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

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ABSTRACT

Background: Modification of commercially available medicine, e.g. splitting or dissolving of tablets or pharmacy compounding, is current clinical practice when desired oral dosage forms are unavailable. These practices are defined as conventional pharmacy compounding techniques and are used to produce medicines that are not commercially available. 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.

1. 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 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 (Heitman et al., 2019; J Saito et al., 2020; Fadda et al., 2024). 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 (Rautamo et al., 2020). This includes orally administering medication off-label that is intended for intravenous use, due to non-availability of oral dosage forms (Rautamo et al., 2020). 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

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increase the risk of toxicity (Taylor and Glass, 2018). Studies that investigated tablet splitting report different outcomes. Some studies report that weight and content variation are minimal, depending on the splitting method (Chaudhri et al., 2022; Habib et al., 2014; Olgac et al., 2021). Others report a high variation in drug dose, and poor compliance with pharmacopeial standards (Habib et al., 2014; Jude et al., 2018). 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 (Bouwhuis et al., 2023; Markman et al., 2010). In one study, compounded hydrocortisone batches were analyzed and 21.4 % did not comply with compendial standards (Neumann et al., 2017). 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 (Barillas et al., 2018; Al-Rayess et al., 2020). 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 Medicine Act (2025).

In recent years, 3D printing (3DP) has been extensively researched for the production of pharmacy compounded medicines (Tracy et al., 2023; Ayyoubi et al., 2021). 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 (Wang et al., 2023). Not only the drug dose can be personalized with 3DP, but also the drug release, taste and shape of medicines can be tailored (Ayyoubi et al., 2021; Varghese et al., 2022; Ayyoubi et al., 2023). 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 (Levine et al., 2024). 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 (Goyanes et al., 2019). 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 (Ayyoubi et al., 2023). It is also a drug that is widely compounded, and described in case studies regarding compounding or modification errors (Neumann et al., 2017; Barillas et al., 2018; Al-Rayess et al., 2020; J Saito et al., 2020).

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 (Ayyoubi et al., 2024). 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 (Ayyoubi et al., 2024). 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 (Ayyoubi et al., 2023).

2. 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).

3. Methods

3.1. 3D printing process

3.1.1. Immediate release hydrocortisone formulations

10 mg hydrocortisone tablets were 3D printed using SSE with the Superion SSE 3D printer (TNO, Eindhoven, The Netherlands). Fig. 1 shows the 3D printing process. 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 (van Kampen et al., 2023). 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.

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 s at 750 RPM, followed by 2 min 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

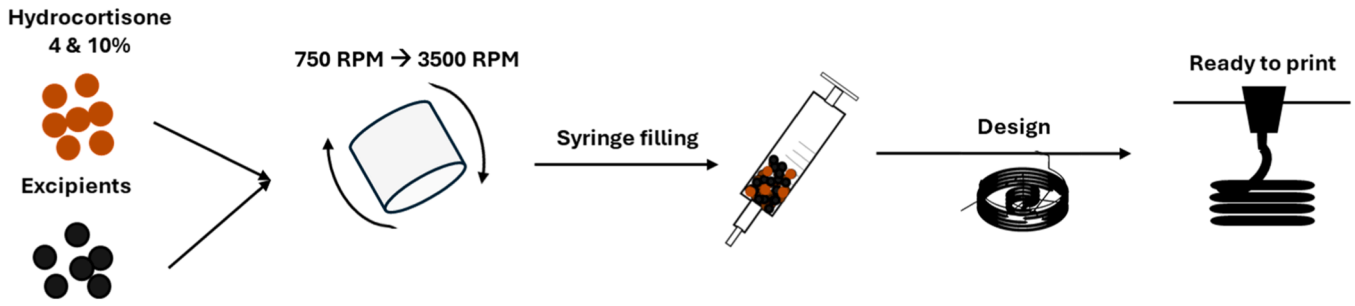

Fig. 1. Semi-solid extrusion 3D printing process: raw materials are weighed and mixed, high speed mixing results in the formation of semi-solid material that is filled in a syringe. The resulting syringe is inserted in the printer. The printer reads the file containing the desired design and prints the final product in a layer-by-layer manner.

Table 1
Tablet dimensions and printing parameters.

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

(mg) and E the amount of extrusion per tablet (movement of the piston) in mm.

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

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

3.1.2. 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 $n = 30$).

3.1.3. 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.

3.2. 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 1 M 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 min, which is held for 1.25 min. Then B increased to 100 % in 0.1 min followed by stabilization for 0.5 min. Then the gradient reverts to initial conditions (40 % B) in 0.2 min and is stabilized for 1.3 min, resulting in a total run time of 3.5 min. 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.

3.3. 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.

3.4. 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 h.

3.5. 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 min for a more detailed look at the release profile.

3.6. Manufacturing costs

We previously published a costing framework that allows for estimation of production costs for 3D printed products (Ayyoubi et al., 2024). 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.

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 (Central bureau of statistics, 2025). Costs were adjusted for inflation in adherence to the guideline of the Dutch National Healthcare institute (Zorginstituut Nederland; ZIN) on economic evaluation studies (Zorginstituut Nederland, 2016). All costs stated here are expressed in 2025 Euros (€).

