.20	2804.40		0.75	0.37	0.37	0.50	formation	F
Total per batch											5.54	4.42	4.42	4.79		
Total per tablet											**0.11**	**0.09**	**0.09**	**0.10**		

Printing

Step	Comments	Type	mated m² needed	Cost per yea	Cost per	Time used	Cost per batc	Source	Fixed/variable
Ink production	production of fil	laboratory	12	17,616.00	11.31	0.57	6.41	Internal information controller	V
Total per batch							6.41		
Total per tablet							**0.13**		

post-printing

Step	Comments	Type	mated m² needed	Cost per yea	Cost per	Batches p	Time used (hc	Cost per batch	Source	Fixed/variable
Labelling/packaging		laboratory	4	2919.7	1.87		0.29	0.55	Internal information c	V
Storage	of finished prod	office	2	1,398.00		1869.60		0.75	Internal information c	F
Total per batch								1.29		
Total per tablet								**0.03**		

Non production rooms

Room descripti	Comments	Type	M2	ed share for	Cost per yea	Cost per	Batches p	Batches prod	Batches produced per ye	Batches prod	Cost per b	Cost per batch (1	Cost per b	Cost per batch	Source	ed/variable
Hallways		office	531	3.00%	11,130.46		1869.60	3739.20	3739.20	2804.40	5.95	0.34	0.34	0.25	nformation	F
Kitchen/coffee area		office	65	3.00%	1,362.94		1869.60	3739.20	3739.20	2804.40	0.72	2.76	2.76	2.07	nformation	F
Sanitary area		office	17	3.00%	362.49		1869.60	3739.20	3739.20	2804.40	0.19	10.32	10.32	7.74		
Offices		office	930	3.00%	19,502.10		1869.60	3739.20	3739.20	2804.40	10.43	0.19	0.19	0.14		
Total per batch											17.30	13.61	13.61	10.21		
Total per tablet											**0.35**	**0.27**	**0.27**	**0.20**		

	TOTAL COST	**0.61**
WC	Ink	0.297
	3D printing	0.314
		0.26
BC	Ink	0.169
	3D printing	0.209
		0.10
SS-WC	Ink	0.051
SS-BC	Ink	0.026
		0.45
Base case	Ink	0.211
	3D printing	0.243

Quality assurance

Quality control

Step	Description	Cost n=1	Amount needed fo	Costs	Source	Fixed/variable
Validation	Content uniformity	47.55	40.00	1,902.04	Confidential	F
Validation	Impurities	57.08	40.00	2,283.33	Confidential	F
Validation	Dissolution study	57.08	24.00	1,370.00	Confidential	F
Validation	Hardness	0.39	50.00	19.60	Confidential	F
Validation	Friability	0.39	50.00	19.60	Confidential	F
Validation	Stability	1,881.12	1.00	1,881.12	Confidential	F
QA raw materials	Identification/content,	47.55	60.00	2,853.07	Confidential	F

	WC	BC	Base case	CS
Total per batch	5.52	2.76	3.68	2.76
Total per tablet	€ 0.11	€ 0.06	€ 0.07	€ 0.06

TOTAL COSTS QA		**0.11**
WC	Ink	0.055
	3D printing	0.055
		0.06
BC	Ink	0.028
	3D printing	0.028
		0.03
SS	Ink	0.028
		0.07
Base case	Ink	0.037
	3D printing	0.037

RESULTS

Scenario	Assumptions	Cost per ink (for 1 tablet)	3D printing costs per tablet	Total per tablet
Base case	- 75% production output - QA 10% dedicated to 3DP - Facility and equipment shared by 2 products -10% materials loss due to production process	1.32	1.02	2.34
Worst case scenario	- 50% production output - QA 10% dedicated to 3DP - Facility, is not shared - Equipment is not shared -20% materials loss due to production process	1.69	1.42	3.11
Best case scenario	- 100% production output - QA 5% dedicated to 3DP - Facility, is shared with one other product - Equipment is shared with one other product - No material loss in production proess	1.10	0.86	1.97
Scaled ink manufacturer scenario best case	Supplier has shared facility, making multiple inks at the same time - Equipment and facility are shared by 4 products - Materials are purchased at lower cost due to large scale orders (70% of cost) - Personnel costs for ink production part due to scaling, more filament is made in shorter time, cleaning is fixed and takes shorter time per tablet relatively, costs are reduced by 66.6%	0.71	0.86	1.58
Scaled ink manufacturer scenario worst-case	- Shared facility, making multiple inks at the same time - Equipment and facility are shared by 2 products - Materials are purchased at lower cost due to large scale orders (70% of cost) - Personnel costs for ink production part due to scaling, more filament is made in shorter time, cleaning is fixed and takes shorter time per tablet relatively, costs are reduced by 30% - 20% material loss due to production process	0.84	1.42	2.26

Lists

This sheet contains all the lists which are used in the drop down menus.

Dropdown menu

QA percentage time dedicated to HC 3DP	type of material	step in fase	type of facility
0%	Disposable	Weighing	Non-production
5%	Raw material	Storage	Production
10%	Container	Weighing/mixing	
	Label	Validation	
		Labelling/packaging	
		Mixing	
		Ink production/printing	
		Ink production	
		Loading ink	
		Printing	
		Packaging	
		Labelling	

6

Chapter 6

Benchmarking pharmaceutical quality and manufacturing costs of 3D printing against conventional compounding methods for personalization of medicine

Sejad Ayyoubi, Amanda J. Holst, Javier E. Maduro, Hugo P.M. van de Kuy, Renz J. van Ee, Daan van de Velde, Britt Valkenburg, Casey Hennep, Julian Quodbach, Liesbeth J. Ruijgrok

European Journal of Pharmaceutical Sciences 2025;212:107180.

Abstract

Background

Modification of commercially available medicine and pharmacy compounding of personalized medicine is clinical practice when desired oral dosage forms are unavailable. 3D printing is an automated compounding technique that allows pharmacists to personalize oral dosage forms. This study aimed to compare the quality of 3D printing hydrocortisone tablets with conventional pharmacy compounded formulations. Secondary and tertiary aims were to assess manufacturing costs of 3D printed tablets and to explore whether modifying the hydrocortisone drug release profile is possible using 3D printing.

Methods

Semi-solid extrusion (SSE) 3D printing was used to produce immediate release and sustained release hydrocortisone tablets. Conventional compounded hydrocortisone formulations were used as comparators, including pharmacy compounded capsules, split tablets, and commercially available tablets dissolved in syringes.

Results

Immediate and sustained release hydrocortisone tablets were printed successfully. The acceptance values (AVs) of 3D printed tablets, tablet dissolved-in-syringe and one batch of pharmacy compounded capsules were ≤ 15. The AVs of the other 2 pharmacy compounded capsules and split tablets were > 15 and did not comply with content uniformity requirements. Personalization of 3D printed tablets was possible with a dose range of 0.5 – 10.0 mg. Costs of 3D printed tablets were <€ 3.00 per tablet for both release profiles.

Conclusion

SSE 3D printing leads to higher quality hydrocortisone tablets compared to conventional pharmacy compounding methods at acceptable manufacturing costs. 3D printing further allows for modification of hydrocortisone release profiles, which is not possible using conventional manufacturing methods. The low dose minitablets are especially suitable for pediatric indications requiring a personalized hydrocortisone dose.

Introduction

There is a high unmet need for personalized medication, especially in the pediatric population and in rare diseases. Commercial products do not always meet the unique patients' needs. Modifying existing medicines to obtain necessary dosages is common practice for pediatric indications, due to a lack of availability of specific dosages (1-3). Conventional methods of personalizing medicines are manual and involve the modification of existing dosage forms, or compounding of capsules. Modification is defined by the manipulation of marketed medicines, which are split, crushed or dissolved before oral administration (4). This includes orally administering medication off-label that is intended for intravenous use, due to non-availability of oral dosage forms (4). Modifying existing dosage forms is associated with decreased product quality, operator and patient-safety risks. Crushing an existing dose may for instance lower the dose due to drug loss during preparation. Crushing may also change drug dissolution and increase the risk of toxicity (5). Studies that investigated tablet splitting report different outcomes. Some studies report that weight and content variation are minimal, depending on the splitting method (6-8). Others report a high variation in drug dose, and poor compliance with pharmacopeial standards (7, 9). Nevertheless, they all conclude that administering commercial dosage forms is always associated with higher quality compared to modified medication.

In terms of uniformity in content and mass, compounding of capsules may be a better alternative compared to modifying existing tablets. For pharmacy compounded capsules, some studies report high deviations in drug content between capsules, while others report a high quality (10, 11). In one study, compounded hydrocortisone batches were analyzed and 21.4% did not comply with compendial standards (12). Due to their manual nature, conventional compounding and drug manipulation always bear the risk of quality changes in the final product. The associated risk greatly depends on the compounded drug substances. For example, variations in hydrocortisone content of compounded formulations can lead to severe clinical consequences and poor disease control in patients with adrenal insufficiency due to either hypocortisolism or hypercortisolism from overdose (13, 14). Fortunately, these are just individual case-studies where errors were made, and pharmacy compounding remains an essential tool to provide medicines to those in need when no commercial alternatives are available. Although pharmacists in the Netherlands do not need to comply with good manufacturing practice regulations, set for industrial scale manufacturing, there are strict regulations in place to assure quality of pharmacy compounded medicines. The Royal Dutch Pharmacy Association provides guidelines on validation and quality requirements for pharmacy compounded capsules. A risk based, worst-case approach should for instance be maintained to validate the capsule filling method and use it to compound non-standardized formulations. Furthermore, validated analytical methods are used to ensure that the capsule filling method is suitable for compounding capsules. The content requirement for validation is 90-110 % in relation to the declared amount, which is regulated by the Dutch Medicines Act (15).

In recent years, 3D printing (3DP) has been extensively researched for the production of pharmacy compounded medicines (16, 17). 3DP is an automated compounding method and comprises different technologies. Extrusion based 3DP methods such as fused deposition modeling (FDM) and semi-solid extrusion (SSE) are among the most widely researched 3DP techniques in pharmaceutics (18). Not only the drug dose can be personalized with 3DP, but also the drug release, taste and shape of medicines can be tailored (17, 19, 20). This is not possible with conventional compounding techniques, such as manual pharmacy compounding of capsules. One study investigated the viability of SSE for tablet production in a hospital setting using SSE 3DP and compared it with pharmacy compounded capsules (21). Here, the quality of SSE tablets was higher when compared to compounded capsules demonstrated by an average drug content of 4.8 ± 0.1 mg, whereas capsules had an average content of 5.1 ± 1.4 mg. The variation is higher in the capsule group, mainly attributed to one capsule with a drug content of 11.0 mg. Furthermore, interviews with pharmaceutical professionals reveal that they agreed unanimously that SSE makes it easier to produce a specific dose for patients that needs non-standard dosages. Another clinical study assessed the variation in plasma drug concentrations of 3D printed tablets versus compounded capsules (22). This study demonstrated lower variation in plasma

concentrations of 3D printed isoleucine versus pharmacy compounded capsules. Nevertheless, the place of pharmaceutical 3DP in compounding personalized medicine is yet to be established.

The aim of this study is to compare the quality of split tablets, tablets dissolved in syringes, compounded capsules and tablets 3D printed via SSE. Hydrocortisone was selected as the study drug, as there is an unmet need for personalized hydrocortisone for patients with adrenal insufficiency, as described earlier (20). It is also a drug that is widely compounded, and described in case studies regarding compounding or modification errors (12-14, 23).

The secondary aim of this study was to gain insights into manufacturing costs of SSE medication. Until now, only one formal costing analysis has been performed for 3D medication using FDM (24). Manufacturing costs of 3D printed immediate release (IR) hydrocortisone tablets using SSE are unknown. Cost insights may aid the implementation of SSE 3DP in standard pharmaceutical practice of compounding magistral preparations. The tertiary aim was to explore whether modifying the hydrocortisone drug release profile is possible using SSE 3D printing. This was demonstrated earlier for FDM, but unknown impurities were formed due to high processing temperatures (24). SSE 3DP utilizes lower printing temperatures which might be a more feasible solution for a thermolabile drug such as hydrocortisone. Currently, it is not possible to compound modified drug release formulations, where the drug is slowly released for instance. Sustained release (SR), personalized, pharmacy compounded drugs would have a major clinical value in specific patient populations, such as in adrenal insufficiency (20).

Materials

Micronized hydrocortisone (HC) and poloxamer 407 were purchased from Duchefa (Haarlem, The Netherlands). Lactose monohydrate (Sorbolac 400) was provided by Meggle (Wasserburg am Inn, Germany). Kollidon SR was provided by BASF (Ludwigshafen am Rhein, Germany).

Methods

3D printing process

Immediate release hydrocortisone formulations

10 mg hydrocortisone tablets were 3D printed using SSE with the Superion SSE 3D printer (TNO, Eindhoven, The Netherlands). Hydrocortisone (10 % w/w) and two excipients, a filler and a thermoplastic polymer, were weighed and mixed by a Flacktek 330-100SE dual asymmetric centrifugation (DAC) speedmixer (RohChem, Hilversum, The Netherlands). Both the 3D printer set-up and the mixing process have been described before (25). Mixing was performed for 30 s at 750 rotations per minute (RPM), followed by 1 min. at 3500 RPM and 2 min at 3500 RPM. The resulting semi-solid was transferred into a stainless steel syringe and placed in the Superion SSE 3D printer. Both mixing and syringe filling were performed under vacuum to prevent air entrapment. The syringe and nozzle temperature were set to 53 °C. The tablet design was created in Grasshopper software (Robert McNeel & Associates, Seattle, US). The dimensions and printing parameters are stated in Table 1.

Table 1. Tablet dimensions and printing parameters

3D printing parameter	10% formulation
Dimensions height x diameter [mm]	1.6 x 8
Calculated volume [mm^3]	80.42
Layer height [mm]	0.27
Tracks	3
Layers	6
Track width [mm]	1.33

To demonstrate personalization in a dose range of 0.5 mg to 10.0 mg, a 4 % hydrocortisone formulation was developed. The formulation was premixed for 30 seconds at 750 RPM, followed by 2 minutes at 3500 RPM. The syringe temperature was set at 62 °C and the nozzle temperature 64 °C. The following dosages were printed: 0.5, 0.6, 0.9, 1.2, 1.4, 1.6, 2.2, 2.7 and 3.0 mg. Tablet designs and corresponding G-codes were generated with TabletCreator software version 2.1.4.0 (TNO, Eindhoven, The Netherlands). The dosages were used as input in TabletCreator software and the API concentration was set at 4 %. The TabletCreator software, designed specifically for the Superion printer, generates a G-code based on the density of the formulation, API%, intended dosage, and amount of tablets to be printed. Instead of Grasshopper, TabletCreator was used for these experiments for easy dose personalization. The density in mg/mm^3 of the formulation is calculated with the equation given below where r is the radius of the syringe (mm), $\bar{x}$ is the average tablet weight (mg) and E the amount of extrusion per tablet (movement of the piston) in mm.

$$Density = \frac{\bar{x}}{\pi * r^2 * E}$$

Printed tablet dimensions of the 0.5 mg and 3.0 mg were measured with a VWR SS digital caliper (Leuven, Belgium).

Conventional compounding comparators

Three products produced with conventional compounding techniques were included in this study for comparison purposes.

(1) 20 mg hydrocortisone commercial tablets split in two halves with a Livsane Pilomat tablet splitter (BENU Direct BV, Maarssen, The Netherlands) by an experienced pharmacy technician.
(2) 10 mg hydrocortisone commercial tablets dissolved in 50 ml tap water in Nutricair Enteral 60 ml syringes (Mediplast, Elsloo, The Netherlands) for oral use by an experienced pharmacy technician.
(3) 10 mg hydrocortisone capsules ordered from three different pharmacies in the Netherlands for comparison purposes (each n=30).

