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ORIGINAL ARTICLE

Design of a Pharmaceutical 3D Printer Using Quality-by-Design Approach

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Abstract

Purpose Pharmaceutical three-dimensional (3D) printing is an innovative production technique which enables the manufacturing of personalized medicine at the point-of-care. A reliable 3D printer is paramount for the successful implementation in clinical practice. In this paper, the design strategy of a pharmaceutical semi-solid extrusion 3D printer is described, where the concept of quality-by-design is applied.

Methods The technical design stages are divided in the conceptual design and detailed design stage. The minimal viable product, critical process parameters and implemented control strategies were defined.

Results The critical process parameter with the highest impact is the temperature of the cartridge during preheating, i.e. prior to the production process. The temperature is controlled with an accurate thermistor, closed feedback loop and thermal isolation. The temperature can be monitored at all times using the graphical user interface and there is an audit trail using the logging system. Software was developed conforming to GAMP5.

Conclusions Build-in control strategies in the design of the pharmaceutical 3D printer can mitigate risks during the production process of personalized medicine. The regulatory landscape surrounding 3D-printed drug products remains challenging. By using this design approach, relevant guidelines were taken into account during the design of a pharmaceutical 3D printer. Future development of the 3D printer should include the incorporation of process analytical technology tools and upscaling of feedstock production to further support the implementation of personalized medicine 3D-printed at the point-of-care.

Keywords 3D printing · Quality-by-design · Personalized medicine · Pharmaceutical technology

Introduction

A growing need for improved patient outcomes of drug treatment incentivizes healthcare to make a paradigm shift towards personalized medicine. Precision dosing, i.e. tailoring the drug dose to an individual patient's need, is the cornerstone of personalized drug treatment aiming at an increased efficacy and reduced risk for adverse drug reactions [1]. However, commercially produced pharmaceutical dosage forms come with a standardized dose and therefore do not support implementation of personalized medicine in clinical practice. Recent developments of innovative technologies such as three-dimensional (3D) printing enable personalized drug manufacturing at the point-of-care, i.e. close to the patient such as in a pharmacy [2, 3]. This challenges the traditional one-size-fits-all mass production of the pharmaceutical industry and allows a shift towards mass personalization. However, unlike traditional drug manufacturing, the possibility to scale-up is still limited and existing regulatory guidelines are not tailored to support the production of 3D-printed personalized medicines [4, 5].

3D printing, also known as additive manufacturing, builds a product in a layer-by-layer fashion onto a print bed. Generally, a computer model is used to design the product that is manufactured with the 3D printer. The greatest flexibility of 3D printing comes from adjusting the geometry of the

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computer model, thereby physically changing the size and form of the pharmaceutical product. This allows adapting the product profile including the drug dose, enabling precision dosing. The advantage of 3D printing over conventional manual compounding is the automation. This reduces the hands-on time needed from specialized, trained pharmacy staff for the preparation of personalized medicine. Compared to regular tablet presses, 3D printers offer the possibility to produce small, individualized batches. In pharmaceutical 3D printing various techniques have been explored and developed to determine their suitability for drug manufacturing. Of these, most often used are extrusion-based techniques, such as fused deposition modelling (FDM), direct powder extrusion (DPE) and semi-solid extrusion (SSE) [6].

When developing new drug formulations, a quality-by-design (QbD) approach is often used as recommended by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) through the ICH guidelines, including ICH Q8: Pharmaceutical Development (R2) [7, 8]. This systematic approach applies statistical, analytical and risk-based management methodology in all stages of drug product design to ensure the quality of the medication. A quality target product profile (QTPP) is first defined for the specific drug product, from which the critical quality attributes (CQA), i.e. physical, chemical, biological or microbiological properties that must meet specific requirements, are identified. Through a risk assessment, the CQA's can be linked to critical material attributes (CMA) and critical process parameters (CPP). By applying appropriate in-process controls (IPC) these critical factors can be monitored and managed.

In contrast, to the best of our knowledge, there is no standard design process for novel pharmaceutical technologies. By combining the concept of 3D printing with the QbD approach, the risks encountered during 3D printing of personalized drug products can be evaluated and subsequently accounted for through build-in control strategies. The aim of this article is to provide a comprehensive, qualitative technical description of a pharmaceutical 3D printer, specifically intended for the production of personalized medicine at the point-of-care, based on a QbD approach. More specifically, the minimal technical requirements of the 3D printer, the critical process parameters and implemented control strategies, and how specific design choices were made, are described.

Methods

The design process consisted of four iterative steps: problem definition, conceptual design, detailed design and evaluation (Fig. 1). This design process led to the development of the DoseRx-1 pharmaceutical 3D printer (Leiden, The Netherlands), i.e. the current design state of the product which is described in this article. A qualitative description of each design step is provided in the results.

The problem was defined as a lack of available personalized dose drug formulations. This resulted in a corresponding conceptual design of a 3D printer able to print personalized drug products. The conceptual design was elaborated in the minimum viable product (MVP), describing the principles of this semi-solid extrusion 3D printer, as well as the technical requirements minimally necessary for the 3D printer to be used at the point-of-care. These requirements were dependent on the QTPP.