4. Results and discussion

4.1. 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.

The 4 % formulation allows for personalization of the drug dose between 0.5 – 3.0 mg (Fig. 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 % (Fig. 2). Doses of 0.5 mg and 0.6 mg demonstrate higher deviations but still within the 10 % limit, set for magistral preparations (EDQM Council of Europe, 2025). 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.

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 (Fig. 3). 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.

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 % (Fig. 2). Splitting hydrocortisone tablets in adrenal insufficiency is still used in clinical practice for pediatric patients (Jude et al., 2018; Watson et al., 2018). The results of the splitting study reveal high content variations of 7.1 %, which may cause loss of disease control (Neumann et al., 2017). 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 (Watson et al., 2018). 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

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	€ 5600
Stability indicating HPLC method	€ 15,000
Annual working hours equipment and personnel	1558
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 %

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

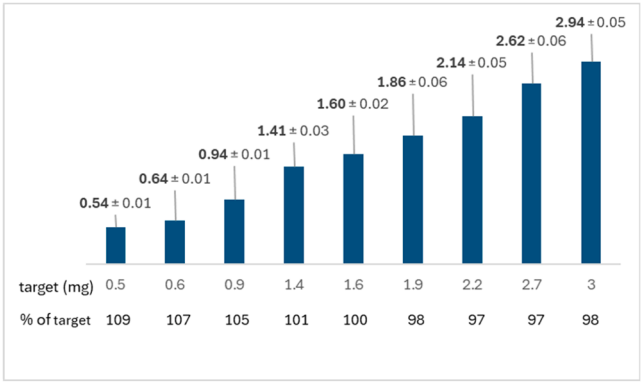

Fig. 2. Low dose SSE hydrocortisone tablet contents, showing the mean content in mg ± SD above the bars, as well as target content and % of content in relation to the target.

AV ≤ 15, which is similar to results described in literature (Markman et al., 2010; Neumann et al., 2017; Umstead et al., 2012). While the quality of pharmacy compounded capsules usually complies with compendial standards, the content is at the lower end of the targeted content (Wasilewski et al., 2023). 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 (D'Hondt et al., 2014). 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 (Frédéric et al., 2024). 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 (Levine et al., 2024). 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 (Levine et al., 2024). 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 min and fall under the definition of an IR product (Fig. 4A). 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 min. 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.

The 3D printed SSE SR hydrocortisone formulation released hydrocortisone over 24 h (Fig. 4B). Drug release is > 80 % in 24 h, 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 h. An FDM 3D printed SR hydrocortisone product was developed in earlier research, however, the processing temperatures during production were up to 150 °C (Ayyoubi et al., 2023). 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 (Ayyoubi et al., 2023). 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 (Ganatra et al., 2025). Drug release profiles in this study were determined for up to 15 h, while patients with adrenal insufficiency require a continuous 24 h cortisol exposure.

5. 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.

At accelerated conditions after 6 weeks, 2 out of 10 samples were not measured due to analysis errors. The results of the remaining samples

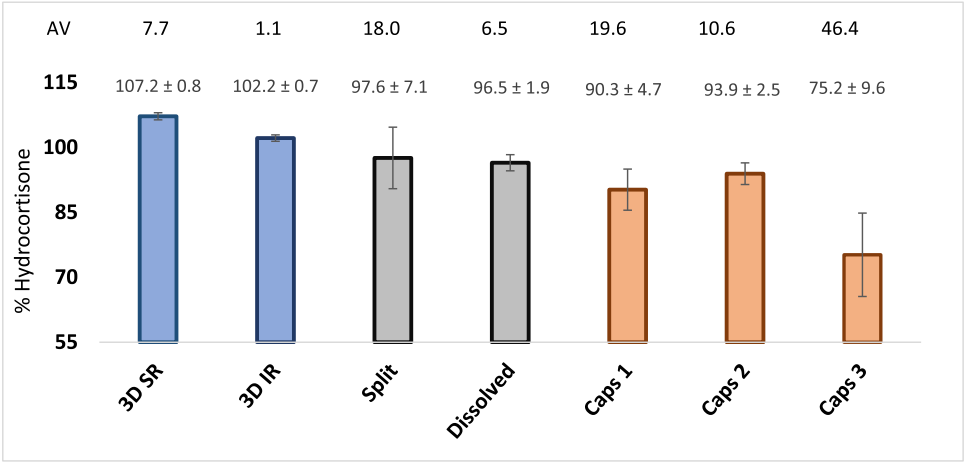

Fig. 3. Average content of $n = 10$ units per formulation (in % of declared 10 mg), standard deviation (%) and acceptance values of the 3D printed hydrocortisone formulations (blue) and pharmacy compounded hydrocortisone formulations including: split tablets, dissolved tablets (grey) and capsules (orange).