Adjusting 3D tablet release profile

Preliminary screening studies were performed to assess whether SSE is useful for adjusting the release profile. 10 mg SR hydrocortisone tablets were printed using the method described above. The nozzle temperature was set at 53 °C, and the syringe at 68 °C. The formulation used in this study consists of hydrocortisone 11.5 % (w/w) and a combination of non-soluble and soluble thermoplastic excipients with a filler. TabletCreator software was used with the following input parameters: formulation density was 1.173 mg/mm3, the minimal aspect ratio (MAR) was 0.2 and the drug dose was set at 10 mg. The MAR defines the tablet height – tablet width ratio.

Content determination

Hydrocortisone contents of all formulations were analyzed in-house using ultra-high performance liquid chromatography (UPLC). All formulations were dissolved in volumetric flasks containing 100 ml MilliQ water

containing 0.15 ml of 1M HCl prior to analysis. SR tablets were dissolved in acetonitrile and MilliQ water (1:2.5), tablets were sonicated at 40 °C until no particles were visible. All formulations were sonicated until formulations were completely dissolved. Analysis was performed on a Shimadzu UPLC-DAD system (Shimadzu, Kyoto, Japan). A Shimadzu SIL-30AC autosampler, Shimadzu LC-30AD pumps, Shimadzu CTO-20AC column oven and a Shimadzu SPD-M20A diode array detector were used. LabSolutions 5.99 (Shimadzu) was used to integrate and monitor the sample results for quantification. Chromatographic separation was performed on an Acquity UPLC BEH C18 column (1.7 µm, 2.1 mm x 50 mm) (Waters, Milford, USA) using a gradient consisting of water (eluent A) and methanol (eluent B). Both eluents contained 0.10 % (22 mM) formic acid and 0.013 % (1.7 mM) ammonium acetate. The gradient starts at 40 % B and increases to 60 % B in 0.15 minutes, which is held for 1.25 minutes. Then B increased to 100% in 0.1 minutes followed by stabilization for 0.5 minutes. Then the gradient reverts to initial conditions (40% B) in 0.2 minutes and is stabilized for 1.3 minutes, resulting in a total run time of 3.5 minutes. The flowrate was 0.5 ml/min and the injection volume was 10 µl. The column oven was heated to 50 °C and the detector was set at 246 nm. This method was validated in terms of linearity (0.1 – 250 µg/ml). The lower limit of quantification was 0.1 ug/ml and the upper limit was 250 ug/ml.

Content uniformity

Content uniformity was assessed for 10 mg SSE IR, sustained release tablets and for conventional compounding methods (n=10) according to the European Pharmacopeia (Ph. Eur.) monography of uniformity of dosage units (2.9.40). Acceptance values (AV) were calculated with a target dosage of 10 mg and an acceptability constant of 2.4. Units were selected randomly per formulation. Formulations comply with Ph. Eur. content uniformity requirements when the AV is ≤ 15.

For the 3D printed low dose hydrocortisone IR tablets, contents of n=3 per intended dosage were analyzed.

Dissolution study

Dissolution tests were performed (n=6) for the 3D printed formulations as well as the ordered capsules using a Ph. Eur. apparatus 2 (SOTAX AT7 smart) at 37 ± 0.5 °C and 100 rpm. Adhering to the Ph. Eur. recommendations on dissolution testing (Ph. Eur. 5.17.1.), simulated gastric fluid (SGF) without enzymes (pH 1.2) was used. 1.5 ml samples were collected in a fraction collector (SOTAX C613/C615) with an autosampler (SOTAX 7smart piston pump CY-750) at predefined timepoints. For the IR formulations, sampling timepoints were 15, 30 and 45 min. For the SR product timepoints were 1, 2, 6, 10, 14, 18, 22 and 24 hours.

Stability study

A 3 month stability study was performed according to the International Council for Harmonization (ICH) guideline Q1A(R2) for the SSE 3D printed tablets to assess whether drug loss occurs over time. Tablets (n = 84) 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 3 months. Content determination (n = 10) was performed at the start of the study, after 6 weeks (t = 1), and after 12 weeks (t = 2). Additionally, a dissolution study (n = 3) was performed after 12 weeks to assess if the drug release profile changed. Dissolution study sampling timepoints were 10, 20, 30, 40, 50, 60 and 120 minutes for a more detailed look at the release profile.

Manufacturing costs

We previously published a costing framework that allows for estimation of production costs for 3D printed products (24). This framework was used to calculate the manufacturing costs of 10 mg IR and SR hydrocortisone tablets printed with SSE. Parameters, settings and assumptions that differ from the FDM costing study were adjusted in the framework and are described in table 2. Parameters and settings that remained the same, were only corrected for inflation. The main differences between the FDM costing study and this study are in the

production process, where different equipment is used for SSE, and production times for personnel. The base case scenario of the FDM cost study was used as comparison as it reflects reality best. Production time was registered with a stopwatch while following a skilled operator during production. Quotes were gathered for the raw materials, speedmixer, speedpress and speedcups.

Table 2. Input parameters that differ from the parameters used by Ayyoubi et al. (2024).

Cost element	Value
Speedmixer	€ 10,051
Speedpress	€ 840
Membrane vacuum pump	€ 5,600
Stability indicating HPLC method	€ 15,000
Annual working hours equipment and personnel	1,558
Tablet printing rate per hour	83
Number of tablets produced annually	129,314
Inflation January 2025 – January 2024	3.30 %
Inflation January 2024 – January 2023	3.20 %
Inflation January 2023 – January 2022	7.60 %

For comparison purposes, the costs of the 3D printer (€ 150,000) remained the same as in the previous FDM costing study. Other equipment and materials were based on quotes. Developing a stability indicating method was assumed to cost €15,000. Inflation rates were based on the data of the Dutch central bureau of statistics (26). Costs were adjusted for inflation in adherence to the guideline of the Dutch National Healthcare institute (Zorginstituut Nederland; ZIN) on economic evaluation studies (27). All costs stated here are expressed in 2025 Euros (€).

Results and discussion

Benchmarking content and release of 3D printing and conventional compounding

A 4% hydrocortisone formulation was developed to produce personalized low dose hydrocortisone tablets for pediatrics. The formulation density was 1.29 mg/mm^3, this value was used as input in tablet creator software. Based on this input, TabletCreator software automatically generates G-codes, based on the inserted %API, target dose and number of tablets to be printed. Table 3 shows the target dosage and corresponding theoretical tablet weights as well as the measured tablet weights.

Table 3. Tablet weights of 3D printed low dose hydrocortisone for pediatrics.

Dosage aim (mg)	Theoretical tablet weight (mg)	Mean tablet weight ± Relative Standard Deviation (mg)
0.5	12.5	12.6 ± 2.2
0.6	15.0	15.2 ± 2.1
0.9	22.5	22.7 ± 2.1
1.4	35	35.4 ± 1.9
1.6	40	40.5 ± 1.8
1.9	47.5	47.9 ± 1.8
2.2	55	55.5 ± 1.1
2.7	Theoretical tablet weight (mg)	68.1 ± 0.9
3.0	12.5	76.0 ± 1.2

The 4 % formulation allows for personalization of the drug dose between 0.5 – 3.0 mg (Figure 1). Odd target doses were printed to demonstrate that personalization is possible without loss of quality with a single syringe. 0.9 – 3.0 mg doses were printed with absolute standard deviation from the target dose within 5 % (Figure 1). Doses of 0.5 mg and 0.6 mg demonstrate higher deviations but still within the 10 % limit, set for magistral preparations (28). The 0.5 mg minitablets weigh 12.6 ± 2.2 mg (Table 3), with a diameter of 3.1 ± 0.1 mm and a height of 1.9 ± 0.1 mm. The larger relative standard deviations in weight, e.g., 17.4 % for the tablets weighing 12.6 mg do not align with the low detected relative standard deviations in content. The 12.6 mg tablet had a target dosage of 0.5 %, and while the measured content was higher with 0.54 %, the relative standard deviation of the content is only 1.8 %. The underlying reason for this discrepancy could not be elucidated. The highest dose of 3.0 mg weighed 76 mg and had a diameter of 5.1 ± 0.1 mm and a height of 3.6 ± 0.1 mm.

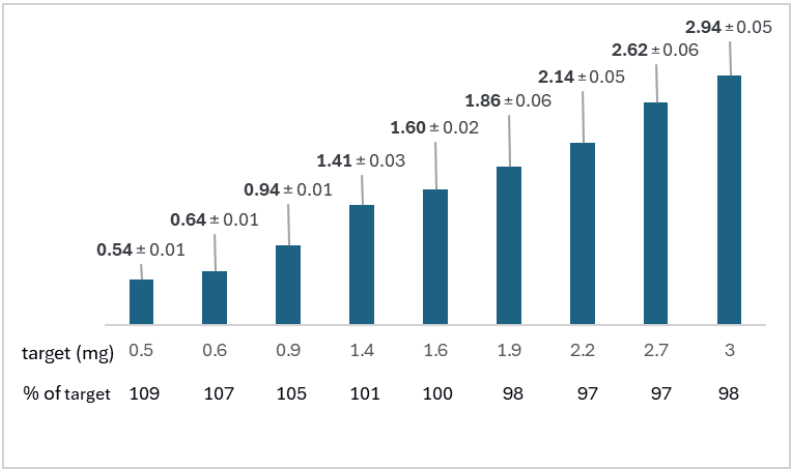


Figure 1. Low dose SSE hydrocortisone tablet contents, showing the mean content in mg ± SD above the bars, as well as target content and % of content in relation to the target.

Furthermore, 10 mg IR and SR hydrocortisone tablets were successfully printed by SSE using a 10 % formulation and compared with other pharmacy compounded methods in terms of content uniformity and dissolution (Figure 2). Content uniformity data demonstrate that the content of SSE 3D printed IR tablets are closest to the target with a content of 102.2 % and a standard deviation (SD) of 0.7 %, which is a lower variation in content compared to the conventional pharmacy compounding methods. The SR 3D tablets demonstrate an AV of 7.7, which is mainly due to the elevated content of 107 % compared to the declared amount. This could be solved by adjusting the tablet size to obtain 100% content. The low standard deviation of 0.8 % shows that high quality batches can be produced with low intra-batch variation in content.

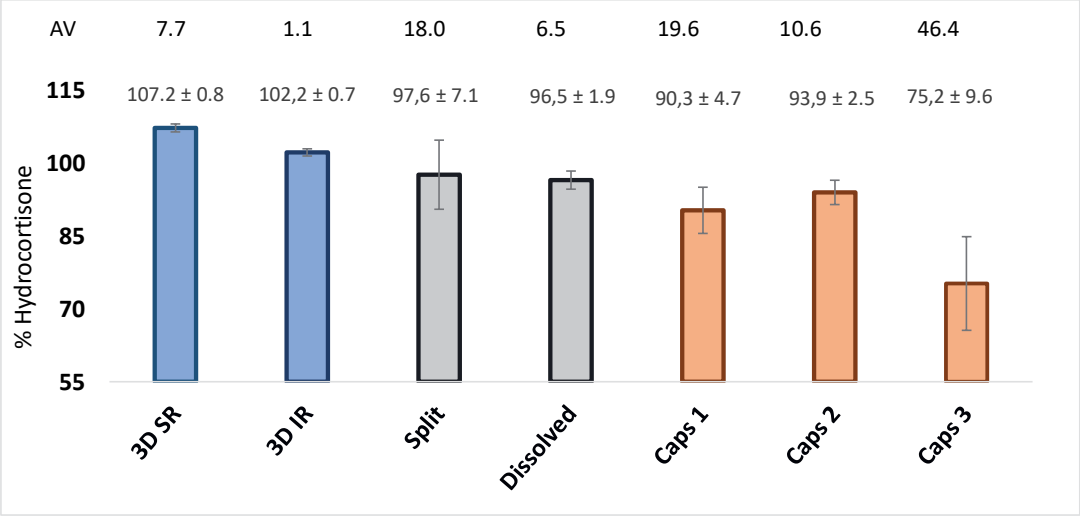


Figure 2. Average content of n=10 units per formulation (in % of declared 10 mg), standard deviation (%) and acceptance values of the 3D printed hydrocortisone formulations (blue) and pharmacy compounded hydrocortisone formulations including: split tablets, dissolved tablets (grey) and capsules (orange).

All formulations, except the split tablets and capsules 1 and 3 comply with the Ph. Eur. requirement of AV ≤ 15. The low AV value of 1.1 for the SSE 3D printed formulations indicates that SSE 3D printed formulations are closest to target and have lowest intra-batch variability with a content of 10.2 ± 0.7 % (Figure 2). Splitting hydrocortisone tablets in adrenal insufficiency is still used in clinical practice for pediatric patients (9, 29). The results of the splitting study reveal high content variations of 7.1 %, which may cause loss of disease control (12). Tablet splitting should therefore not be considered as good clinical practice. Our results corroborate the findings from a study where caregivers split hydrocortisone tablets, resulting in 25 % of caregivers not being able to produce a dose within 20% of the theoretical value (29). Pharmacy compounded hydrocortisone capsules are a common option when commercial dosages are unavailable in clinical practice. In this study, two out of three capsule batches did not comply with the Ph. Eur. requirement of AV ≤ 15, which is similar to results described in literature (11, 12, 30). While the quality of pharmacy compounded capsules usually complies to compendial standards, the content is at the lower end of the targeted content (31). One study demonstrates that there is a risk of API loss during preparation, where adhesion to the mortar surface accounted for the highest amount of API loss (32). In the same study, the API amount in capsules was found to vary between 90 – 97 % of the declared amount. Other reasons for deviation of target in pharmacy compounded capsules may be operator training and skill, or a suboptimal mixing method (33). Another study that compared SSE 3DP with pharmacy compounded capsules also found that SSE printing is closer to the target content with a lower deviation (21). One of the tested capsules had a metoprolol content of >200 %, which was attributed mostly to the large content deviation; excluding this capsule would match the average content of the capsules with the SSE products. In our study, the quality of pharmacy compounded capsules seems to be poorer, which might be due to hydrocortisone being a difficult-to-compound drug demonstrated by the studies mentioned earlier where capsules showed large variations in content. Interviews performed with pharmaceutical professionals regarding SSE demonstrate agreement in the field for adaptation of the technology for compounding (21). Interviewees stressed that it makes it easier to produce personalized doses for patients who need non-standard

doses. The SSE 3DP process in this study differed from our setup, where it required a drying step post printing in a vacuum oven. The SSE production process in our study did not require post printing processing, which makes the printing process even more efficient in hospital pharmacy. Furthermore, the metoprolol study stresses that capsules, which had a size of 4, have relatively large dimensions for a pediatric population. SSE metoprolol tablets had an average diameter of 7.2 ± 0.2 mm and a height of 1.7 ± 0.2 mm, comparable to the dimensions demonstrated in our study.

Drug release studies demonstrate that capsules and 3D printed dosage forms comply with the Ph. Eur. recommendation of 80 % release in < 45 minutes and fall under the definition of an IR product (Figure 3A). 3D printed formulations release the drug more slowly due to the polymer containing matrices, whereas the capsules contain the API as powder. One of the pharmacy compounded capsules only released 88 % of the target dose within 45 minutes. The other capsule batches did reach 100 % whereas content data demonstrated between 90 – 94 % for Capsules 1 and 2. This may be due to inhomogeneity in hydrocortisone content within batches.

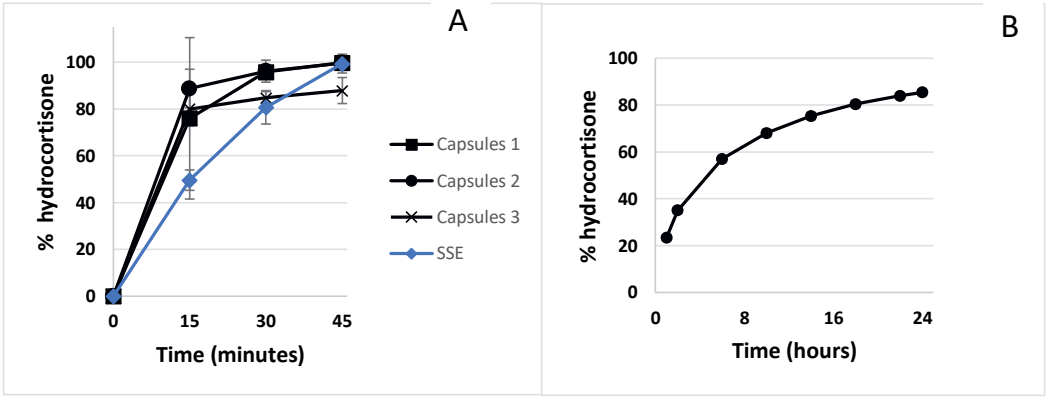


Figure 3. (A) Drug release profiles of the IR 3D printed formulation (blue) and pharmacy compounded capsules (black) in % of 10 mg target. (B) Drug release profile of the SR hydrocortisone formulation (n=6).