During the detailed design stage, the design of the 3D printer was further defined. First, a QTPP was designed which then was tested with a specific drug product, namely 3D-printed sildenafil tablets used in a previously conducted clinical trial studying the bioavailability [2]. There is a clinical need for a low dosage strength and flexible formulation containing sildenafil, suitable for the treatment of young children with pulmonal hypertension. Additionally, sildenafil is difficult to print with SSE, as the solubility in the used carrier (PEGylated fatty acids) is low. It forms a suspension, introducing challenges such as

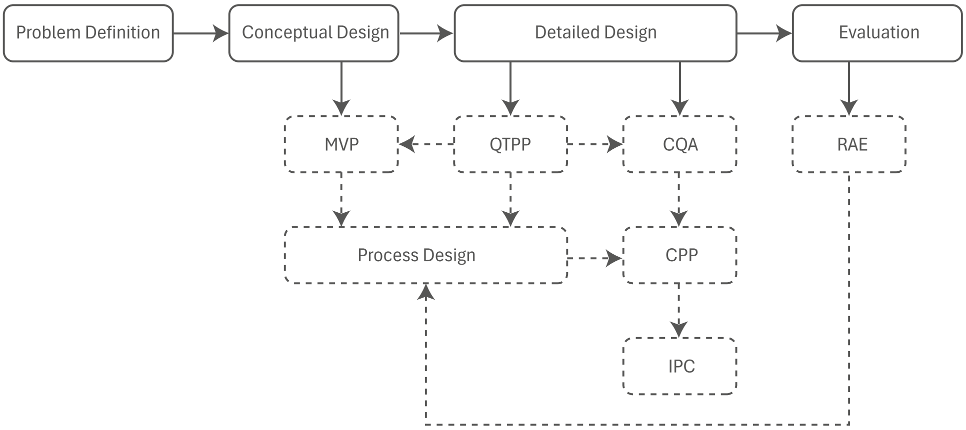


Fig. 1 Overview of the design process. The minimum viable product (MVP), quality target product profile (QTPP), critical quality attributes (CQA), critical process parameters (CPP) and in-process controls (IPC) are all linked. During evaluation a risk assessment and evaluation (RAE) is performed

settling behavior and clogging. From the QTPP, the critical quality attributes (CQA) were defined that are necessary to ensure that the tablets produced with the 3D printer comply with pharmaceutical standards. The QTPP drafted for the 3D-printed sildenafil tablets is used in this article for demonstration purposes.

The QTPP together with the MVP resulted in a detailed description of the production process. This article focusses on the 3D printing process. Preprocessing, e.g. development and production of the feedstock, and the post-processing steps, e.g. analytical methods and cleaning processes, are considered out of scope. A concise overview of the production process steps, including non-critical process parameters, is provided in the Supplementary Materials. Based on previous research, prospective risk assessments and evaluations (RAE), and factory and site acceptance tests, the process parameters were defined as either critical or non-critical. In a risk assessment and evaluation, each process step was scored (low, medium, high) on the severity of the risk for the patient/operator, the product and the data integrity if a process step were to fail, the probability of a process failure to occur, and the detectability of a process failure. The detailed results of the tools to determine the criticality of the process steps are not provided in this article, but are available upon individual request. The overall risk of CPP's on the respective CQA's is provided. Based on iteration of the tests and RAE, the 3D printer design was adapted and control measures were implemented as described in this article.

Results

Quality Target Product Profile

The QTPP of 3D-printed sildenafil tablets as it was used in the previously performed clinical trial is shown in Table 1. The following CQA's were identified: sildenafil citrate identity, content and homogeneity, release kinetics, uniformity of weight and deviation from theoretical weight, chemical and microbiological stability, mechanical strength, and packaging. The attribute targets and their criticalities are dependent on circumstances, e.g. on the drug product and intended treatment population. For example, the tablet size was defined not critical for the use in healthy adults but could be critical for pediatric patients. Likewise, for sildenafil citrate the dissolution profile was an immediate release product, while for other drug products extended or sustained release may be applicable.

Not all compendial tests may be suitable for 3D-printed drug products. An alternative requirement for the weight distribution was used in this QTPP. The Ph. Eur. monograph

Table 1 Quality target product profile (QTPP) of 3D-printed sildenafil tablets

QTPP element	Target	Criticality	Justification
Dosage form	Tablet	Not applicable	-
Route of administration	Oral	Not applicable	-
Dosage form strength	10 mg sildenafil (as citrate)	Not applicable	Ensured through content uniformity
Dosage design	Immediate release	Not applicable	Ensured through release kinetics
Tablet size	Max. diameter: 7.5 mm Max height: 3.5 mm	Not critical	Intended for use by healthy adults in the clinical trial
Appearance	Round; off-white; layered	Not critical	Concerns an open-label trial
Container closure system	Suitable for this drug product	Critical	Needed to ensure shelf life
Weight	Meets Ph. Eur. 2.9.5, or RSD ≤ 4.0% Deviation between mean weight and theoretical weight ≤ 3.0%	Critical	Needed to ensure dosage strength
Content uniformity	Meets Ph. Eur. 2.9.40	Critical	Must meet compendial standard
Release kinetics	Immediate release: meets Ph. Eur. 2.9.3: ≥ 80% of labelled content dissolved at 45 min	Critical	Pharmaceutical equivalence requirement: must meet compendial standard for immediate release kinetics
Mechanical strength	No splitting of layers and/or breaking off large pieces of tablet after standard handling	Critical	Needed to ensure dosage strength after handling
Microbiological purity	Meets Ph. Eur. 5.1.4	Critical	Needs to be safe to use in humans: must meet compendial standard
Stability	Stable for at least 6 months at 25 °C	Critical	Needs to be safe to use in humans for complete shelf life of the product

2.9.5. *Uniformity of mass of single-dose preparations* requires weight measurement of at least 20 dosage form units, e.g. tablets, to assure that the mass is uniformly distributed. In pharmacy preparation often a more rigid standard is applied when only 10 units are weighed. A relative standard deviation (RSD) of $\leq 4.0\%$ for tablets with an average weight ≤ 300 mg, or otherwise an RSD of $\leq 3.0\%$, assures that the manufactured tablets adhere to the Ph. Eur. Monograph 2.9.5 [9]. Additionally, the deviation between the measured average weight and the theoretical weight should be $\leq 3.0\%$ [9]. This ensures that the 3D-printed tablets comply with weight specifications in accordance with the production protocol, i.e. to ensure the drug products are 3D-printed accurately. As 3D printing provides ample flexibility for personalized drug products, we consider it an important additional specification, though it is not a compendial requirement.