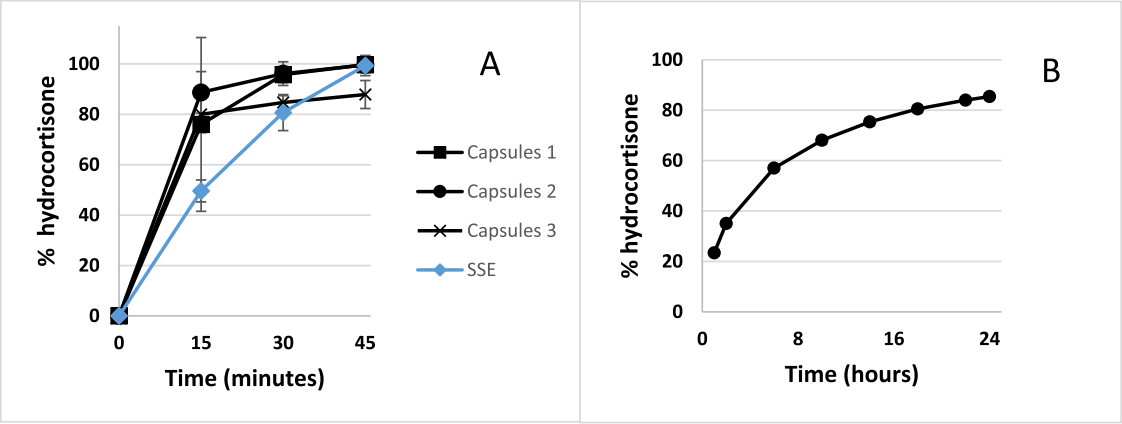

Fig. 4. (A) Drug release profiles of the IR 3D printed formulation (blue) and pharmacy compounded capsules (black) in % of 10 mg target. (B) Drug release profile of the SR hydrocortisone formulation ($n = 6$).

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	-

were well within limits (EDQM Council of Europe, 2025). 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 min (Fig. 5). At $t = 0$ after 2 h, 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.

Degradation products were investigated previously in FDM 3D printed hydrocortisone SR tablets (Ayyoubi et al., 2023). 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. A long term stability study was not performed as 3D printing is considered a point of care manufacturing technique with limited time to administration.

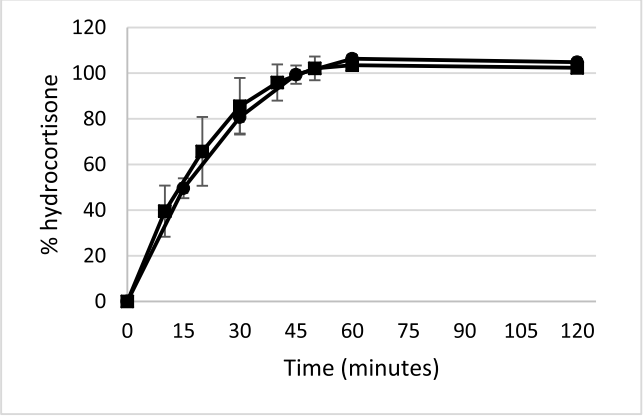

Fig. 5. dissolution study data from $t = 0$ (•) and $t = 12$ weeks (■), $n = 6$.

6. 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 (Ayyoubi et al., 2024). 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 (Ayyoubi et al., 2024). 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 were 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.

Another study performed a cost-time comparison between conventional compounding of capsules and automated capsule filling using a 3D printer with an SSE head (Rodríguez-Maciñeiras et al., 2025). It was concluded that the price of the SSE capsules was 20 % to 35 % lower

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

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 (Ayyoubi et al., 2024). Scaling up could give price-volume advantages. Scaling up SSE 3D printing requires additional development of syringe filling equipment, which constitutes a feasible task. For instance, automated syringe filling systems would allow large-scale fabrication of pre-filled syringes. Pharmacists could then purchase these 'cartridges' and print the desired, personalized tablets for the individual patient.

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.

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 (Rodríguez-Maciñeiras et al., 2025). 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 (Ayyoubi et al., 2023).

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

7. 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 (Fadda et al., 2024). 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 (Neumann et al., 2017; Barillas et al., 2018; Al-Rayess et al., 2020). 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 (Uçar et al., 2016). 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 (Yin et al., 2014; Ryu and Lee, 2012; Lafeber et al., 2022). 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 h, 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 (Levine et al., 2024).

However, there remains a gap to be addressed for good clinical implementation of personalized 3D printed medicines. Although 3D printing tablets lead 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 (Ayyoubi et al., 2023). 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 (EDQM Council of Europe 2022). 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.

CRediT authorship contribution statement

Ayyoubi S: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Holst AJ:** Investigation, Data curation. **Maduro JE:** Investigation, Formal analysis, Data curation. **Van der Kuy PHM:** Writing – review & editing. **Van Ee RJ:** Writing – review & editing, Supervision. **Van de Velde D:** Writing – review & editing, Supervision. **Valkenburg B:** Data curation. **Hennep C:** Data curation. **Quodbach J:** Writing – review & editing, Supervision. **Ruijgrok EJ:** Writing – review & editing, Supervision, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2025.107180.

Data availability

Data will be made available on request.

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