The 3D printed SSE SR hydrocortisone formulation released hydrocortisone over 24 hours (Figure 3B). Drug release is > 80 % in 24 hours, complying with the Ph. Eur. recommendation of > 80 % release in the predefined timeframe. Error bars are included in the figure, but the intra-batch variation is < 1.7 % per timepoint, and error bars are not visible. The average hydrocortisone content was 107 %, and was not fully recovered during the experiment, meaning the actual release is longer than 24 hours. An FDM 3D printed SR hydrocortisone product was developed in earlier research, however, the processing temperatures during production were up to 150 °C (20). In FDM printing, the API is exposed to higher temperatures for a longer time, leading to drug degradation and the formation of unknown impurities of hydrocortisone (20). APIs are first exposed to high temperatures for the production of filaments, following exposure to printing temperatures. In this research, a maximum temperature of 68 °C was used. Compared to FDM, the exposure time of API to high temperatures is significantly less, as there is no filament production step. 3D printed SR hydrocortisone tablets have been developed in one study, with a similar 3D printing technique (34). Drug release profiles in this study were determined for up to 15 hours, while patients with adrenal insufficiency require a continuous 24 h cortisol exposure.

Stability

Contents at each stability time point are within 10 % of the target, demonstrating stability (Table 4). However, this should be confirmed with a validated stability indicating analysis method.

Table 4. Hydrocortisone contents (n=10) after production, at t=6 weeks and t=12 weeks in 2 conditions.

	Hydrocortisone content as % of declared content ± SD	
Condition	**25 °C, 60 % RH**	**40 °C, 75 % RH**
After production	102.2 ± 0.7	102.2 ± 0.7
6 weeks	99.9 ± 1.5	99.1 ± 0.8
12 weeks	97.1 ± 0.8	-

At accelerated conditions after 6 weeks, 2 out of 10 samples were not measured due to analysis errors. The result of the remaining samples were well within limits (28). The 12-weeks samples were not measurable due to tablet adhesion to the container caused by softening of the tablets. This might be due to water absorption causing plastification of poloxamer, but this has be confirmed in further research. Tablets should thus be stored at 25 °C, 60 % RH.

Dissolution complied after 3 months at 25 °C, 60 % RH with > 80 % release in 45 minutes (Figure 5). At t=0 after 2 hours, the release was 104.8 % ± 1.4 %, while at t=12 weeks, the release was 102.4 % ± 0.8 %, demonstrating stability in terms of drug release over 12 weeks.

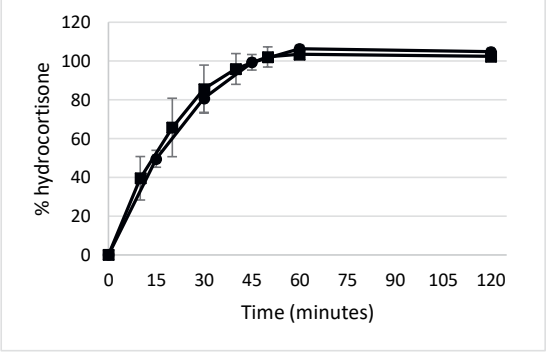


Figure 5. dissolution study data from t=0 (•) and t=12 weeks (▪), n=6.

Degradation products were investigated previously in FDM 3D printed hydrocortisone SR tablets (20). The presence of degradation products was not tested in this study, but the printing temperature used here was much lower compared to processing temperatures in the previous FDM study (110 – 150 °C), which should reduce or completely avoid degradation.

Manufacturing costs

Our analysis indicates that the manufacturing costs of 3D printed SSE IR and SR tablets are € 2.59 and € 2.52 per tablet, respectively (Table 5). In this case, development costs of a stability indicating method were included in the costing framework. The populated costing framework can be found in the supplementary material. Data and costs of production times, equipment, materials, facility, quality assurance and general input parameters have been added to estimate the manufacturing costs. The approach is similar to a previous publication and has been extensively described (24). This study is the first scientific costing analysis for SSE 3D printed tablets, elucidating manufacturing costs.

The previous costing study has been performed for FDM 3D printing, resulting in manufacturing costs of € 2.34 in the base case scenario (24). The base case scenario is a scenario that best reflects the standard practice. Assumptions made for the base case scenario were for instance that the manufacturing output was 75% to acknowledge variability in manufacturing output. 10% material loss was assumed during the production process based on experience during product development. Another assumption was that the facility and process was dedicated to producing a single product. Furthermore, the costs of quality assurance personnel was calculated by assuming that this department dedicated 10% of their time for the pharmaceutical 3D printing process. Other parameters in the base case were a maximum printing rate of 120 tablets per h, annual facility runtime and personnel working hours were 1558 h and an annual manufacturing output of 186,960 tablets. When corrected for inflation, the cost per tablet in the base case scenario is € 2.68, close to the SSE costs. However, the FDM costing study did not consider costs for a stability indicating method and may underestimate the manufacturing costs.

Table 5. Costs of manufacturing of one 3D printed tablet for three different hydrocortisone formulations.

Scenario	Ink manufacturing cost	3D printing cost	Total cost per tablet
SSE immediate release	€1.37	€1.22	€2.59
SSE sustained release	€1.30	€1.22	€2.52
FDM base case	€1.51	€1.17	€2.68

Another study performed a cost-time comparison between conventional compounding of capsules and automated capsule filling using a 3D printer with an SSE head (35). It was concluded that the price of the SSE capsules was 20 % to 35 % lower compared to the conventional compounding method. This research mainly focused on the preparation time of both techniques, excluding costs of, for instance, the equipment and stability testing, which may lead to an underestimation of 3D print costs. Our analysis includes these categories.

Table 6 displays the manufacturing costs per cost category and formulation. Although final costs are similar for FDM and SSE, taking a closer look into the cost categories reveals differences. Personnel costs are the largest driver of costs and similar for the techniques, as tablet production times are comparable. Quality assurance (QA) costs are higher for SSE, as for SSE the costs for a stability indicating method are included. If these costs were included for FDM, the QA costs would be comparable. Future optimization of SSE printing

technology by using multiple nozzles simultaneously, reducing waste and justification that a stability indicating method is not needed, will likely reduce costs per tablet.

In terms of equipment and facility, FDM is more expensive. FDM requires additional equipment, such as a GMP-compliant hot-melt extruder and winder to produce filaments. The extruder is the main cost driver in the equipment category for FDM. It is also the cost driver for the facility in FDM as an extruder necessitates more production area . Detailed costs per category can be found in the costing framework added as Supplementary material. A large advantage, however, is that FDM is better scalable compared to SSE. Hot-melt extrusion is a continuous manufacturing method where hundreds of meters of filament can be produced, packaged and distributed for point of care manufacturing (24). Scaling up could give price-volume advantages. Scaling up SSE 3D printing requires additional development of syringe filling equipment, which constitutes a feasible task.
The economic findings in this study can aid the implementation of 3D printing in clinical practice where SSE would fit better for low volume indications for a limited number of patients. FDM, due to existing scalability options, could be better suited for high volume production where pharmacists purchase filaments and produce personalized doses for their own patients.

Table 6. Manufacturing costs per formulation, per cost category.

Scenario	Personnel	Materials	Equipment	Facility	QA
SSE immediate release	€1.66	€0.15	€0.15	€0.41	€0.21
SSE sustained release	€1.58	€0.16	€0.15	€0.41	€0.21
FDM base case	€1.55	€0.16	€0.30	€0.52	€0.08

The limitations of using this cost calculating approach applied here have been extensively described by Ayyoubi et al. (2024). In summary, the main limitation of this costing approach is that it only accounts for manufacturing costs. Other costing categories, such as R&D, regulatory, profit margins, taxes, marketing and logistics were not considered. Another limitation of this study is that costs of manufacturing manually pharmacy compounded capsules have not been identified. Although one study demonstrated that with 3D printing manual labor is reduced by 55 % and preparation time by 10% compared to conventional capsule filling, a comprehensive cost analysis has not been performed (35). Manual capsule filling will likely be cheaper compared to 3D printing as setting up a stability indicating analysis method is not necessary and due to low cost equipment. 3D printing, however, does allow pharmacists to manufacture personalized medicine with modified release profiles which is impossible with conventional pharmacy compounding methods. The SR tablets can for example reduce tablet intake from three times a day to once daily for patients with adrenal insufficiency, where treatment fits the unmet medical need better compared to registered hydrocortisone tablets (20).

Conclusion

This is the first study to compare the pharmaceutical quality of 3D printed hydrocortisone tablets with other standard methods to personalize oral dosage forms. Hydrocortisone was used as a case drug as it is in the list of most pharmacy compounded drugs for children (3). IR formulations with 4 % and 10 % API load were printed, allowing for accurate dose personalization from 0.5 mg to 10.0 mg. The 4 % hydrocortisone SSE formulation allowed to print minitablets with diameters as small as 3 mm, which is convenient in pediatrics in terms of palatability. SSE 3D printed tablets had the lowest AV of <1.1 and were well within the pharmacopeial requirement. Split tablets and two pharmacy compounded capsules from separate pharmacies did not comply with pharmacopeial content uniformity requirement with AVs of 18.0, 19.6 and 46.4, respectively. Pharmacy compounded capsules were ordered from different pharmacies in The Netherlands, and showed contents between 75 – 94 % of the declared amount. For the 3D printed tablets, the contents were closer to target with 96 – 103 %. These results indicate that 3D printed formulations are of higher quality compared to conventional pharmacy compounding methods. There are multiple case reports with errors in pharmacy compounded hydrocortisone leading to serious clinical adverse events, with most cases in pediatrics (12-14). In these instances, it may be better to use 3D printing for manufacturing personalized hydrocortisone tablets instead of conventional pharmacy compounding methods. Currently the standard of care in the Netherlands for pediatric adrenal insufficiency patients is a 1 mg/ml pharmacy compounded hydrocortisone liquid oral formulation because dosing is based on body surface area (BSA). The recommended hydrocortisone dose is 8-10 mg/m^2 per day divided into two or three doses (36). For a 3 year old with a BSA of 0.63 m^2, the dosing regimen would be 2.5 – 3.2 mg (morning), 1.3 – 2.6 mg (afternoon), 1.3 – 2.6 mg (early evening). The liquid formulation is standard of care because it facilitates easier dosing of the required amounts. It is well known that there is a risk of dosing errors when caregivers prepare and administer liquids (37-39). In this case, and in cases of narrow therapeutic window drugs, 3D printing of tailor-made tablets would provide a safer and high quality alternative.

Costs of SSE printed IR and SR formulations were estimated between €2.50 and €3.00 per tablet, which is similar to earlier published manufacturing cost per tablet of an FDM 3D printed formulation. While pharmaceutical 3D printers are being optimized and scaled up, costs could be reduced in the future. The economic part of this study contributes to the field by providing an economic justification of 3DP manufacturing costs which can be used by decision makers and professionals considering to implement 3DP. Costs of pharmacy compounding were not considered but are likely lower compared to 3DP due to low-cost equipment. In contrast, 3D printing allows for modifying drug release profiles, demonstrated by the SR formulation developed in this study. This formulation releases 80 % of the drug in 24 hours, which cannot be realized by using conventional pharmacy compounding methods. The viability of this technology in hospital pharmacy has already been demonstrated, it is now time to translate it to the clinic for the benefit of patients (21).

However, there remains a gap to be addressed for good clinical implementation of personalized 3D printed medicines. Although 3D printing tablets leads to higher quality magistral products, a downside compared to conventional pharmacy compounding methods, such as manual capsule filling, may be that a stability indicating method is necessary for thermo-sensitive APIs. This is not standard practice for pharmacy compounded capsules. By applying heat and mechanical forces during printing and mixing, this may be necessary for 3D printed products. In the case of hydrocortisone, applying temperatures > 100 °C in FDM led to unknown impurities while thermal degradation data from DSC and TGA suggested degradation > 200 °C, indicating an instability (20). This implies that for hydrocortisone, a stability indicating analysis method is necessary when applying heat during the production process. Developing stability indicating methods can be time consuming, possibly complicating quick responses to arising needs for personalized medicine with 3D printing. A stability indicating method may not be necessary when working with low temperatures, thermostable APIs, and/or if a scientific plausibility check does not indicate thermal instabilities. An open access platform where thermal stability and compatibility data as well as stability indicating analysis methods are shared would aid in the implementation of pharmaceutical 3D printing. The Royal Dutch pharmacy association has a guideline on

preparing pharmacy compounded suppositories where the production technique is based on thermoplastic polymers, similar to 3D printing (40). The guideline states that a shelf-life of 1 month below 25 °C can be given for APIs with unknown chemical of physical stability where a processing temperature of 45 °C or lower has been used. A similar guideline would also aid implementation of 3D pharmaceuticals in clinical practice.

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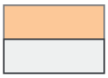
Supplementary material: populated costing framework

Instructions

This template is designed as a tool to help pharmaceutical 3D printing developers to estimate product manufacturing cost.

These cells require user input:

These cells present outcomes based on user input



A comprehensive explanation of use and interpretation of the costing framework and methodology reflected in this template is described in "Ayyoubi et al. 2024". We strongly advise to first read the detailed instructions before using this template.