Compendial requirements for the assessment of the mechanical strength of tablets are not suitable for 3D-printed tablets [10]. Ph. Eur. Monographs 2.9.7 *Friability of uncoated tablets* and 2.9.8 *Resistance to crushing of tablets* describe the tests to determine the mechanical strength of tablets. However, 3D-printed tablets are not compressed, which is the assumed manufacturing method by the tests, but built layer upon layer. This means the mechanical strength is not dependent on particle adhesion, but rather on layer adhesion. No compendial test exists for testing layer adhesion, therefore tablet integrity after standard handling was used as a requirement in this QTPP. Since tablets produced at point-of-care do not undergo rigid handling comparable to industrially produced tablets, the tablet integrity test can be used, but a specific test for layer adhesion is warranted.

Minimum Viable Product (MVP)

The pharmaceutical 3D printer design should allow manufacturing of drug products as defined in the QTPP. The 3D printer is designed to be operable conform GMP standards as described in EudraLex Volume 4 [11]. Technical design aspects that were considered for the MVP were the printhead, cartridge, print bed and the respective position of the printhead hereupon, user interface and design software. Their materials are selected to comply to GMP standards for cleaning and chemical interaction.

The printhead is purposefully designed for SSE 3D printing of personalized medicine. The general principle of SSE is the extrusion of a semi-solid mixture from a cartridge or syringe. Typically a gel or paste is used as the semi-solid substance in question. The semi-solid is accurately deposited onto the print bed in a layer-by-layer fashion. This technique operates at a low production temperature and no solvents are needed to obtain a printable feedstock reducing the risk of chemical instability. In addition, without the use of solvents, the production process is simplified as solvents do not have to be evaporated from the drug product after printing. It reduces the number of production steps and no test for residuals is required. Typically, non-Newtonian substances are used in SSE 3D printing [12, 13]. Therefore, the printhead is designed to be able to process these types of feedstock, where rheology is especially important for printability.

An important part of the printhead is the cartridge. It is designed as a reusable stainless-steel cartridge with a unique identifier to allow traceability. A reusable cartridge makes it possible to use more expensive materials with low chemical interactivity, to employ precision machining operations, tightly integrating functionality into one part and to help reduce waste. Stainless steel AISI316L was specifically selected because it is widely used in biotech and pharmaceutical equipment, and it can be cleaned through many cleaning procedures. Multiple cartridge volume sizes are available to accommodate production of drug products for multiple patient populations. A small cartridge size allows careful extrusion of a limited volume, making it more suitable for high-resolution tablets, e.g. minitablets. Larger cartridges allow production of high-volume drug products, e.g. tablets with high dosages of an active pharmaceutical ingredient (API) intended for the adult patient population. The cartridge is fully encased with a heating mat and isolation materials to keep a consistent temperature within the cartridge. This results in an even extrusion of the feedstock onto the print bed.

The printhead is connected to pressurized air or equipped with a mechanical plunger, which allow controlled extrusion of the feedstock from the cartridge through the use of a piston. Pneumatic actuation has a relatively high systematic error, decreasing the printing accuracy, specifically for smaller drug products, e.g. when printing mini tablets. Mechanical actuation has a larger physical volume and weight, as the actuator scales up with the size of the cartridge. The size of a pneumatic actuator have, does not depend on the stroke of the cartridge, making them more suitable for high volume drug products requiring larger cartridges.

The print bed is made of AISI316L stainless steel and is removable from the pharmaceutical 3D printer to allow easy cleaning. The distance between the print bed and the nozzle of the cartridge is critical for the uniformity of tablet weight and mechanical strength. Keeping a constant distance between the print bed and the nozzle is dependent on at least three factors (Fig. 2). The print bed and the movement of the nozzle in the XY plane must be planar and parallel, and any distortions need to be measured in a multipoint grid. The difference in height on the various grid points then can be corrected through the movement of the nozzle in the Z direction, compensating for the errors and effectively making the two planes to be planar and

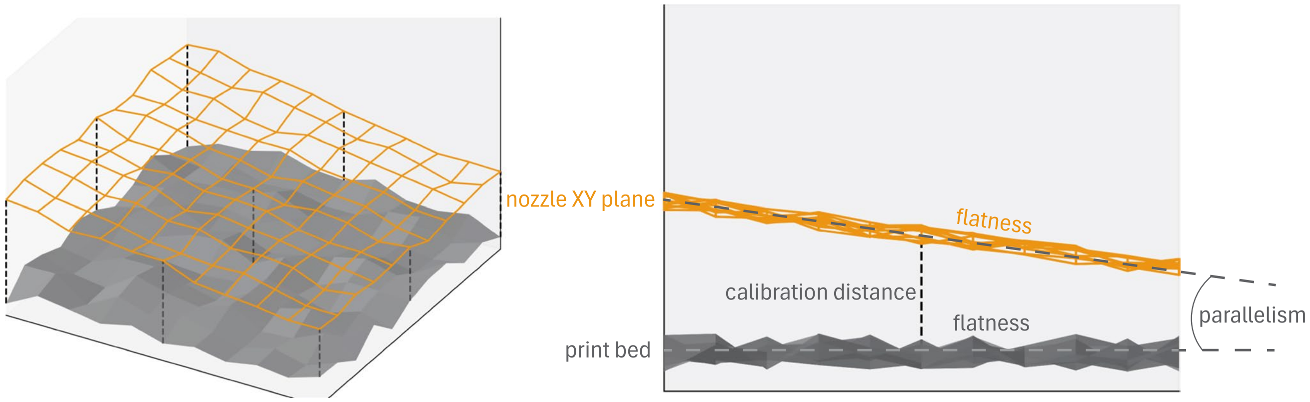


Fig. 2 Visual representation of flatness and parallelism of the print bed (bottom) and the nozzle XY plane (top). The print bed and movement of the nozzle in the XY direction are not perfectly planar, nor parallel to each other

parallel. Finally, the exact distance between the two planes is measured and set, based on the production parameters. Additionally, if multiple printheads are used, all printheads have to be calibrated so their nozzles have equal offsets from the print bed. This would, for example, occur when printing polypills.

The enclosure of the pharmaceutical 3D printer is designed to provide a protected production environment. It is closed during manufacturing to prevent manual intervention in the production process and to allow the fan to rid the production environment of residual heat from the production process. Opening the enclosure results in immediate termination of the production process, protecting the operator from burns or mechanical injury.

The software used to direct the pharmaceutical 3D printer is developed conform GAMP5, a framework to ensure that pharmaceutical computerized systems are of high quality and comply with the applicable regulations [14]. The design software, e.g. for geometrical design of the drug product, accepts parametric input. This allows for a simplified design process of the drug product, reducing the risk of production errors. Through the graphical user interface (GUI), the actual values of printer parameters are shown, e.g. the live cartridge temperature at any given time. During the production process these values are logged, allowing an audit trail and therewith root-cause analysis in case of any production abnormalities. Furthermore, the GUI has a login system to ensure only qualified personnel can operate the 3D printer. Role assignments are integrated in the login system to limit functionalities to the qualifications of a specific user, e.g. an administrator, but not an operator, is allowed to create new users. The GUI also has basic operating functions, such as input parameters for a production process, and starting and stopping the production process.

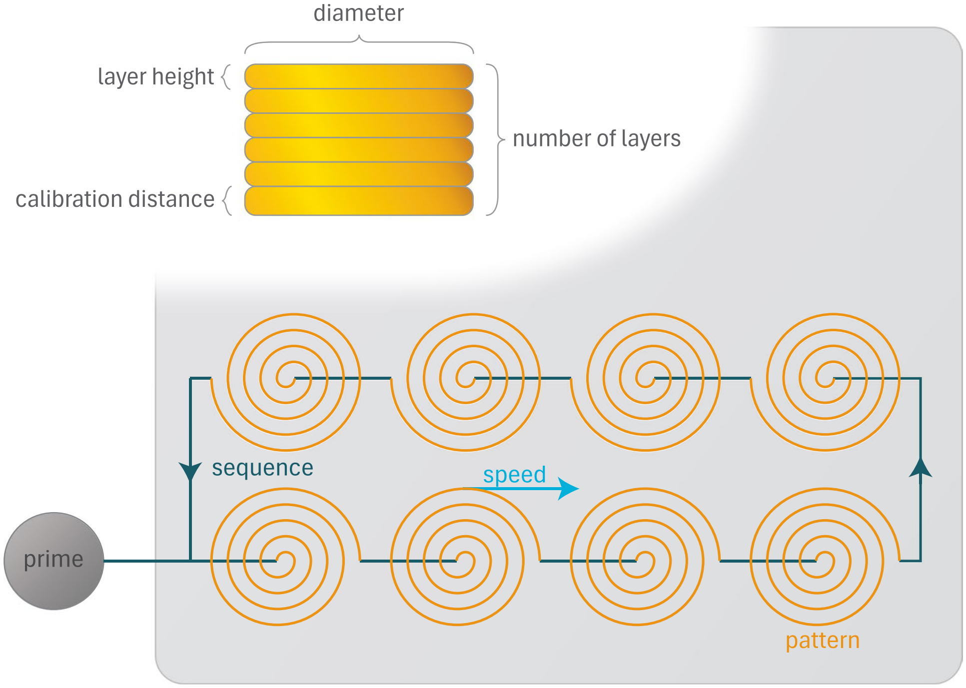
Production Process Description

The production process of personalized 3D-printed drug products generally consists of three phases, namely preprocessing, production and post-processing. Preprocessing consists of preparing the cartridge for production, i.e. making the feedstock and filling the cartridge. In this article, the feedstock is the printable substance or mixture which can include an API. During the production phase a filled cartridge is used to manufacture personalized drug products for an individual patient. The same cartridge can be used to provide multiple patients with their respective personalized medication. In the post-processing phase, the drug products are analyzed and packaged, and the pharmaceutical 3D printer is cleaned. In this article, the pre- and post-processing phase are considered out of scope.

The production phase consists of five steps, namely 1) defining the production program using parametric design, 2) initialization of the 3D printer, 3) priming of the cartridge, 4) 3D printing, and 5) finalization of the production process. A schematic overview of the production phase steps and the associated process parameters can be found in Supplementary Materials. In the first step, the 3D printing parameters are chosen and defined using parametric design software (Fig. 3). For example, when the drug products in question are tablets, the number of tablets, shape, target mass, layer height, and the number of printheads are defined. Furthermore, the printing sequence, i.e. the order in which the tablets are 3D-printed, is determined. It also defines the number of rows and columns, and whether the drug products are 3D-printed per layer or per drug product.

During the initialization step, the cartridge is installed in the printhead. The cartridge is slid into the printhead, meaning it is completely enclosed by the heating mat, leaving only the outer tip of the nozzle exposed to the environment. The plunger is lowered until it touches the piston in the cartridge.

Fig. 3 Overview of the printing sequence, where the cartridge first is primed, then moved onto the print bed where it prints layers in the predefined shape/pattern at a certain movement speed



The nozzle is then calibrated to the print bed, making sure the nozzle is at the correct distance from the print bed. The printhead moves to its starting location, i.e. home position. Finally, the cartridge and the nozzle are heated to their respective temperature using the heating mat and thermistors. The preheating temperature and duration are dependent on the melting or glass temperature, thermal conductivity and heat capacity of the feedstock, and are chosen to ensure it is at a printable, thick semi-solid consistency to prevent settling of any solid components.