Personnel						
Working hours per year	1558	hours	1558	hours		Hakkaart-van Roijen L, Linden N van der, Bouwmans C, et al. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. Diemen: Zorginstituut Nederland; Collective labour agreement university medical centers The Netherlands 2024-2025, schaal 6, trede 6 Zorginstituut Nederland. Guideline for conducting economic evaluations in healthcare [in Dutch: Richtlijn voor het uitvoeren van economische evaluaties in de
Pharmacist assistant salary per year	€ 39,060	Euro	€ 39,060	Euro		
Pharmacist assistant salary holiday pay, social security contributions, benefits	39%	percent	39%	percent		
Pharmacist assistant cost per minute	€ 0.58	Euro	€ 0.58	Euro		
Scaling effect, producing more ink costs less time (%)						
Quality Assurance (QA) department salary per year	€ 1,001,627	Euro	€ 1,001,627	Euro		Approximation from the head of the backoffice of the hospital pharmacy, based on costs of current QA department. Adjusted for inflation
Estimated QA time dedicated to HC3DP	5%	Percent	5%	Percent		Assumption: based on communication with the headmedical coordinator of the backoffice of the hospital
QA cost per year	€ 50,081		€ 50,081			
QA cost per minute	€ 0.54	Euro	€ 0.54	Euro		
Qualified person costs per year incl holiday, social sec, benefits	€ 230,735	Euro	€ 230,735	Euro		IMTA costing tool, corrected for november 2024, correction based on consumer price index, assumed that qualified person costs are similar to a medical specialist.
Qualified person cost per minute	€ 2.05	Euro	€ 2.05	Euro		
[PLEASE ADD SPECIFIC TIMES IN THE Personnel TAB]						
Materials						
Estimated material loss during production	10%		10%			Assumption
Volume discount	-		-			Assumption
[PLEASE ADD SPECIFIC MATERIALS IN THE Material TAB]						
Equipment						
Working hours per year	1558	hours	1558	hours		Hakkaart-van Roijen L, Linden N van der, Bouwmans C, et al. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. Diemen: Zorginstituut Nederland;
Filament batch production time		minutes		minutes		
Amount of filament defined per filament batch		cm		cm		
Number of tablets per defined batch	50	tablets	50	tablets		Set
Filament use for defined tablet batch		cm		cm		Calculated
Filament use per tablet in defined batch	0	cm		cm		Calculated
Max tablet printing rate	83	tablets/hour	83	tablets/hour		Calculated
Manufacturing output	75%	Percent	75%	Percent		Assumption
Max batches production ouput per year	2586.28		2586.28			
Max tablets production output per year	129314	tablets	129314	tablets		
[PLEASE ADD SPECIFIC EQUIPMENT IN THE Equiment TAB]						Assumption

Facility								
	Office	€	801.81	euro/m2	€	801.81	euro/m2	*Internal data controller*	adjusted with inflation januari 2025-2022
	Laboratory	€	1,683.91	euro/m2	€	1,683.91	euro/m2	*Internal data controller*	adjusted with inflation januari 2025-2022
	Overhead		29%	percent		29%	percent	*Internal data controller*	
	Equipment and facility shared by amount of products:		1	products		1	products	*Assumption*	
	[PLEASE ADD SPECIFIC FACILITY PARAMETERS IN THE Facility TAB]								
Quality									
	Content uniformity	€	55.06	euro/tablet	€	55.06	euro/tablet	*Quote*	adjusted with inflation januari 2025-2022
	Impurities	€	65.38	euro/tablet	€	65.38	euro/tablet	*Quote*	adjusted with inflation januari 2025-2022
	Dissolution	€	65.38	euro/tablet	€	65.38	euro/tablet	*Quote*	adjusted with inflation januari 2025-2022
	Hardness	€	0.45	euro/tablet	€	0.45	euro/tablet	*Quote*	adjusted with inflation januari 2025-2022
	Friability	€	0.45	euro/tablet	€	0.45	euro/tablet	*Assumed to be similar to hardness*	adjusted with inflation januari 2025-2022
	Stability	€	2,157.65	euro/formulation	€	######	euro/formulation	*Quote*	adjusted with inflation januari 2025-2022
	Raw material quality testing per package	€	573.54	euro	€	573.54	euro	*Quote*	adjusted with inflation januari 2025-2022
	[PLEASE ADD SPECIFIC QUALITY PARAMETERS IN THE QA TAB]								
	Inflation januari 2025 (year to year change)		3.30%		1.033	3.30%		*Central bureau of statistics. Inflation decreases to 3.3 percent in January. Updated 13 february 2025, accessed 17 february 2025, available via https://www.cbs.nl/en-gb/news/2025/07/inflation-decreases-to-3-3-percent-in-*
	Inflation januari 2024 (year to year change)		3.20%		1.032	3.20%		*Central bureau of statistics. Inflation decreases to 3.3 percent in January. Updated 13 february 2025, accessed 17 february 2025, available via https://www.cbs.nl/en-gb/news/2025/07/inflation-decreases-to-3-3-percent-in-*
	Inflation januari 2023 (year to year change)		7.60%		1.076	7.60%		*Central bureau of statistics. Inflation decreases to 3.3 percent in January. Updated 13 february 2025, accessed 17 february 2025, available via https://www.cbs.nl/en-gb/news/2025/07/inflation-decreases-to-3-3-percent-in-*	

PERSONNEL

Pre-printing

Step	Staff	Cost per minute	Time per batch in minutes (IR)	Costs (IR)	Time per batch (SR)	Costs (SR)	Fixed/variable
Preparing	Pharmacy assistant	0.58	10	5.81	10	5.81	V
Weighing	Pharmacy assistant	0.58	8	4.65	5	2.90	V
vacuum	Pharmacy assistant	0.58	5	2.90	3	1.74	V
Mixing	Pharmacy assistant	0.58	5	2.90	4	2.32	V
Syringe filling	Pharmacy assistant	0.58	5	2.90	4	2.32	V
Extruding	Pharmacy assistant	0.58					V
Total per batch				19.17		15.10	
Total per tablet				0.38		0.30	

Printing

Step	Staff	Cost per minute	Time in minutes (IR)	Costs IR	Time in minutes (SR)	Costs (SR)	Fixed/variable
Loading ink	Pharmacy assistant	0.58	1	0.58	1	0.58	F
3D printing	Pharmacy assistant	0.58	22	12.78	36	20.91	V
Total per batch				13.36		21.49	
Total per tablet				0.27		0.43	

Post-printing

Step	Staff	Cost per minute	Time in minutes (IR)	Costs IR	Time in minutes (SR)	Costs (SR)	Fixed/variable
Cleaning	Pharmacy assistant	0.58	30	17.42	30	17.42	F
packaging/label	Pharmacy assistant	0.58	15	8.71	15	8.71	V
batch-release	Qualified pharmacist	2.05	2.5	5.14	2.5	5.14	V
Total per batch				31.27		31.27	
Total per tablet				0.63		0.63	

Quality assurance

Scenario	Staff	cost per year	max amount of tablets per year	sts per tablet scenario	cts per tablet scenario	Fixed/variable
IR	quality assurance	50,081.35	129314	0.39		F
SR	quality assurance	50,081.35	129314		0.39	F

	Scenario IR	Scenario SR	FDM SR
TOTAL COSTS PERSONNEL	**1.66**	**1.58**	**1.55**
Ink	0.89	0.81	0.872
3D printing	0.77	0.77	0.680

MATERIALS

Pre-printing

Step	Type	Description	Supplier	Cost per gram/unit	Amount needed for 1 batch (=50 tabl	Costs IR	Costs SR	Source	ıed/variable
Weighing	Raw material	Hydrocortisone	Duchefa Pharma	€ 3.39	0.50	1.70		Confidential	V
Weighing	Raw material	Poloxamer 407	Duchefa Pharma	€ 0.46	2.00	0.91		Confidential	V
Weighing	Raw material	Lactose Sorbolac 400	Meggle Pharma	€ 0.02	2.50	0.06		Confidential	V
Weighing	Raw material	Hydrocortisone	Duchefa Pharma	€ 3.39	0.50		1.70	Confidential	V
Weighing	Raw material	Kollidon SR	BASF	€ 0.22	1.00		0.22	Confidential	V
Weighing	Raw material	Poloxamer 407	Duchefa Pharma	€ 0.46	2.25		1.03	Confidential	V
Weighing	Raw material	Lactose Sorbolac 400	Meggle Pharma	€ 0.02	1.18		0.03	Confidential	V
Weighing	Disposable	Face masks (FFP1, API	RS components BV	€ 2.51	1.00	2.51	2.51	Accessed on 08-01-2025, availal	V
Weighing	Disposable	Gloves nitrile, CL.10	VWR	€ 0.22	2.00	0.44	0.44	Internal procurement system, s	V
Weighing	Disposable	Speedcups	RohChem	€ 0.41	0.50	0.21	0.21		
Loading ink	Disposable	Gloves nitrile, CL.10	VWR	€ 0.22	2.00	0.44	0.44	Internal procurement system, s	V
Total per batch						6.26	6.56		
Total per tablet						€ 0.13	€ 0.13		

Printing [COPY FROM PRE-PRINTING STEP IF NECESSARY]

Step	Type	description	supplier	cost per gram/unit	amount needed for 1 batch (=50 tabl	Costs	Source	Fixed/variable

post-printing

Step	Type	Description	Supplier	Cost per gram/unit	Amount needed for 1 batch (=50 tabl	Costs	Source	Fixed/variable
Packaging	Disposable	Gloves:detaching prir	VWR	€ 0.22	2.00	0.44	Internal procu	V
Packaging	Container	Tablet container 15 m	Spruyt Hillen	€ 0.22	1.67	0.36	Confidential	V
Labelling	Label	Zebra PolyPro 3000T	Zebra	€ 0.01	1.00	0.01	Accessed on 0	V
Total per batch						0.80		
Total per tablet						€ 0.02		

	TOTAL COSTS MATERIALS	Comments
Scenario IR	0.15	
Scenario SR	0.16	
FDM SR	0.162	

EQUIPMENT

pre-printing

Step	Description	Supplier	Purchase price	Annual ma	Life expec	Cost per year incl	Share (%)	Cost per mi	Time used		Costs SSE	Source	Fixed/variable
Weighing/mixing	Fume hood	Interflow	€ 9,490.00	474.50	10.00	1059.26	100.00	0.01	8.00	I	0.09	Confidential quote	F
Weighing	Analytical balance (x2)	Mettler toledo	€ 20,000.00	1000.00	10.00	2557.97	100.00	0.03	8.00	I	0.22	Confidential quote	F
Weighing	Spoon	Pharma hygiene	€ 9.00	0.45	10.00	1.15	100.00	0.00	8.00	I	0.00	Accesed on 29-08-	F
Vacuum	vacuum	Leybold, TRIVAC D 16 B	€ 5,600.00	280.00	10.00	716.23	100.00	0.01	5.00	I	0.04	Internal procurem	F
mixing	Speedmixer	RohChem SpeedMixer™ (DAC 150.1 FVZ-K)	€ 10,051.00	502.55	10.00	1285.51	100.00	0.01	5.00	I	0.07	Confidential quote	F
Filling	Speedpress	RohChem	€ 840.00	42.00	10.00	107.43	100.00	0.00	5.00	I	0.01	Confidential quote	F
Total per batch										I	0.42		
Total per tablet										€	0.01		

Printing

Step	Description	Supplier	Purchase price	Annual ma	Life expec	Cost per year incl	Share (%)	Cost per mi	Time used	osts scenario SS	Source	Fixed/variable
printing	3D printer	Confidential	€150,000.00	€7,500.00	10	€30,869.55	100.00%	0.33	22.00	I 7.26	Confidential quote	F
Total per batch										I 7.26		
Total per tablet										I 0.15		

post-printing

Step	Description	Supplier	Purchase price	Annual ma	Life expec	Cost per year incl	Share (%)	Cost per mi	Time used	Costs scenario s	Source	Fixed/variable
labelling	Label printer	zebra (x2) https:	2919.7	145.99	10.00	373.43	100.00	0.00	15.00	I 0.06	Confidential quote	F
Total per batch										I 0.06		
Total per tablet										I 0.00		

	TOTAL COSTS EQUIPMENT	I	**0.15**
IR/SR	Ink	I	0.01
	3D printing	I	0.15
		I	**0.30**
FDM SR	Ink	I	0.194
	3D printing	I	0.169

FACILITY

Pre-printing

Room descripti	Comments	Type	Estimated m² needed	Cost per year	Cost per	Batches produced per year	Time used (hc	Cost per batch (scenario	Source	ixed/variable
Weighing/mixing	of raw materials	laboratory	2	3,367.82	2.16		0.38	0.83	information cc	V
Storage	of raw materials,	office	4	3,207.23		2586.28		1.24	information cc	F
Storage	equipment/tools	office	2	1,603.61		2586.28		0.62	information cc	F
Total per batch								2.69		
Total per tablet								0.05		

Printing

Step	Comments	Type	imated m² needed	Cost per year	Cost per	Time used (hour) per batch	Cost per batc	Source	Fixed/variable
Printing	3D printing	laboratory	4	6,735.63	4.32	0.38	1.66	Internal information controller	V
Total per batch							1.66		
Total per tablet							0.03		

post-printing

Step	Comments	Type	imated m² needed	Cost per year	Cost per	Batches produced per year	Time used (hc	Cost per batch	Source	Fixed/variable
Labelling/packa	of finished produc	laboratory	4	5,872.00	3.77		0.29	1.10	Internal information c	V
Storage	of finished produc	office	2	1,398.00		1869.60		0.75	Internal information c	F
Total per batch								1.85		
Total per tablet								0.04		

Non production rooms

Room description	Comments	Type	imated m² nee	Estimated share for 3DP (%)	Cost per year	Batches produced per	Batches produced per year (SR)	Cost per batch (scenario IR)	Cost per batch (scenario SR)	Source	Fixed/variable
Hallways		office	531	3.00%	12,767.48	2586.28	2586.28	4.94	4.94	information cc	F
Kitchen/coffee area		office	65	3.00%	1,551.93	2586.28	2586.28	0.60	0.60	information cc	F
Sanitary area		office	17	3.00%	415.80	2586.28	2586.28	0.16	0.16	information cc	F
Offices		office	930	3.00%	22,370.40	2586.28	2586.28	8.65	8.65	information cc	F
Total per batch								14.35	14.35		
Total per tablet								0.29	0.29		

IR & SR	**TOTAL COST**	**0.41**
	Ink	0.22
	3D printing	0.20
FDM SR	**TOTAL COST**	**0.52**
	Ink	0.242
	3D printing	0.279

cheaper than FDM, due to no use of extruder, less production space is needed

Quality assurance

Quality control

Step	Description	Cost for 1 unit	Amount needed for validation per	Costs	Source	Fixed/variable
Validation	Content uniformity	€ 55.06	40.00	2,202.39	confidential	F
Validation	Impurities	€ 65.38	40.00	2,615.33	confidential	F
Validation	Dissolution study	€ 65.38	24.00	1,569.20	confidential	F
Validation	Hardness	€ 0.45	50.00	22.37	confidential	F
Validation	Friability	€ 0.45	50.00	22.37	confidential	F
Validation	Stability	€ 2,157.65	1.00	2,157.65	confidential	F
QA raw materials	Identification/conten	€ 55.06	60.00	3,303.58	confidential	F
Developing a stabili	HPLC method	€ 15,000.00	1.00	15,000.00	confidential	F
				Scenario SSE		
Total per batch				10.40		
Total per tablet				**€ 0.21**		

	TOTAL COSTS QA		**0.21**
IR/SR	Ink		0.10
	3D printing		0.10
FDM	**TOTAL COSTS QA**		**0.08**
	Ink		0.042
	3D printing		0.042

due to FDM study not including SI HPLC method

RESULTS

Scenario	Assumptions/comments	Cost per ink (for 1 tablet)	3D printing costs per tablet	Total per tablet
SSE immediate release hydrocortisone		€ 1.37	€ 1.22	€ 2.59
SSE sustained release hydrocortisone		€ 1.30	€ 1.22	€ 2.52
FDM base case	corrected for inflation	€ 1.51	€ 1.17	€ 2.68

Lists

This sheet contains all the lists which are used in the drop down menus.

Dropdown menu

QA percentage time dedicated to HC 3DP	type of material	step in fase	type of facility
0%	Disposable	Weighing	Non-production
5%	Raw material	Storage	Production
10%	Container	Weighing/mixing	
	Label	Validation	
		Labelling/packaging	
		Mixing	
		Ink production/printing	
		Ink production	
		Loading ink	
		Printing	
		Packaging	
		Labelling	
		Filling	

7

Chapter 7

General discussion

General discussion

There is a lack of appropriate, commercially available, pharmaceutical treatments for patients with rare diseases (1-4). This also goes for patients with adrenal insufficiency, a rare disease, which is characterized by an insufficient endogenous cortisol production (5). Patients are treated with hydrocortisone, a synthetic form of cortisol, to maintain healthy plasma cortisol levels. However, the commercially available hydrocortisone tablets are not suitable due to a failure in mimicking the natural circadian cortisol rhythm, or lack of dose flexibility (6, 7). Thus, there exists an unmet medical need for a personalized, sustained release, hydrocortisone formulation that more effectively addresses the therapeutic requirements of patients with adrenal insufficiency.

Pharmacy compounding can be used in the absence of an authorized, commercially available treatment (8). Pharmaceutical 3D printing can be utilized as a pharmacy compounding technique for the production of personalized medicine (9). It allows for the personalization of the drug dose, release profile, color, shape, and taste of a pharmaceutical product (10, 11).

We hypothesize that pharmaceutical 3D printing can be used to manufacture a personalized, sustained release hydrocortisone product for patients with adrenal insufficiency. Several efforts are needed to test this hypothesis; one must choose a suitable 3D printing technique, be able to modify the drug release profiles using 3D printing, demonstrate dose flexibility, and test the quality against compendial standards. Furthermore, to aid implementation, quality and cost insights should be identified and compared against conventional pharmacy compounding methods. The studies presented in this thesis aim to contribute to these knowledge gaps. **Table 1** summarizes the key findings and messages from the included studies.