After the cartridge is uniformly preheated, the priming step starts. The aim of the priming step is to extrude feedstock that may have been extensively heated in the nozzle compartment during preheating or exposed to air through the nozzle opening for prolonged periods of time, as well as ensuring a constant and even extrudate from the nozzle. The nozzle heater only heats the very tip of the cartridge where feedstock is extruded. The nozzle itself only contains < 1μL of material. An excess of 280μL is extruded to ensure complete flushing of the nozzle compartment prior to printing. The 3D printing process starts immediately after priming (Fig. 4). The drug products are produced per the predetermined production program made with the parametric design software. Pressure is applied to the piston, either mechanically or pneumatically, resulting in extrusion of the feedstock from the nozzle during printing. The cartridge diameter and the nozzle diameter determine how much feedstock can be extruded in a specific time frame, where more volume is moved with a larger cartridge diameter and more volume can be extruded with a larger nozzle diameter. Between tablets, printing is halted by means of retraction, defined as a combination of retraction amount, i.e. the upwards movement distance of the piston, and the retraction speed, i.e.

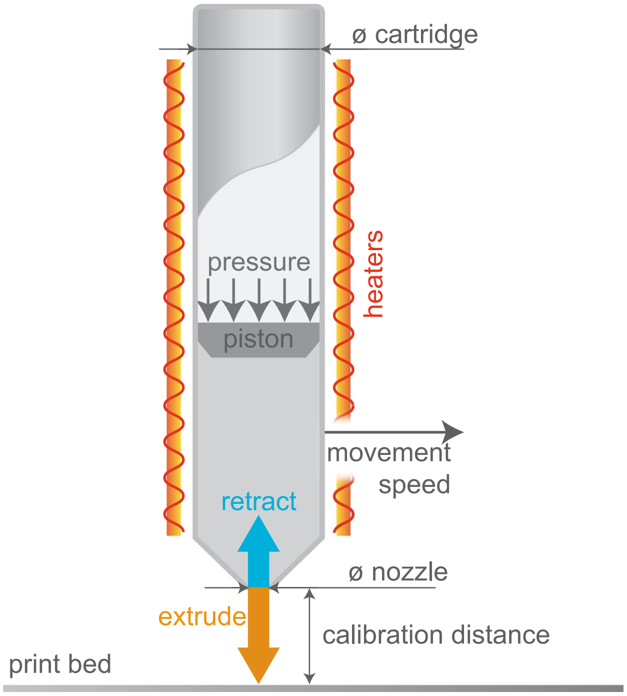
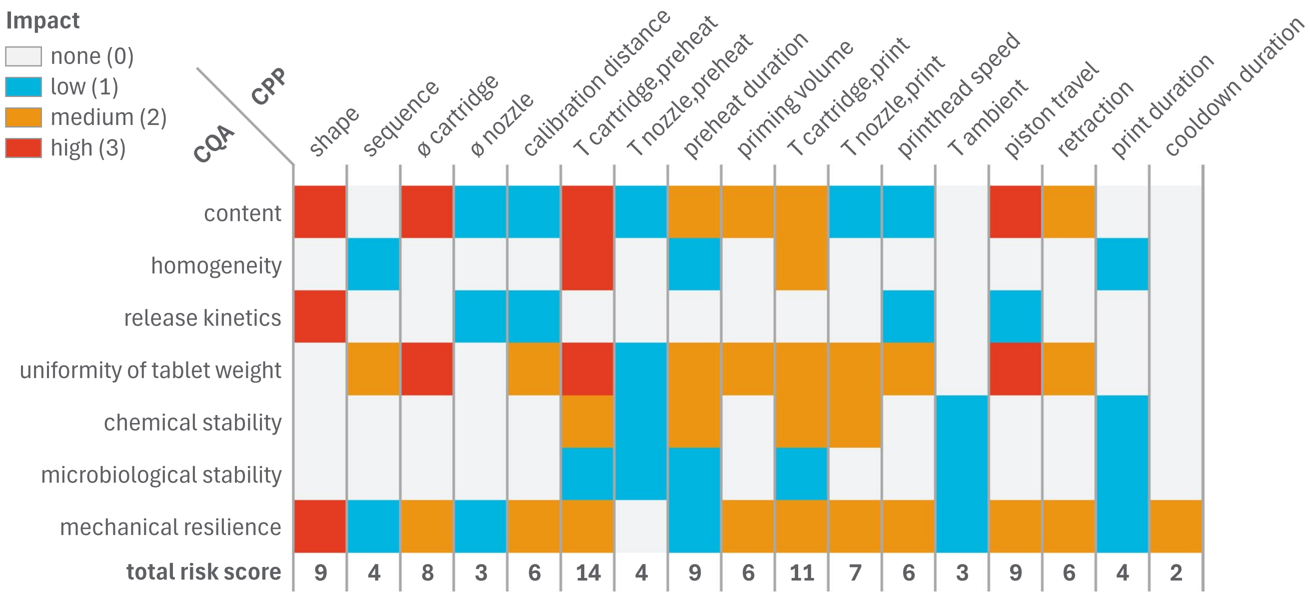


Fig. 4 Schematic representation of the semi-solid extrusion printhead during 3D printing



Impact
⬜ none (0)
🟦 low (1)
🟧 medium (2)
🟥 high (3)