Table 1. *Key findings and messages of this thesis.*

Ch.2	• Drug dissolution in fused deposition modeling (FDM) 3D printing can be modified by adjusting the type or concentration of excipients and adjusting the surface-area-to -volume ratio in the digital design.
Ch.3	• A 10 mg sustained release hydrocortisone formulation was developed for patients with adrenal insufficiency with FDM 3D printing. • Tablet height was correlated with the drug dose, which provides an easy method to personalize the drug dose. • Thermal degradation of hydrocortisone was observed due to exposure to high processing temperatures used in FDM. Temperature as well as the thermal exposure time affected thermal degradation.
Ch.4	• SSE is more suitable for the manufacturing of thermolabile drugs, such as hydrocortisone. • Common excipients, such as poloxamer 407 and polyethylene glycol 4000 can be used as a matrix with good printing properties in SSE. • These excipients are also safe for use in children.
Ch. 5	• An open-access costing tool was developed to calculate the manufacturing costs of 3D printed medicines. • The manufacturing cost of one FDM 3D printed 10 mg hydrocortisone tablet was between €1.58 - € 3.11.
Ch.6	• Immediate release and 24 h sustained release hydrocortisone tablets can be successfully printed using SSE. • The quality of SSE 3D printed hydrocortisone is higher compared to manipulated and conventionally compounded hydrocortisone capsules. • The manufacturing cost of one SSE 3D printed 10 mg sustained release hydrocortisone tablet is similar to the cost of an FDM tablet presented before.

Suitability of 3D printing as a pharmacy compounding method

The studies presented in this thesis focus on SSE and FDM 3D printing. However, 3D printing refers to a diverse group of manufacturing technologies with their own advantages and disadvantages regarding medicine production. In this section, we describe the properties of the most researched technologies in pharmaceutics. The suitability of these technologies are addressed in the context of pharmaceutical 3D printing as a pharmacy compounding method,

The most researched 3D printing technologies in pharmaceutics are binder jetting, VAT polymerization, powder bed fusion, material jetting and material extrusion (12-14). In binder jetting, a liquid binding solution is deposited by the printer nozzle onto a powder bed which contains powder particles (15). The wetted powder particles adhere together layer-by-layer, forming the final product. Due to the large equipment and lack of flexibility in product design, binder jetting is less suitable for point of care manufacturing compared to other 3D printing techniques (13, 15). It is, however, used by Aprecia Pharmaceuticals for industrial-scale production of fast disintegrating tablets (16). Powder bed fusion 3D printing is similar to binder jetting, with the main difference being a laser or beam that is directed onto the raw powders for adhesion, instead of liquid (17). In material jetting, liquid droplets are deposited onto a platform which are then cured or solidified (15). Although this technique seems promising, the technology is still at an early stage regarding pharmaceutical 3D printing. Researchers often adapt commercial desktop material jetting printers, resulting in limitations in terms of pharmaceutical quality (18).

In VAT polymerization 3D printing, a light beam is directed into a liquid photopolymer solution. The photopolymers solidify due to the light beam, forming the final product. This technology is also less suitable in a hospital pharmacy setting compared to others due to the lack of safe polymers and photo-initiators for human use (19). In conclusion, material extrusion techniques such as FDM and SSE seem most promising in pharmacy compounding due to the high number of formulation development-, implementation- and clinical publications, simple and relatively inexpensive equipment, and commercially available pharmaceutical printers (13, 15, 20-24).

Our work in **Chapters 3 and 6** demonstrated that SSE is more suitable compared to FDM for printing thermolabile medicines due to the use of lower processing temperatures, while maintaining critical quality attributes such as a sustained dissolution profile. The lowest processing temperature used to manufacture sustained release hydrocortisone in FDM was 110 °C, while the highest temperature in SSE was 68 °C. Furthermore, in **Chapter 3**, we found that the thermal exposure time also increases thermal degradation. A slower printing speed led to more degradation of hydrocortisone. In FDM, the API is exposed to higher temperatures for a longer time, mainly due to the use of hot melt extrusion for the production of filaments (25).

Studies report efforts to reduce the FDM extrusion and printing temperature to as low as 70 °C and 90 °C, respectively, for thermolabile drugs (26, 27). However, this is still a higher temperature and longer exposure time compared to temperatures and thermal exposure times in SSE. In terms of suitability in a hospital pharmacy setting, SSE seems therefore to be the most promising technique in pharmacy compounding, especially for thermo-sensitive APIs.

Thermal implications

Usually, elevated temperatures are used in pharmaceutical 3D printing. Temperature is therefore identified as an important critical process parameter in extrusion-based pharmaceutical 3D printing (28, 29). It is a factor that appears in most chapters of this thesis. This section is therefore dedicated to our formulation development work in the context of processing temperatures and thermal stability.

High processing temperatures used in FDM led to the formation of unknown impurities in the final product, as described in **Chapter 3**. The extrusion and printing temperatures were initially set at 170 °C and 200 °C respectively, resulting in a hydrocortisone recovery of 70.9 % ± 1.2. To increase the recovery, processing temperatures were lowered by 10 °C steps until printing failure. We were able to lower the extrusion and printing temperatures to 110 °C and 150 °C, respectively, which resulted in an average recovery of 100.4 % ± 5.5. However, four unknown impurities with concentrations > 0.2% were found at even the lower processing temperatures. Finally, we lowered the hot melt extrusion transit-time to decrease thermal exposure, which resulted in 2 unknown impurities. Unknown impurities with a concentration of > 0.2 % and > 0.5 % should be identified and qualified, respectively (30).

Identification and qualification of unknown impurities can be time-consuming and costly (31). It requires, for instance, the development and validation of suitable analytical methods for the identification and quantification of the impurities, which could also be outsourced (30). Furthermore, acceptance criteria of the unknown impurities should be established based on the biological safety of the unknown impurity, which requires a toxicological assessment (30). Instead of identification and qualification of the unknown impurities, we chose to change the manufacturing technology to SSE 3D printing, which is characterized by lower processing temperatures and thermal exposure times (32).

Before developing a sustained release formulation using SSE, we first screened 27 suitable carrier materials for SSE printing, presented in **Chapter 4**. The excipients were screened for printability at a temperature below 80 °C. Dual axial centrifuge (DAC) mixing was applied to obtain semi-solid material. We found that lactose in combination with PEG 4000 or poloxamer 407 could be successfully extruded by the printer. Other carrier materials were less suitable, either due to safety risks in children or because of errors in forming a semi-solid material, syringe filling, or extrudability. Glycerol monostearate was, for instance, hard to process due to fast solidification. This prevented proper syringe filling, as it requires the material to have a certain softness during filling. Furthermore, we found that the formation of good semi-solid material is dependent on the ratio of lactose/carrier material. More lactose was needed to cause enough friction for the fat-based excipients to melt during DAC. Factors affecting semi-solid material formation, extrudability and printability were thermal properties of excipients (e.g. melting point and glass transition temperatures), viscosity, ratio of excipients, and solidification speed of the semi-solid material. These factors were also identified as critical in other printability studies (33-36) .

The findings in **Chapter 4** were used to formulate immediate and sustained release hydrocortisone formulations with SSE, using low temperatures.

Chapter 6 presents results of immediate and sustained release formulations for adrenal insufficiency using SSE. The processing temperature did not exceed 68 °C, while critical quality attributes such as content uniformity and dissolution profiles complied with compendial requirements. However, impurities may not have been detected due to the lack of a stability-indicating analysis method. This is a limitation of the study presented in **Chapter 6**. A stability-indicating analysis method, including a forced thermal degradation study, should therefore be applied before clinical implementation. This is also underlined in the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (ICH) guideline on the validation of analytical procedures (37). It states that a demonstration of stability-indicating properties through appropriate forced degradation samples are needed.

Our findings identify temperature and thermal exposure time as critical process parameters (CPP) in pharmaceutical 3D printing, which is also supported by other studies (28, 29). In one study, authors performed a risk analysis of CPPs on critical quality attributes (CQA) and found that pre-heating of the cartridge in SSE printing can have a high impact on the drug content, homogeneity, and weight uniformity of the final product (29).

A stability-indicating analytical method may be redundant when providing a rational scientific justification that the API is thermally stable at the used processing temperatures and thermal exposure times. This should be documented in a risk-analysis prior to validation of the manufacturing process.

Chapters 2 and 3 describe the use of thermogravimetric analysis (TGA) to estimate the thermal degradation temperature of nifedipine and hydrocortisone. TGA is also used by others for this purpose (27, 38). As TGA only reflects loss of volatiles, it may be useful for an indication of physical degradation, but does not take into account the formation of degradants, or potency loss (39). This is also illustrated in **Chapter 3,** where TGA data show that hydrocortisone is stable above 200 °C, but unknown impurities were still formed with processing temperatures of ≤ 150 °C. Next to heat, thermal exposure time, mechanical stress, moisture, and excipients may also have an influence on stability (26). This underlines the need for a stability-indicating analytical method.

Generally, there is little information available on the thermal stability of APIs. An open-access platform where thermal stability data is shared would greatly aid in the broader implementation of pharmaceutical 3D printing.

Modification of the drug release profile

In order to develop a sustained release hydrocortisone tablet for patients with adrenal insufficiency, we first explored the factors that influence the drug release in FDM 3D printing. At that time, there was only literature on sustained release products manufactured with FDM, hence the use of FDM 3D printing. **Chapter 2** presents 3D printed sustained release formulations using nifedipine, which was selected as a model drug.

The type of excipients significantly influenced the dissolution profile of nifedipine. Kollidon VA 64, a water-soluble co-polymer, was found to enhance the drug release rate of 3D printed nifedipine (40). While ethyl cellulose, a water-insoluble polymer, decreased the drug release rate of 3D printed nifedipine (41). Ethyl cellulose based formulations did not release the complete dose within 24 hours.

The design had a more limited effect on the release rate. The surface area of the final product was increased by 1.6-fold, which led to a faster release rate. However, this formulation also contained a higher concentration of Kollidon VA 64. The increased release rate in this study can therefore not only be attributed to the higher surface area.

Others have shown that the design does influence the release rate of a 3D printed product. In one study, an infill of 100 % led to a slower release rate compared to a 65 % infill setting (42). 80 % of the drug was released in 15 minutes and 50 minutes, using 65 % and 100 % infill, respectively. The infill % refers to the volume that fills the inside of an object. Setting the infill at 100% leads to a complete fill inside the object. Setting it at 50% leads to cavities inside the object, in this case, the object carries a higher surface area inside. The relationship between the infill and surface area is, however, not linear (42).

We used this knowledge to develop a 3D printed, 10 mg sustained release hydrocortisone formulation for patients with adrenal insufficiency. **Chapter 3** presents drug release data of 10 mg hydrocortisone tablets manufactured with FDM 3D printing. These ring-shaped tablets released hydrocortisone gradually over 24 hours. The dissolution profiles within a batch and between batches were stable, demonstrated by an intra-batch variability of < 2.78 % and a similarity factor f2 of 54.7. Hydroxypropyl cellulose and polyethylene oxide were used as polymeric matrix formers. Formulations containing Kollidon VA 64 and ethylcellulose did not have the desired sustained release effect over 24 hours or did not meet the European Pharmacopeia (Ph.Eur.) recommendation of > 80 % release in 24 hours.

The dissolution profile of 3D printed hydrocortisone was compared to Plenadren, a commercially available, dual-release hydrocortisone formulation authorized for patients with adrenal insufficiency. Plenadren exerts an initial burst in hydrocortisone release, followed by a sustained release profile over 24 hours. The 3D printed hydrocortisone lacks the initial burst, but this can be solved by adding an immediate release tablet to the

treatment. Furthermore, Plenadren is only available 5 and 20 mg strengths, limiting the necessary treatment personalization (43).

3D printed hydrocortisone tablets can be personalized by adjusting the tablet height. In **Chapter 3**, we found a high correlation between the designed tablet-height and the hydrocortisone dose (R^2 = 0.996), facilitating easy dose personalization. However, the impact of changing the tablet height on the drug release profile was not investigated. Theoretically, larger tablets would lead to a slower release rate due to a decreased surface area/volume ratio. This can be solved by retaining the surface area/volume ratio when changing the tablet size (44).

3D printed hydrocortisone for patients with adrenal insufficiency

The work in this thesis is focused on the development of 3D printed, personalized hydrocortisone formulations for adrenal insufficiency, which was realized in **Chapters 3 and 6**. This section describes other reports of 3D printed hydrocortisone tablets and marketed formulations for adrenal insufficiency and places our work in that context.

Two studies developed personalized hydrocortisone tablets using SSE and FDM with dosages ranging from 1 to 8 mg for pediatric adrenal insufficiency but focus on immediate release while a more sustained physiological release is needed (45, 46). Other studies developed a sustained release hydrocortisone formulation using SSE. They demonstrated release profiles ranging from 8 hours to a maximum of 15 hours release, while physiologically there is a need for 24 h plasma cortisol with a high concentration early in the morning, followed by a gradual decrease towards the night (11, 47).

In another study, researchers managed to manufacture a triple pulsatile tablet with great potential of mimicking the physiological cortisol plasma concentrations (48). However, FDM was used as the printing technique with processing temperatures of 170 °C and 190 °C. The thermal stability of the final products was not investigated thoroughly while hydrocortisone is thermolabile, as demonstrated in **Chapter 3** (49-51). One study did address the thermal degradation of 3D printed hydrocortisone but focused on immediate release formulations in congenital adrenal hyperplasia (52). FDM was used with processing temperatures of 140 °C and 180 °C, impurities > 0.2 % were found in all tablets, including one impurity > 0.5 % (52). The ICH Q3B guideline has a qualification requirement for unknown impurities > 0.5 % (30). Identification and qualification of impurities can be an expensive, labor intensive and time-consuming process, especially when the aim is to personalize medicine at a point of care location (31, 53, 54). Lastly, none of the mentioned studies have looked into cost implications of 3D printed hydrocortisone, which we describe in **Chapter 5**.

The sustained release hydrocortisone formulation presented in **Chapter 6** mitigates the shortcomings of the formulations in the mentioned studies due to the use of lower temperatures while maintaining a 24 h sustained release profile.

There is a marketed hydrocortisone formulation, Efmody®, which is administered in the morning and evening. It mimics the diurnal and nocturnal rise in cortisol, whereas other marketed hydrocortisone formulations do not (55, 56). It is, however, only available in fixed dosages and currently only registered for the treatment of congenital adrenal hyperplasia in adolescents aged 12 years and over and adults. (56, 57). The dose flexibility needed in adrenal insufficiency still gives ground for 3D printed hydrocortisone for patients that need an, otherwise, unavailable dosage.

Pharmaceutical 3D printing implementation research

Quality and cost insights are important before implementing a new technology in clinical practice. In **Chapter 6**, we compared the quality of 3D printed hydrocortisone against conventional compounding techniques and provide manufacturing cost insights of 3D printed hydrocortisone.

In **Chapter 6,** we found that 3D printed tablets have a better content uniformity compared to conventionally prepared and manipulated hydrocortisone. Manipulated hydrocortisone was defined as tablet splitting and dissolving tablets in a syringe. While conventional preparations were defined as manual capsule filling. These methods are used in daily practice to personalize a drug dose in the absence of a commercially available product (8, 58). The content uniformity requirement of the Ph.Eur. is an acceptance value (AV) of ≤ 15. The AV indicates how close the dose is in relation to the declared dose and takes into account the intra-batch variation in content. A lower AV stipulates a lower deviation from the declared content and a lower intra-batch variability. 3D printed and dissolved tablets complied with the Ph.Eur. AV requirement, whereas 2 out of 3 batches of pharmacy compounded capsules and split tablets failed to meet the requirement.

Failure to meet content uniformity requirements can affect patient safety. Two case reports describe clinical adverse events in patients related to an error in pharmacy compounded hydrocortisone (59, 60). Manipulation of tablets by splitting and dispersing commercial tablets in liquids are also associated with safety risks (61-63). Tablet splitting can lead to dose inaccuracies, while errors with liquids are associated with dosing errors due to solubility, inexperience, or calculating errors (62, 63). Often, these methods are used to prepare otherwise unavailable doses in clinical practice. In **Chapter 6**, we also present results of non-commercially available hydrocortisone dosages such as 0.6 and 1.4 mg that meet Ph.Eur. content uniformity requirements. In the absence of commercially available, authorized medicines, 3D printing is thus a manufacturing technique that can be used to manufacture high quality pharmaceutical products.