CQA \ CPP	shape	sequence	ø cartridge	ø nozzle	calibration distance	T cartridge,preheat	T nozzle,preheat	preheat duration	priming volume	T cartridge,print	T nozzle,print	printhead speed	T ambient	piston travel	retraction	print duration	cooldown duration
content	🟥	⬜	🟥	🟦	🟦	🟥	🟦	🟧	🟧	🟧	🟦	🟦	⬜	🟥	🟧	⬜	⬜
homogeneity	⬜	🟦	⬜	⬜	⬜	🟥	⬜	🟦	⬜	🟧	⬜	⬜	⬜	⬜	⬜	🟦	⬜
release kinetics	🟥	⬜	⬜	🟦	🟦	⬜	⬜	⬜	⬜	⬜	⬜	🟦	⬜	🟦	⬜	⬜	⬜
uniformity of tablet weight	⬜	🟧	🟥	⬜	🟧	🟥	🟦	🟧	🟧	🟧	🟧	🟧	⬜	🟥	🟧	⬜	⬜
chemical stability	⬜	⬜	⬜	⬜	⬜	🟧	🟦	🟧	⬜	🟧	🟧	⬜	🟦	⬜	⬜	🟦	⬜
microbiological stability	⬜	⬜	⬜	⬜	⬜	🟦	🟦	🟦	⬜	🟦	⬜	⬜	🟦	⬜	⬜	🟦	⬜
mechanical resilience	🟥	🟦	🟧	🟦	🟧	🟧	⬜	🟦	🟧	🟧	🟧	🟧	🟦	🟧	🟧	🟦	🟧
total risk score	9	4	8	3	6	14	4	9	6	11	7	6	3	9	6	4	2

Fig. 5 Results of the risk analysis of relation between CPP and CQA. The impact of a CPP on a CQA is scored as none (0), low (1), medium (2) or high (3)

the movement speed with which the piston moves upwards. As the 3D printer operates at a low temperature, but not ambient, the 3D-printed tablets have to cool briefly before recovering them from the print bed.

Critical Process Parameters

From the production phase (Section 3.2; Supplementary Materials), the following process parameters are defined to be critical: drug product shape, printing sequence, cartridge diameter, nozzle diameter, calibration height, preheat cartridge temperature, preheat nozzle temperature, preheat duration, priming volume, 3D printing cartridge temperature, 3D printing nozzle temperature, 3D printing duration, printhead movement speed, extrusion speed, retraction, ambient temperature, and cooling duration. Figure 5 shows the results of the risk analysis on the effect that the CPP's have on the CQA's and their relative criticality. The impact of the CPP's on the CQA's is scored as either no, low, medium or high risk. The scores are based on previous research, prospective risk assessments and evaluations, and factory and site acceptance tests.

The CPP with the highest risk is the cartridge temperature during preheating. During the preheating stage, the feedstock is exposed to heat for a prolonged period of time. If the temperature is too high, the viscosity of the feedstock can become too low. This potentially leads to settling of solid components, as well as leaking through the nozzle during the preheating period, and liquid deposition during the 3D printing stage. Prolonged exposure to a high temperature, i.e. the preheating duration, can also result in chemical instability of any of the individual components. In contrast, if the temperature is too low, the feedstock will be too solid to be printable during the printing stage. Even if it is printable, the extrudate will be inconsistently printed, reducing the layer adhesion and thus the mechanical strength. The consequences of a low temperature can be resolved, while the consequences of a too high temperature are likely to be irreversible, e.g. a settled suspension due to high temperature cannot be reliably resuspended in the cartridge.

Similarly, the nozzle temperature is also critical during preheating, and both the cartridge and nozzle temperature are critical during the 3D printing stage. However, the impact of these process parameters is limited compared to the cartridge temperature during preheating. The feedstock exposed to the nozzle temperature during preheating is expelled during the priming stage. Nonetheless, there is a chance overexposed feedstock is not expelled during the priming stage, e.g. from limited flow in the nozzle or heat radiation to the cartridge. During the 3D printing stage, the feedstock is moved constantly, resulting in decreased exposure to an incorrect temperature. Substantial temperature deviations can still lead to unsuccessful production, i.e. from settling of solid components, liquefaction or solidification of the feedstock. An increased temperature combined with prolonged exposure, e.g. during long production runs, can result in chemical instability. Conversely, heating at body temperature for a prolonged period of time could stimulate microbial growth. A high ambient temperature prevents solidification of the drug products after production. If the drug products are not completely solidified before recovery from the print bed, the layer adhesion is reduced with a decreased mechanical strength as a result. On the other hand, if the ambient temperature is too low, the extrudate will solidify too quickly during 3D printing, also resulting in reduced layer adhesion.

The shape of the drug product, defined in the production program with the parametric design software, determines the drug content as well as the release kinetics. If the shape is completely filled with mixture, i.e. 100% infill, small tablets will contain less API compared to large tablets. If the same shapes are made with less infill, the surface area to volume ratio increases, therewith increasing the drug release rate [15]. Besides geometrical settings, the extruded amount of feedstock influences the correct formation of the shape of the drug product. The extruded amount is the resultant of the cartridge diameter, the downwards movement of the piston, i.e. piston travel, and the nozzle diameter. An increase in the cartridge diameter and piston movement leads to a higher volume shift of the feedstock. The nozzle diameter is the bottleneck of the extruded amount per time unit. The nozzle diameter should be large enough to be able to process the volume shift. A smaller nozzle will have a greater back pressure on the feedstock, changing the viscosity and elastic recovery of the feedstock as it is likely and preferably a non-Newtonian substance [12]. The correct nozzle diameter is even more important when solid particles are present in the feedstock as these particles can clog the nozzle, obstructing the 3D printing process.

Furthermore, the printing sequence, calibration height, printhead movement speed in the XY direction and retraction are defined as CPP’s. The printing sequence determines in which order drug products are printed onto the print bed and whether they are 3D-printed per layer or per drug product. In a previous study it was determined that multiple rows and columns, allowing continuous 3D printing, is beneficial for the uniformity of weight [10]. Moreover, the printing per layer or per drug product also influences the solidification of a layer prior to printing the subsequent layer on top, possibly impacting the mechanical strength.

The calibration height, i.e. the calibrated distance between the nozzle and the print bed, defines the height for the first layer. If the actual value is higher than the expected value, the extruded amount will not be enough to fill the void between the nozzle and the print bed. The first layer will not properly adhere to the print bed, resulting in reduced mechanical strength, or even no adherence of the layers at all. Conversely, if the actual height is lower than expected, the layer gets squished, leading to contamination of the nozzle and reduced mechanical strength.

The printhead improves layer adhesion by moving slowly enough to allow proper deposition of the extrudate. Increasing the printhead movement speed, combined with a proportional increase in extrusion speed, can decrease printing duration, therewith reducing the exposure time of the feedstock to the cartridge and nozzle temperature.

Retraction, consisting of the retraction speed and retraction length, is needed to produce multiple drug products, e.g. multiple tablets, in a single production run that are detached from each other. Too little retraction leads to stringing at the end of the drug products, while too much retraction leads to infiltration of air in the feedstock. Both compromise the drug content, the uniformity of weight, mechanical strength and, in case of too little retraction, visual appearance.

Mitigations and Control Strategies

After identifying the process parameters and their criticality, several mitigations were identified and implemented. As each CPP has a different mechanism of impacting the print process, different types of mitigation were employed (Table 2). IPC’s are used when a specific set point needs to be reached and maintained. IPC’s are used when Impact is high, as they are often complex to implement. Generally, IPC’s are feedback control loops, that base the control input on real-time measurements of the system, although feed-forward control strategies can also be used. Calibrations are employed to make sure that CPP’s are within specification over time. Finally, specifications can be set to ensure the printing process is executed in a predictable and repeatable manner. These specifications can be set in the software, for instance when generating the print path, but are also found in standard operating procedures. Additionally,

Table 2 The mitigation strategies used for each critical process parameters (CPP)

CPP	Impact	Mitigation
Shape	**9**	IPC, specification
Sequence	**4**	specification
ø cartridge	**8**	specification
ø nozzle	**3**	specification
Calibration distance	**6**	calibration
T cartridge,preheat	**14**	IPC, calibration, specification
T nozzle,preheat	**4**	IPC, calibration, specification
Preheat duration	**9**	specification
Priming volume	**6**	specification
T cartridge,printing	**11**	IPC, calibration, specification
T nozzle,printing	**7**	IPC, calibration, specification
Printhead speed	**6**	IPC, specification
T ambient	**3**	specification
Piston travel	**9**	IPC, specification
Retraction	**6**	specification
Print duration	**4**	specification
Cooldown duration	**2**	specification

tighter manufacturing tolerances can be specified to decrease the impact of geometry or measurements on the printing process.

The cartridge and nozzle temperature are controlled using a thermistor suitable for use over the range from −80 °C –+150 °C, with a top precision of ±0.1 °C in the range of 0 –+70 °C. The thermistors of the cartridge and the nozzle keep the cartridge and nozzle at specified temperatures using a feedback loop. The temperatures can be regularly checked by the operator through the GUI, while the temperature curves can be retraced using the logging system (Fig. 6). Initially, the temperature increases during the preheating phase until it reaches the input temperature. During the 3D printing phase, the thermistors aim to keep the temperature at the input temperature. Small fluctuations are inevitable, though with the use of the used thermistors should not exceed ±0.1 °C with a maximum target temperature of 70 °C. Isolating materials around the cartridge and the nozzle ensure minimal loss of energy towards the environment, minimizing temperature fluctuations and preheat time. To ensure a stable environmental temperature during heating, the enclosure of the 3D printer is equipped with a fan.

The flow of the extrudate from the nozzle is controlled using a closed feedback loop on the piston travel distance [16]. The feedback loop ensures movement of the piston at a constant speed, i.e. the extrusion speed, which indicates that a constant volume is extruded throughout the printing process irrespective of the viscosity of the feedstock over time. For this to be true, the condition must be met that the diameter is the same throughout the cartridge. Therefore, a strict fabrication tolerance on the cartridge diameter is needed. Obstruction of the nozzle or insufficient preheating can be detected by a decreased travel distance of the piston. Therewith, the production process can be terminated in a timely manner.

Correct deposition of the extrudate onto the print bed is controlled through a 3-level calibration process, where the distance between the nozzle and print bed, the parallelism between the print bed and the XY nozzle plane, and the flatness of both planes is determined. The distance between the nozzle and print bed is determined using a DIN 2275 T2 calibrated feeler gauge. By setting the distance with this feeler gauge on three points on the print bed, the parallelism of the planes is ensured. Finally, the flatness of both planes is ensured by the fabrication tolerance of the print bed and the linear gantry.

Discussion

In this article we present the design of a pharmaceutical 3D printer, suitable for use at the point-of-care, using a QbD approach. The QbD approach, that is widely employed in the development of new drug formulations, was successfully applied to the design decisions for a pharmaceutical 3D printer. Through the design process, process parameters and their influence on CQA's have been identified using a risk assessment. The cartridge temperature during preheating and 3D printing, as well as the duration of the exposure of the feedstock to this temperature, were considered especially critical and were controlled using a closed feedback loop with a precision thermistor and isolating materials. Moreover, the temperatures of both the cartridge and the nozzle can be checked live during 3D printing of the drug products as an IPC, as well as in retrospect through a built-in logging system. By implementing control strategies into the design of the pharmaceutical 3D printer, risks can be mitigated during the production phase, allowing use of the 3D printer at the point-of-care for the production of personalized drug products.