Quality and regulatory aspects of pharmaceutical 3D printing

Prior to implementation, a pharmacy compounded product must comply with certain quality requirements and regulatory frameworks. This section discusses the critical process parameters, critical quality attributes, laws, and regulations regarding pharmaceutical 3D printing with SSE.

Quality implications

Typically, oral 3D printed pharmaceutical products are printed in a tablet shape (32). **Table 2** states general critical quality attributes (CQAs) and quality requirements for the 10 mg SSE printed sustained release tablets presented in **Chapter 6**. The requirements are based on the Ph.Eur., in addition to the general monograph on pharmaceutical preparations, and national good preparation practices (GPP) published by the Royal Dutch Pharmacy Association (In Dutch: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie; KNMP). Furthermore, the Dutch Medicines Act (in Dutch 'besluit geneesmiddelenwet') states that pharmacy compounded medicines require a content within 90 – 110 % of the declared content. It is more stringent than Ph.Eur. *2.9.6. Uniformity of content of single-dose preparations, which* requires 85 – 115 % of the declared content.

Table 2. Product validation tests, CQAs and quality requirements for 10 mg sustained release hydrocortisone printed by SSE.

Abbreviations: numbers refer to Ph.Eur. chapters and monographs, Dutch Medicines Act (DMA; in Dutch 'geneesmiddelenwet'), Lab oratory of Dutch pharmacists (LNA, in Dutch; Laboratorium der Nederlandse Apothekers (64), Total Aerobic Microbial Count (TAMC) and Total Yeast and Mold Count (TYMC), Standard deviation (SD), Relative SD (RSD), .

Test/CQA	Guideline	Requirement
Organoleptic properties	-	White, uncoated tablets with visible layers.
Content uniformity	2.9.40 DMA	Random sampling conforms 2.9.40. AV ≤ 15 (2.9.40) 90 – 110 % of declared content (DMA) Targeted sampling from different parts of the syringe to demonstrate homogeneity AV ≤ 15 (2.9.40) 90 – 110 % of declared content (DMA)
Weight uniformity	LNA	RSD ≤ 4%
Unknown impurities	ICHQ3B(R2)	Reporting threshold 0.05 %. Identification threshold > 0.20 % or 20 µg, whichever is lower. Qualification threshold > 0.50 % or 200 µg, whichever is lower.
Microbiological quality	2.6.12 5.1.4	TAMC < 1000, TYMC < 100 (5.1.4) Absence of E.Coli (5.1.4) See 2.6.12 for full set of requirements.
Dissolution	2.9.3 5.17.1	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time. (2.9.3) ≥ 80 % in 24 h (5.17.1)
Friability	2.9.7	≤ 1 % weight loss < 1 cracked, cleaved or broken tablets
Resistance to crushing	2.9.8	Only reporting

While most Ph.Eur. requirements for conventional tablets are also applicable for SSE tablets, it is not the case for mechanical testing (65). Mechanical requirements are intended for compressed tablets. SSE tablets are likely to fail due to the physical layer-by-layer nature of the tablets. Softening instead of breaking is noticed with our SSE tablets (unpublished data); the resistance to crushing test may therefore indeed not be suitable for SSE tablets. However, the pharmacopeial resistance to crushing test described in Ph.Eur 2.9.8. does not have a hard requirement; data should only be reported.

The suitability of friability testing for SSE tablets is also questioned in literature (65). However, unpublished friability data from our SSE sustained release hydrocortisone tablets and other studies suggest that in certain cases they may comply (66). Unpublished data from our group also demonstrated that our SSE printed sustained release tablets comply with the Ph.Eur. microbiological quality requirements of non-sterile pharmaceuticals.

Destructive analytical methods to verify the quality of 3D medicines before batch-release may not be feasible due to the small manufacturing scale. Some studies describe nondestructive methods, such as Raman and near infrared (NIR) spectroscopy prior to batch-release. However, these methods need to be validated for each product and require modeling of data acquired from other analytical equipment which can be time-consuming and costly (67).

Results from the proposed tests in **Table 2**, such as content uniformity, homogeneity, and weight uniformity may be used as a justification for weight verification as a surrogate batch-release criterium. Integration of a balance in a 3D printer has also been described in literature, which would facilitate easy weight verification and batch-release (68). In a validated manufacturing process, weight verification can suffice as a release criterium for 3D printed tablets, making destructive per-batch tests redundant. This could be similar to the release criterium described in the Dutch GPP guideline on the preparation of pharmacy compounded capsules (64, 65). Here, the weights of the content of 10 capsules from a batch are identified. The batch can be released if the relative standard deviation is ≤ 4 %. The requirement of the Dutch GPP is more stringent compared to the Ph. Eur. requirement described in *2.9.5. Uniformity of mass of single-dose preparations*, which requires a relative standard deviation of < 7.5 % for uncoated tablets with a mass between 80 and 250 mg. Weight based batch-release is a trade-off between quality assurance and practicality due to low manufacturing volumes in extemporaneous compounding. The SSE 3D printed hydrocortisone tablets, described in **Chapter 6** are currently being prepared for clinical implementation in a hospital pharmacy manufacturing unit. The preparation involves the validation of the manufacturing process, qualification of personnel, shelf-life testing, and validation of the final product (**Table 2**),

Relevant regulations for pharmacy compounding of 3D printed products

The MHRA has published a guidance on 'human medicine modular manufacture and point of care regulations 2025' to support point of care manufacturing by ensuring safety and quality of personalized medicine near or at the site of treatment. The guidance outlines for instance that a POC master file, including the state of control over the POC system, must be kept up to date by the hub site (69). The hub site is defined as the central licensed sight, and is connected to 'spoke' sites, which are defined as supply sites. This guidance is limited to organizational and documentational aspects. It describes for instance the files and licenses a POC manufacturer should submit and apply for. That processes, responsible persons and manufacturing locations should be described. This guideline may be useful during inspections to evaluate whether POC manufacturers have the right documents, licenses and control over their organization, but pragmatic technical requirements are not mentioned.

Some studies that address regulatory aspects for pharmaceutical 3D printing conclude that there is a lack of a regulatory framework for this technology (70, 71). However, existing regulations that are already in place, are also applicable to pharmaceutical 3D printing (28). Good manufacturing practice (GMP) guidelines as well as

national GPP guidelines provide room for the introduction of innovative manufacturing techniques. For instance, GMP annex 15 and the national Dutch GPP guideline state that critical process parameters (CPP) and CQAs should be identified as a result of a risk-analysis and subsequently validated, regardless of manufacturing technique (72). The differences between 3D printing and conventional manufacturing techniques are mainly in the CPPs, which in turn influence CQAs (29). The CQAs and CPPs for SSE have already been identified in our work (**Table 2**), and in other studies, facilitating a validation framework (28, 29).

Furthermore, hospital pharmacies are authorized to prepare pharmaceutical products under national GPP guidelines in the absence of commercial alternatives (28, 72). Extemporaneous compounding is allowed, provided that the preparation is carried out according to validated protocols and a scientific clinical rationale is given, stating the unmet need for the individual patient (72).

The Dutch national GPP describes that validation of the manufacturing process in extemporaneous compounding should be performed using a model-drug, based on a risk-analysis (72). This risk-based approach is also underlined by national good preparation practices guidelines for hospital pharmacy compounding (28).It is also applicable to pharmacy compounded 3D printed medicines and involves CQA testing against predefined requirements, such as stated in **Table 2**, to ensure high quality. Compliance with predefined CPP requirements, such as temperatures, thermal exposure time, and mixing times should be demonstrated. Additionally, thermal stability and shelf-life studies should be performed. The product can be dispensed after successful validation, where individual batches can be released based on weight, given that a strong correlation is shown between drug content and tablet weight. Yearly re-validation based on a risk-analysis is necessary to ensure continuity in dispensing the drug and maintaining quality control in extemporaneous compounding.

The regulations are more strict in the case of pharmacy-to-pharmacy delivery, which is characterized by the compounding of higher volumes of non-commercially available medicines, usually by large compounding facilities. Differences with the regulation for individual extemporaneous compounding are for instance that it requires product registration in the national medicinal products database, and an active pharmacovigilance system (73). Furthermore, large scale production does require destructive, per-batch testing of the final drug product which is redundant in extemporaneous compounding for the individual patient (74). The cut-off between extemporaneous compounding and larger volume compounding is set by the duration of treatment and number of patients (73). Small scale extemporaneous dispensing is defined as dispensing to up to 50 unique patients per month for long-term (more than a week) use of medication. Or dispensing to up to 150 patients per month for short-term use (a week or less). If production volumes are related to a higher number of patients, the regulations for pharmacy-to-pharmacy delivery should be followed.

In the case of compounding of 3D printed tablets for a clinical trial, a different regulatory pathway could be followed (28). It necessitates the submission of an investigational medicinal product dossier, containing documentation regarding the formulation, in-process controls, and printing procedure to competent authorities. One study describes the regulatory pathway of SSE printed tamoxifen, prepared for a clinical trial (28). The ink was defined as an intermediate in this process and was manufactured and stored under defined quality conditions. Batch-release requirements were redundant when process parameters during ink manufacturing stayed within limits

Validation of the manufacturing process and the tests described in **Table 2** should be performed using validated analytical procedures (37). This may, however, not be feasible in most pharmacies due to the lack of dedicated manufacturing and quality control facilities, qualified personnel, and financial purposes. The KNMP has published guidelines for pharmacy compounding of formulations, ranging from suppositories to tablets. These guidelines are based on a pragmatic approach to facilitate pharmacists to manufacture otherwise unavailable medicines for individual patients. By following the guidelines, a local pharmacy is not burdened by an extensive validation trajectory regarding the production and/or analytical method. The guidelines address the complete manufacturing of final products, from starting materials to shelf-life, detailed production parameters, and batch-release criteria (64). The guideline for suppositories states for instance which processing temperatures

should be used and which shelf-lives can be attributed when following this protocol (75). It describes for instance a standard shelf-life for suppositories with unknown physical and chemical stability of 1 month, below 25 °C. The Formulary of Dutch pharmacists (in Dutch: Formularium der Nederlandse Apothekers; FNA) provides validated preparation guidelines which make validation completely redundant, provided that the pharmacist use the same formulation, batch-size, materials, equipment, and manufacturing method. These national GPP guidelines relieve the pharmacist from time-consuming and costly validation studies. Similar pragmatic guidelines should be drafted to ensure widespread adoption of pharmaceutical 3D printing for the benefit of the patient.

Economic viability

Cost insights are important for the implementation of 3D printing in a (hospital) pharmacy setting. In order to gain insights into the manufacturing cost of a 3D printed hydrocortisone tablet, we developed a generic open-access costing tool in **Chapter 5**. It was applied to the FDM 3D printed hydrocortisone presented in **Chapter 3** and the SSE 3D printed hydrocortisone in **Chapter 6**. We found a manufacturing cost per tablet of €2.52 and €2.68 for SSE and FDM, respectively. One other paper mentions the cost-effectiveness of 3D printing in a community pharmacy compounding setting (9). This paper reports a reduction of 20 – 35% in costs when 3D printing minoxidil compared to conventional manual capsule filling. This was mainly attributed to a decreased workload of the operator when 3D printing. However, equipment, validation, and maintenance costs were not included. Our work demonstrated that these aspects increase the price per unit. 3D printing equipment is, for instance, more expensive compared to a manual capsule filling device. Nevertheless, the reduction of workload for pharmacy personnel due to automatization is an important finding, especially in times of personnel shortages (76, 77). Automatization of manual labor leaves room for pharmacy personnel to focus on other tasks at hand.

A 3D printed sustained release hydrocortisone tablet is more expensive compared to the generic immediate release hydrocortisone formulations available on the market (57). However, research has shown that modified hydrocortisone formulations have an added clinical value compared to the generic tablets (78-80). In order to ensure broad implementation of 3D printed pharmaceuticals, financial agreements should be made with healthcare insurers. Cost-effectiveness studies would aid in these discussions. More research is needed to demonstrate the cost-effectiveness of 3D printed tablets with a focus on sick days, disease control, mortality, morbidities, quality of life, ability to work, hospital or general practitioner visits, and other relevant parameters.

Future directions

Expanding the portfolio for adrenal insufficiency

The studies presented in this thesis are limited to a sustained release hydrocortisone formulation for adrenal insufficiency. We have developed a 10 mg sustained release hydrocortisone formulation which mimics the diurnal physiological cortisol plasma concentrations. However, in healthy individuals, the cortisol rise starts around 4 a.m. Patients usually wake up with hypocortisolemia until the first dose is administered. By expanding the portfolio with a 3D printed, delayed release formulation administered before bedtime, the natural nocturnal rise in cortisol can be mimicked, leading to better disease control.

There are reports of 3D printed, delayed release hydrocortisone products, manufactured with SSE and FDM (81, 82). Most studies demonstrate a 2-hour delay in the release of the study drug, while the cortisol rise naturally starts around 4 a.m. If administration of the delayed release product would be at 10 p.m., at least a 6-hour delay is necessary. One study using FDM demonstrated that the shell thickness can be adjusted to fine-tune the delay time. Depending on the shell thickness, a delay in release was achieved from 3 to 6 hours after administration in dissolution studies (83). Another study using FDM reports a delay in drug release of up to 8 hours (84). However, there is no literature on 3D printed delayed release products using SSE with a delay > 2

hours, while SSE seems to be the most suitable technique in hospital pharmacy. More formulation research using SSE to print multi-material, core-shell, delayed release products is needed.

As mentioned before, the marketed hydrocortisone Efmody® does mimic the nocturnal physiological cortisol rise, but is only available in limited strengths and is solely registered for congenital adrenal hyperplasia. 3D printing may provide a viable alternative for patients with adrenal insufficiency who need a non-available dosage. Our group has recently performed exploratory research to develop a delayed release hydrocortisone product (unpublished data). **Figure 1** shows preliminary drug release data of a core-shell formulation, where the shell is printed using FDM, while the core was printed with SSE. A 12 h dissolution study was performed (n=6) with a formulation that consisted of a 1.5 mm shell thickness printed with FDM, and 30 % hydrocortisone loaded core printed with SSE (**Figure 1)**.

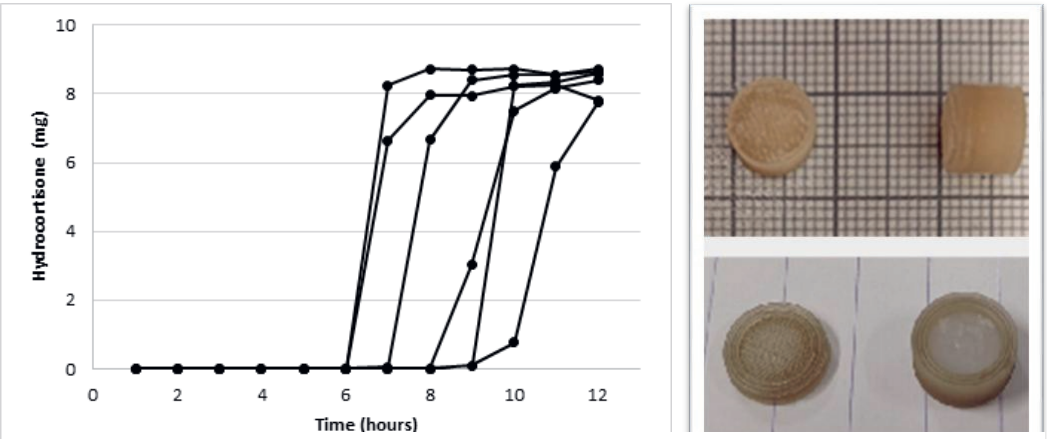


Figure 1. Dissolution profile of the delayed release formulation (left). Top and side view of delayed release tablets (top right), and cut tablet (bottom right). The cut tablet clearly shows the core-shell structure. The shell is printed first until a cup-like structure is formed, this FDM printed cup is subsequently filled with the SSE core containing hydrocortisone. After core filling, the printers switches to FDM to finish the tablet by printing the lid on top.

Dissolution data show a delay in release of 6 to 10 hours, which is close to the desired delay time of 8 hours. However, intra-batch variation of the lag time was high. Future research will be directed at reducing the intra-batch variation, controlling the timing of release, confirming that the high printing temperature of the FDM shell does not impact the stability of the hydrocortisone in the core, or formulating a shell using SSE instead of FDM printing to avoid the use of high temperatures.

Broader implementation of pharmaceutical 3D printing

Researchers usually produce pharmaceutical inks as well as the final products themselves. This process limits, however, broader implementation and access to personalized pharmaceuticals to patients, as not all pharmacies are equipped with the facility and qualified personnel for ink production and 3D printing. **Chapter 5** proposes an organization that manufactures dedicated pharmaceutical inks. In this scenario, pharmacists can purchase pre-filled syringes and solely focus on printing a personalized drug for the individual patient. It requires formal recognition of 3D inks as pharmaceutical intermediates (28). Focusing only on the printing part lowers the threshold for implementation. In this scenario, pharmacies do not handle raw pharmaceutical powders, need less space, and quality control can be limited to batch-release based on tablet weight.

A similar process is already in place for parenteral antibiotics and oncolytic medicines (73). Pharmacies purchase a licensed product, e.g. a flask containing powder for parenteral use. After reconstitution, the

necessary dosage is filled in a bag or syringe for intravenous administration. This approach would aid in the implementation of 3D printing in regular care at a broader level and has been described for another automated dosing technology (85). There are large compounding facilities in the Netherlands, such as Apotheek A15, that manufacture medicine that are not commercially available. From a public perspective, such compounding facilities which have the right facilities, qualified personnel and suitable quality management systems, could manufacture inks in higher volumes. The ink can be kept in stock, given that they are tested under defined quality criteria.

Future applications

Next to rare diseases, pharmaceutical 3D printing can also be used as a tool to provide high quality, personalized products for pediatrics (86). There is a lack of suitable formulations for pediatric diseases. This has led to the use of unlicensed or off-label medicines designed for adults, which accounts for 45 % to 60 % of all administrations in the European Union (EU) (87). The lower prevalence of diseases, ethical challenges of conducting clinical studies in children, and possibly a low return of investment possibly hinder the development and commercialization of suitable medicines (88). The pediatric population is defined by a high heterogeneity regarding pharmacotherapy. Physiological properties that may determine the drug dose, e.g. body surface area, body weight, and organ maturation, are highly variable in children in comparison to adults. For instance, the body size and weight of an average child increase up to 20-fold from birth to adulthood, highlighting the need for a personalized pharmacotherapeutic approach (87). The lack of commercial formulations has led to a practice where, for instance, a sildenafil oral liquid is prepared in the pharmacy instead of dispensing the licensed tablets in pediatric pulmonary hypertension (8). The use of inadequate drug formulations can lead to safety issues with certain excipients and swallowing or palatability difficulties, negatively impacting adherences. Off-label use of medicines is associated with an increased risk of adverse drug reactions (89).

In **Chapter 6,** low dose hydrocortisone tablets are presented for the treatment of pediatric adrenal insufficiency. Non-commercially available dosages such as 0.6 and 1.4 mg were manufactured with high quality. Currently, pediatric adrenal insufficiency patients in the Netherlands are treated with a pharmacy compounded oral liquid formulation which offers flexible dosing. However, liquids are associated with dosing errors when prepared and administered by caregivers (90-92). In this case, 3D printed tablets may provide a safer alternative.

3D printing can also be used to address issues related to drug shortages or discontinuation of production by industry (93). The technology facilitates fast and flexible production of medicines in this context, given that the raw API in question is still available.

Another future potential of pharmaceutical 3D printing lies in the intersection with therapeutic drug monitoring and other dose-guiding diagnostics such as pharmacogenetic testing. In therapeutic drug monitoring (TDM), drug dose recommendations are usually based on plasma concentrations of drugs. In pharmacogenetic testing, genetic polymorphisms are analyzed to explain or predict drug therapy outcomes (94). TDM and pharmacogenetic testing may result in dosing recommendations of dosages that are not commercially available. 3D printing could be used to customize the dosage.

Other innovative real-time analysis tools, such as smartwatches measuring cortisol plasma, could also be coupled with 3D printing. Conceptually, the best outcome for patients would be continuous data collection over time by the pharmacist, which can be used to individualize treatment by 3D printing (**Figure 2**).

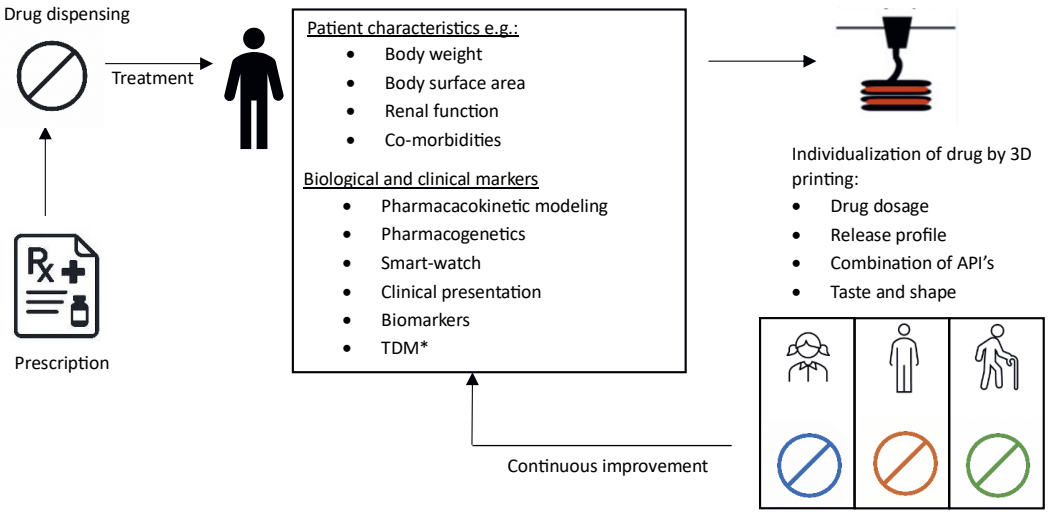


Figure 2. Continuous optimization of pharmacotherapy by 3D printing of individualized medicine, based on patient-specific metrics and therapeutic drug monitoring. * Therapeutic drug monitoring.

Several scientific reports describe a smartwatch that measures or tracks plasma cortisol levels (95-97). In the future, data generated from this tool and other tools might be used by the pharmacist to adapt the hydrocortisone formulation based on the individual patients need in adrenal insufficiency. Further research should elucidate the feasibility of coupling similar sensors with 3D printing for continuous control and optimization of pharmacotherapy in adrenal insufficiency.

Our findings led to high quality, immediate and sustained release hydrocortisone products. These formulations can be used as a base for the development of other products for rare and pediatric diseases with an unmet medical need. As mentioned before, drug development for pediatrics and rare diseases is going slow. To quote EURORDIS, an alliance of rare disease patient organizations (98):

'small, fragmented patient populations often fall below the threshold of commercial viability, leaving treatments undeveloped and communities underserved'

Our findings show that pharmaceutical SSE 3D printing, as a pharmacy compounding method, is an answer to tackle this problem. Existing quality and regulatory frameworks can be used to provide patients with high quality, personalized medicines, in the absence of commercial alternatives.

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8

Chapter 8

English summary

Summary

There is a lack of suitable hydrocortisone formulations for patients with primary adrenal insufficiency. It is a rare disease, also known as Addison's Disease, with a prevalence of 1-2 patients per 10,000 people. The cornerstone of the treatment consists of glucocorticoid and mineralocorticoid replacement therapy, usually in the form of oral hydrocortisone and fludrocortisone. Long term glucocorticoid replacement therapy consists of three times daily hydrocortisone treatment with 10 mg immediately on waking, 5 mg at midday, and 5 mg in the early evening. The current three times daily treatment with hydrocortisone does not mimic the physiological circadian plasma cortisol in patients. In normal physiology, cortisol is highest in the morning and gradually decreases throughout the waking day. However, the current standard of care consists of multiple daily dosing, leading to fluctuating plasma cortisol concentrations. This leads to an increased risk of developing co-morbidities and mortality. Modified release hydrocortisone products have been marketed but are only available in fixed dosages. The degree of cortisol deficiency is subject to interindividual variation related to differences in genetic and environmental influences. There is therefore a need for a hydrocortisone formulation that better mimics the gradual physiological cortisol plasma-concentrations, with the ability of flexible dose adjustment.

We hypothesize in this thesis that using pharmaceutical 3D printing, a sustained release hydrocortisone formulation can be developed which mimics the physiological situation better. We tested this hypothesis by studying different 3D printing techniques, quality of printed tablets and the cost of manufacturing.

Pharmaceutical 3D printing is a relatively new technology for medicine manufacturing. The most researched 3D printing methods are extrusion-based methods such as semi-solid extrusion (SSE). SSE printed products have already entered clinical trials and commercial, pharmaceutical grade SSE printers are already marketed, making this technology one of the most mature ones. The production process involved the pre-mixing of raw pharmaceutical materials, where in some cases heat is applied, to form a semi-solid material. The semi-solid material is subsequently loaded into a syringe, forming the pharmaceutical ink. A predefined design is generated with 3D printing software which contains the movement instructions of the printer. The design and the ink are fed to the printer which then prints the material in a layer-by-layer manner, forming the final product. Heat is applied during printing to ensure material flow through the printer nozzle. The deposited material hardens due to exposure to room temperature after printing, which ensures the mechanical integrity of the final product. Research in recent years has demonstrated that this technique allows the pharmacist to adjust the drug dosage, release profile, shape, and taste of pharmaceutical products. These properties make pharmaceutical 3D printing especially suitable as an extemporaneous pharmacy compounding method. Extemporaneous compounding is defined as the practice of preparing medicinal products for an individual patient when there is no commercial alternative available. Pharmacists in the Netherlands are allowed by law to manufacture medicinal products for their owns patients when suitable commercial alternatives are lacking.

In **Chapter 2**, fused-deposition modeling (FDM) 3D printing was explored as a 3D printing technique to develop sustained release formulations, using nifedipine as a model drug. Two factors had the highest influence on drug release, the excipients and the design. Pores were designed into the pellets to increase the surface area, which led to a faster drug release. Furthermore, this research demonstrated that by balancing water-soluble and water-insoluble excipients, the drug release can be fine-tuned. More water-soluble excipients led to faster release rates, while the opposite was observed with more water insoluble excipients. However, nifedipine was used as a study drug with no clinical value.

To show true clinical value, a shift was made to 3D print personalized sustained release hydrocortisone for patients with adrenal insufficiency. There is a lack of formulations that mimic the gradual physiological cortisol release in patients with adrenal insufficiency, where the drug dose can be personalized. **Chapter 3** describes

an FDM 3D printed hydrocortisone formulation that releases 10 mg hydrocortisone over 24 h. Content uniformity and drug release were compliant to the European Pharmacopeia guidelines. Tablet size and drug dose were highly correlated, which could be used for easy dose personalization. However, the high processing temperatures of > 100 °C led to impurities in the final product.

Although the potential of pharmaceutical 3D printing has been demonstrated by researchers worldwide, no formal costing analysis studies have been published. In **Chapter 4,** an initial effort is presented to elucidate the manufacturing costs of pharmaceutical 3D printing. A micro-costing study was performed in a hospital pharmacy setting. Costs related to facility, personnel, materials, and equipment were considered. An open-access costing framework was developed to calculate the cost of one 3D printed tablet. The framework was applied to the sustained release hydrocortisone formulation presented in chapter 3, resulting in costs of €1.97-3.11 (best-case-worst-case) per tablet. It was previously unknown whether it would cost tens of euros or a few eurocents to manufacture a 3D printed tablet. Identifying the manufacturing costs of a 3D printed formulation in a hospital pharmacy setting can aid in the implementation of this technology in hospital pharmacy and further health technology assessment.

Clinical translation of the personalized hydrocortisone formulation was still lacking due to the impurities caused by high printing temperatures shown in **Chapter 3**. A shift to semi-solid extrusion (SSE) 3D printing was made.

Prior to developing the SSE hydrocortisone sustained release formulation, we first screened 27 excipients that are suitable for this printing technique. In **Chapter 5**, we found that a combination of lactose with poly ethylene glycol 4000, or poloxamer 407 had good printing properties at processing temperatures of < 80 °C. Furthermore, we found that these excipients are also suitable for pediatrics, based on the STEP database. This knowledge was used to develop the sustained release hydrocortisone formulations for patients with adrenal insufficiency.

In **Chapter 6**, personalized immediate release and a sustained release hydrocortisone formulations are presented with processing temperatures of < 100 °C. It was possible to accurately print tablets ranging from 0.5 to 10.0 mg hydrocortisone. The quality of the 3D printed products was higher compared to conventional pharmacy compounded methods, demonstrated by low acceptance values. 3D printed tablets were compared to split and solubilized commercial tablets and pharmacy compounded capsules ordered from three independent pharmacies in the Netherlands. Furthermore, the costing framework in **Chapter 4** was applied to the SSE tablets, resulting in costs of <€ 3.00 per tablet for both release profiles. No impurities were observed. However, a stability-indicating analysis method was not used. Compendial testing of these formulations while using a stability indicating analysis method is now the only barrier to clinical implementation of personalized, 3D printed hydrocortisone for patients with adrenal insufficiency.

There are, however, some challenges for broader implementation of pharmaceutical 3D printing as an extemporaneous compounding method. Validation of manufacturing processes and analytical methods may not be feasible in most pharmacies due to the lack of dedicated manufacturing and quality control facilities, qualified personnel, and financial purposes. Pragmatic guidelines are needed to facilitate pharmacists to manufacture 3D printed medicines. The Royal Dutch Pharmacy Association (In Dutch: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie; KNMP) has guidelines for extemporaneous compounding of formulations, ranging from suppositories to tablets. The guidelines address the complete manufacturing of final products, from starting materials to shelf-life of the final product, detailed production parameters, and batch-release criteria. This relieves the pharmacist from stability testing and validation of processing temperature ranges. Similar pragmatic guidelines should be drafted to ensure widespread adoption of pharmaceutical 3D printing for the benefit of the patient.

Currently, pharmacists produce pharmaceutical inks as well as the final products themselves. This limits however broader implementation and access to personalized pharmaceuticals to patients as not all pharmacies are equipped with the facility and qualified personnel for ink production and 3D printing. **Chapter 4** proposes an organization that manufactures dedicated pharmaceutical inks. In this scenario, pharmacists can purchase pre/filled syringes and solely focus on printing a personalized drug for the individual patient. Focusing only on the printing part lowers the threshold for implementation.

Furthermore, higher temperatures are used in 3D printing compared to conventional pharmacy compounding techniques. High processing temperatures can lead to thermal degradation and impurity formation when applied to an active pharmaceutical ingredient (API). As most conventional manufacturing techniques do not apply heat, there is little information available on the thermal stability of API´s. An open access platform where thermal stability data is shared would also greatly aid in the broader implementation of pharmaceutical 3D printing.

Finally, in order to ensure broad implementation of 3D printed pharmaceuticals, financial agreements should be made with healthcare insurers. Cost-effectiveness studies would aid in these discussions. More research is needed to demonstrate the cost-effectiveness of 3D printed tablets with a focus on sick days, disease control, mortality, morbidities, quality of life, ability to work, hospital or general practitioner visits, and other relevant parameters.

The work presented in this thesis is focused on adrenal insufficiency, however, 3D printing can also be used for other populations with an unmet need such as in pediatrics. 45 % to 60 % of all pediatric drug administrations in the European Union are unlicensed or off label due to the lack of suitable formulations. Furthermore, the pediatric population is defined by a high heterogeneity regarding pharmacotherapy. Physiological properties that may determine the drug dose, e.g. body surface area, body weight, and organ maturation are highly variable and subject to changes in children in comparison to adults. 3D printing could be used to manufacture non-commercially available dosages of specific medicines.

Relevant patient characteristics, used to determine the optimal pharmacological treatment, change over time. Ideally, this is monitored, and the pharmacological treatment is adapted continuously over time to ensure the best treatment for the patient. For adrenal insufficiency, the first steps have been taken in the monitoring of plasma cortisol by a smartwatch. We foresee a future where the pharmacist can periodically monitor real-time individual health-related patient data, generated by similar smart technologies, and when necessary, can 3D print a personalized therapy for the individual patient.

Appendix

Appendix

Dutch summary
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Nederlandse samenvatting

De beschikbare hydrocortison tabletten voor de behandeling van bijnierschorsinsufficiëntie zijn suboptimaal. Patiënten met bijnierschorsinsufficiëntie kunnen onvoldoende endogene cortisol produceren. Hierdoor zijn ze levenslang afhankelijk van dagelijks cortisol intake in de vorm van hydrocortison. De huidige behandeling, bestaande uit driemaal daags directe afgifte hydrocortison tabletten, is echter suboptimaal. In gezonde mensen is het cortisol in het bloed hoog bij het wakker worden. Over de dag heen wordt dit langzaam afgebouwd. Midden in de nacht ontstaat er weer een stijging van cortisol, leidende tot de ochtendpiek. De huidige behandeling bootst dit onvoldoende na, en zorgt voor pieken en dalen in het bloed. Deze fluctuaties zijn geassocieerd met een lagere kwaliteit van leven, hogere risico op mortaliteit en co-morbiditeiten. Inmiddels zijn er hydrocortison formuleringen op de markt gekomen met langzame afgifte, die de gezonde situatie beter nabootsen. Echter, deze zijn beschikbaar in vaste doseringen terwijl er grote interindividuele verschillen bestaan in de dosering. Er is dus een behoefte aan een hydrocortison formulering die de gezonde situatie beter nabootst, met de mogelijkheid tot het personaliseren van de dosering.

Onze hypothese is dat met 3D printen, hydrocortison tabletten kunnen worden geproduceerd die de fysiologische situatie beter nabootsen, waarbij de dosering gepersonaliseerd kan worden. Dit hebben wij getest door onderzoek te doen naar de formulering, 3D printtechniek, kwaliteit en productiekosten van 3D geprinte hydrocortison.

In de afgelopen jaren is er veel onderzoek verricht naar farmaceutisch 3D printen als een methode om op maat gemaakte medicijnen te bereiden. Het is mogelijk om de dosering, afgifteprofiel, smaak en vorm van een tablet aan te passen aan de individuele behoefte van een patiënt. Hiermee is het een geschikte methode om in kleine volumes, op maat gemaakte medicijnen te maken voor de individuele patiënt. 3D print technologieën gebaseerd op extrusie, zoals semi-solid extrusion (SSE), zijn inmiddels ook onderzocht in klinische studies en daarmee het dichtst bij klinische toepassing. Het bereidingsproces omvat meerdere stappen. Ruwe farmaceutische grondstoffen worden gemengd, in sommige gevallen onder hogere temperaturen. Het halfvaste materiaal dat hierbij wordt gevormd, wordt gegoten in een spuit. Deze gevulde spuit, ook wel farmaceutische inkt genoemd, wordt vervolgens geladen in de printer. De printer print het materiaal in de spuit op een plat oppervlakte door de inhoud van de spuit eruit te persen onder een verhoogde temperatuur. Laagje voor laagje wordt het materiaal neergelegd, waarbij het materiaal uithardt door blootstelling aan kamertemperatuur. Voorafgaande het printen wordt er een design gecreëerd met behulp van een digitale software. Vaak betreft het een object met karakteristieken van een tablet. Dit object wordt vertaald naar print instructies via een printer specifieke software.

In **Hoofdstuk 2** beschrijven wij het gebruik van fused deposition modeling (FDM) 3D printen om te onderzoek of het mogelijk is om tabletten te maken met verlengde afgifte. Hieruit bleek dat de hulpstoffen en de design invloed hebben op het afgifteprofiel. Wordt er meer wateroplosbare hulpstof gebruikt, dan is de afgifte sneller. Wanneer meer niet-wateroplosbare hulpstoffen worden gebruikt, dan kan de afgifte vertraagd worden. De invloed van design op de afgifte is geassocieerd met het tablet oppervlakte. Wanneer een tablet gaten bevat, is de afgifte sneller doordat er een groter oppervlakte is gecreëerd. In dit onderzoek werd nifedipine gebruikt als geneesmiddel. Het 3D printen van dit medicijn heeft echter geen toegevoegde waarde.

In **Hoofdstuk 3** wordt dezelfde 3D print techniek gebruikt, maar dan met hydrocortison als medicijn. Hier laten beschrijven we de ontwikkeling van een 3D geprinte hydrocortison formulering die hydrocortison over 24 uur afgeeft, waarbij de dosering gepersonaliseerd kan worden. Echter, door de hoge productie temperaturen > 100 °C, werden onbekende onzuiverheden waargenomen.

Ondanks de onzuiverheden hebben we de productiekosten onderzocht. Tot nu toe was er geen formeel kostenonderzoek gedaan met 3D geprinte medicijnen. In **Hoofdstuk 4** presenteren wij een kostenbepalingstool waarmee de productieprijs per 3D geprint tablet bepaald kan worden. Voor de verlengde afgifte hydrocortison tabletten gepresenteerd hebben wij dit gedaan op basis van de ontwikkelde kostenbepalingstool. Afhankelijk van de scenario bleken de productiekosten tussen €1.58 en €3.11 per tablet te liggen. De tool is ook toepasbaar voor andere 3D printtechnieken en kan gebruikt worden als financiële onderbouwing voor het klinisch toepassen van 3D printen en voor financiële afspraken met zorgverzekeraars.

Bij FDM 3D printen worden temperaturen boven 100 °C gebruikt. Bij het ontwikkelde hydrocortison product in **Hoofdstuk 3** werden door het gebruik van deze hogere temperaturen daarom onbekende onzuiverheden waargenomen. Deze onbekende onzuiverheden zijn waarschijnlijk thermale degradatieproducten van hydrocortison. Hierom werd besloten om over te stappen naar SSE 3D printen, waar temperaturen onder 100 °C worden gebruikt in het productieproces. **Hoofdstuk 5** beschrijft directe afgifte, en verlengde afgifte hydrocortison formuleringen geproduceerd met SSE. Onzuiverheden werden niet waargenomen, echter, een stabiliteits-indicerende analytische methode is nodig om dit te bevestigen. De kwaliteit van 3D geprinte hydrocortison werd tevens vergeleken met magistraal bereide capsules door 3 verschillende apotheken, gehalveerde tabletten en opgeloste tabletten. Dit zijn conventionele technieken om de dosering te personaliseren. 3D geprinte, een batch van de capsules en opgeloste tabletten voldeden aan de gehalte eis van de Europese Farmacopee. Twee van de drie capsule batches, en gehalveerde tabletten voldeden niet aan deze eis. 3D printen leidt dus tot hogere kwaliteit producten vergeleken met conventionele technieken voor het personaliseren van medicijnen. Daarnaast stelt 3D printen de apotheker in staat het afgifteprofiel van een medicijn aan te passen, wat onmogelijk is met conventionele technieken.

Alvorens de producten beschreven in **Hoofdstuk 5** naar de patiënt te brengen, moeten de productieproces en analytische methode worden gevalideerd. Dit is echter niet altijd praktisch uitvoerbaar voor elke apotheek door het ontbreken van ruimtes en faciliteiten, personeel, financiën en kennis. De Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP) heeft richtlijnen voor het produceren van apotheekbereidingen zoals capsules en zetpillen. Bij zetpillen wordt bijvoorbeeld voor medicijnen met onbekende fysisch-chemische stabiliteit een houdbaarheid toegekend van 1 maand. Soortgelijke richtlijnen voor 3D geprinte producten zouden een bredere beschikbaarheid bevorderen.

Een scenario waarbij de inkt door een gespecialiseerd fabrikant wordt bereid zou bredere beschikbaarheid ook bevorderen. In **Hoofdstuk 4** stellen we dit scenario voor omdat het apotheken minder faciliteit, kennis en financiële middelen kost om te 3D printen. Het produceren van inkt kost ruimte en er moet gewerkt worden met ruwe grondstoffen. Door dit uit te besteden hoeft de apotheek alleen te focussen op het 3D printen voor de individuele patiënt. Conceptueel is dit vergelijkbaar met het logistieke proces van voor toediening gereedmaken (VTGM). Hierbij koopt een apotheek bijvoorbeeld een flacon met poeder in voor parenterale toediening. In de apotheek wordt dit product vervolgens voor toediening gereedgemaakt door het op te lossen en de juiste dosering op te trekken voor de individuele patiënt. Op dezelfde manier kan er dan inkt ingekocht, en vervolgens geprint worden in een unieke dosering voor de individuele patiënt.

Naast toepassing van 3D geprinte medicijnen voor zeldzame ziekten kan het ook leiden tot betere uitkomsten bij andere populaties, zoals pediatrische ziekten. 45 tot 60 % van alle pediatrische geneesmiddeltoediening in de Europese Unie bestaan uit het gebruik van off-label of niet-gelicentieerde medicijnen. Vaak zijn er geen geschikte, commercieel beschikbare medicijnen voor kinderen. Een van de oorzaken is dat de pediatrische populatie een sterk heterogene groep is. Er zijn grote verschillen in fysiologische parameters die die de dosering bepalen, zoals verschillen in lichaamsgewicht en lichaamsoppervlakte. Geneesmiddelen die bedoeld zijn voor volwassenen worden vaak gemodificeerd om geschikt te maken voor kinderen. Voorbeelden hiervan zijn het

breken en oplossen van tabletten om de juiste dosering te realiseren. In sommige gevallen worden drankjes of capsules bereid door een apotheek. De resultaten van het onderzoek in **Hoofdstuk 5** laten zien dat 3D printen leidt tot producten met een hogere kwaliteit vergeleken met conventionele technieken. Als bewijs werden er doseringen hydrocortison geproduceerd die niet commercieel beschikbaar zijn, zoals 0.6 mg en 1.4 mg.

In de toekomst kan 3D printen gekoppeld worden aan slimme monitoring-technologieën zoals smart-horloges. Verschillende onderzoeken presenteren bijvoorbeeld resultaten van een smart-horloge die plasma-cortisol kan meten. Deze data kunnen in de toekomst periodiek gecontroleerd worden door de apotheker waarbij die de dosering en afgifteprofiel constant aanpast middels 3D printen. Op deze manier heeft de patiënt continu de beste farmacotherapeutische behandeling. Om dit te realiseren is meer onderzoek nodig naar de koppeling van slimme monitorings-technologieën met 3D printen voor continue optimalisatie van farmacotherapie.

Curriculum Vitae

Sejad Ayyoubi was born in Samangan, Afghanistan March 11th, 1994. His family came to the Netherlands in 1996 due to the second Afghan civil war. After studying chemistry for a year at the Hogeschool van Arnhem en Nijmegen, he started his Bachelor of pharmacy at Utrecht University and subsequently a master in 2017. He performed his research project at the Complutense University of Madrid, where he first came in touch with pharmaceutical 3D printing. His research project led to the first publication of this thesis and was graded with a 10/10. During his masters, he took place in the board of the Avicenna Excellence Program, which is an extracurricular program for ambitious master- and PhD students regarding innovation in healthcare. He presented first-line pharmacotherapy guidelines throughout the country for general practitioners and pharmacists as an FTO moderator next to his studies.

His internship in Madrid sparked his interest in pharmaceutical 3D printing to produce better pharmaceutical products that could improve patient outcomes. After returning home from his internship, he actively engaged with medical specialists, pharmacists and patient organizations to identify unmet medical needs that could be solved using 3D printing. Prof. Dr. Nienke Biermasz from the Leiden University Medical Center, treating patients with adrenal insufficiency, mentioned that better hydrocortisone treatments are needed in this population. Furthermore, Willem Meulenhoff, back then head of pharmacy at Apotheek Haagse Ziekenhuizen, gave Sejad the opportunity to work there after his masters. Willem Meulenhoff purchased a 3D printer which led to the first sustained release 3D printed cortisol tablets made in the Netherlands.

Following this, the Erasmus MC provided a PhD position to further develop the cortisol tablets under supervision of Dr. Liesbeth Ruijgrok, Prof. dr. Hugo van der Kuy, and Dr. Julian Quodbach. This work was awarded the ‘best abstract’ award during the national hospital pharmacy conference ‘Ziekenhuisfarmaciedagen’ in 2021.

Portfolio

Presentations		
2021	Oral presentation Postuniversitair opleidingsprogrammadag, Vlaamse Vereniging voor ziekenhuisapothekers	Online presentation
2021	Oral presentation Ziekenhuisfarmaciedagen 2021	Utrecht, The Netherlands
2022	Poster presentation 13th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology	Rotterdam, The Netherlands
2022	Oral presentation 3D pharma printing conference	Online presentation
2023	Poster presentation Dutch medicine days	Oss, The Netherlands
2023	Oral presentation Ziekenhuisfarmaciedagen 2023	Arnhem, The Netherlands
2024	Oral keynote presentation GMP & GDP driedaagse	Nijkerk, The Netherlands
2024	Poster presentation 14th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology	Vienna, Austria
2024	Poster presentation 26th European Congress of Endocrinology	Stockholm, Sweden
2024	Oral presentation II international conference on 3D printed medicines, tissues and microfluidics	Madrid, Spain
2024	Oral presentation European Society For Paediatric Endocrinology 62nd annual meeting	Liverpool, United Kingdom
2025	Oral presentation Erasmus School of Health Policy & Management	Rotterdam, The Netherlands
2025	Poster presentation 3D PharmaPrint Healthcare Symposium	Rotterdam, The Netherlands
2025	Oral presentation Health economics/Health technology assessment group UMCU	Utrecht, The Netherlands
2025	Oral presentation Forum Inkoopcoördinatoren Pharmacie	Utrecht, The Netherlands

Courses		
2021	Basiscursus regelgeving en Oganisatie Klinisch Onderzoek (BROK)	Rotterdam, The Netherlands
2021	English scientific writing	Rotterdam, The Netherlands
2022	3D printing of medicines – Clinical relevance and business models	Hamburg, Germany
2022	Scientific integrity	Rotterdam, The Netherlands
2024	Validatie van analytische methodes: nieuwe ICH richtlijnen in de praktijk	Nijkerk, The Netherlands

Teaching and other activities		
Supervision of research projects		
2021	2 MSc theses	Pharmacy
2022	4 MSc theses	Pharmacy Biopharmaceutical sciences
2023	3 MSc theses	Pharmacy Biopharmaceutical sciences
2024	3 MSc theses	Pharmacy Biopharmaceutical sciences
2025	1 MSc, 1 BSc thesis	Pharmacy, biology

Teaching courses and workshops		
2022	Preparing parenteral medication for medical students	Erasmus MC
2022	Pharmacology during and after pregnancy for specialized nurses in training	Erasmus MC
2022	Assessment of prescribing exams medical students	Erasmus MC
2023	Preparing parenteral medication for medical students	Erasmus MC
2023	Pharmacology during and after pregnancy for specialized nurses in training	Erasmus MC
2023	Assessment of prescribing exams medical students	Erasmus MC
2024	Preparing parenteral medication for medical students	Erasmus MC
2024	Pharmacology during and after pregnancy for specialized nurses in training	Erasmus MC
2024	Assessment of prescribing exams medical students	Erasmus MC
2025	Preparing parenteral medication for medical students	Erasmus MC
2025	Pharmacology during and after pregnancy for specialized nurses in training	Erasmus MC
2025	Assessment of prescribing exams medical students	Erasmus MC

Other activities

2021	-	Batch-release of hospital pharmacy preparations (0.2 FTE)	Erasmus MC
2025			
2024	-	Implementation and validation of production process	Maasstad
2025			Ziekenhuis

Awards		
2021	Best abstract, Ziekenhuisfarmaciedagen 2021	Utrecht, The Netherlands

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