With the current design of the 3D printer, most of the identified CPP's are controlled. Risks remain in the flexibility of defining the production program, though this is also the advantage of 3D printing at the point-of-care, i.e. flexibility in the shape of the drug product allows precision dosing. This intrinsically has the risk of introducing a drug product design error. The software used to program the shape should be robust and give confidence that the correct shape is produced for every production run. Therefore, we chose to use parametric design software. In parametric design print path generation, assumptions are made by the programmer regarding the shape of the drug product and the

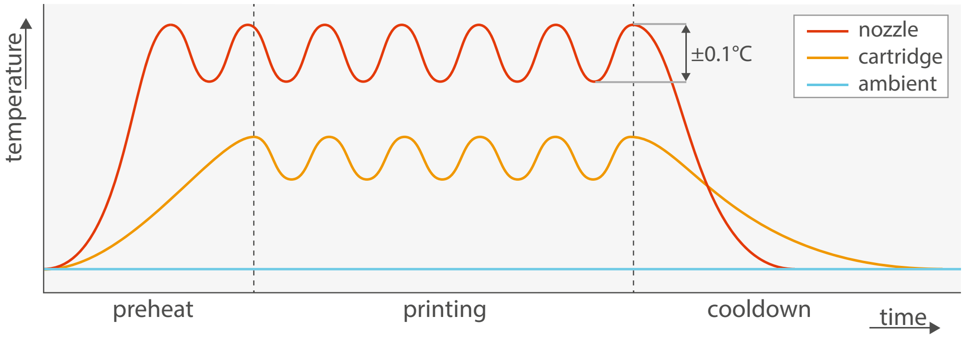


Fig. 6 Schematic temperature curves of the cartridge (orange), nozzle (red) and ambient temperature (blue), with a temperature tolerance of ±0.1 °C

user's 3D printer. This limits the drug product design possibilities, but also reduces the design error. As this parametric design software was specifically developed for personalized drug products, the needed flexibility is built in. This is unlike computer-aided design (CAD) and slicer software, which are commonly used in 3D printing. With CAD software, virtually any shape can be created, which allows production of intricate structures or visually appealing drug products, e.g. to regulate drug release profiles [17] or for pediatric patients [18], respectively. Slicer software then converts this computer model into a readable file by the 3D printer. The user-friendliness and technical capabilities of these applications vary and it should be carefully considered whether they meet all requirements.

Besides documents describing the common process for medical device development, e.g. US FDA regulation 21 CFR 820 Subpart C Design Controls and ISO 13485 [19, 20], the International Medical Device Regulators Forum (IMDRF) issued a document in 2023 where the concept of a medical device production system (MDPS) was introduced, i.e. considering the raw materials, production and post-processing equipment, software and digital files, operating instructions, and the resultant medical device thereof as a coherent system [21], including key considerations for the MDPS design development and validation activities [22]. Although a 3D printer is not a medical device and the document explicitly stated that drug products are outside the scope of these documents, a similar construction could be considered for 3D printing of personalized medicine at the point-of-care. This integral approach allows greater confidence in the functioning of the system as a whole. Regardless of the used system, the responsible pharmacist should always do a final check whether the envisioned production process indeed results in the correct dose and suitable dosage form for the individual patient.

Across different 3D printing techniques for production at the point-of-care, the relation between the CQA's drug content and release kinetics, and CPP's is investigated most often, generally using a design of experiments. The identified CPP's can vary between different 3D printing techniques. In inkjet printing, also known as drop-on-demand, the pressure channel, system calibration, nozzle size and dispensed volume were defined as CPP's [23]. Process parameters affecting CQA's in SLS are laser power, scan speed and layer thickness [24]. While with FDM 3D printing, the printing temperature, speed and tablet design, including tablet size, infill percentage and layer height, were found to be CPP's [25, 26]. Interestingly, for extruding techniques the nozzle size is often defined as a CPP which influences the visual quality of 3D-printed drug products, because the printing resolution is lower. However, smaller layer heights with the same nozzle can result in high resolution drug products with only a limited effect on the quality attributes [27]. This allows the design of a cartridge with an integrated nozzle.

In this study, no design of experiments was performed, therefore the impact size of the CPP's on the CQA's and the consequential design space of each CPP were not determined. The design space is likely to vary between feedstock, as it is dependent on material attributes [8], but not determined in this study. The aim of this study was to develop a pharmaceutical 3D printer which can print a wide range of feedstock. Therefore, the control strategies on the CPP's were defined independent of the design space and CMA's. During the preprocessing phase, i.e. during development and production of the feedstock, the design space of each CPP for that specific feedstock should be determined as well as the CMA's. The design space and CMA's should be determined for each 3D printer which is able to process the feedstock, to allow considering the feedstock as part of an MDPS.

Currently, the pharmaceutical 3D printer can only be used at the point-of-care with specialized compounding facilities. Indeed, the pre- and post-processing phases limit the use at other point-of-care facilities. The preprocessing phase ideally takes place at a centralized production facility, e.g. the pharmaceutical industry or experienced production pharmacies. Their equipment and know-how allows proper development and production of feedstock, which could be considered as intermediary drug products. Rigid quality control and stability studies can be performed at these centralized production facilities. Subsequently the intermediary products can be distributed to point-of-care facilities with a pharmaceutical 3D printer, where the final drug product is produced for an individual patient. This concept was successfully investigated in an international multicenter study with automated dosing technology [28]. The cartridges in this paper were designed to be reusable, i.e. they can be used in a circular system, where the cartridge is either prefilled by the feedstock manufacturer, or refilled at the point-of-care by the end-user. The cleanliness of the cartridges and the 3D printer are very important, but not addressed in this paper. Therefore, before use at the point-of-care, the 3D printer should pass cleaning validations to ensure no cross contamination occurs between batch productions.

To truly allow integration at point-of-care facilities, the pharmaceutical 3D printers should be equipped with in-line or post-processing tools to ensure consistent quality and an end product that complies to the specifications. Process analytical technology (PAT) tools have been investigated to analyze CQA's. Near-infrared spectroscopy has been investigated as an in-line PAT tool, i.e. integrated analysis in the production line, for drug content measurements [29, 30]. Others have integrated a balance in the print bed to measure the weight of the drug products during manufacturing [28, 31]. Post-processing can be streamlined by printing directly in the final packaging, e.g. blisters [28]. While technically challenging due to the layer height being a CPP in pharmaceutical 3D printing, direct-to-package printing limits the contact time of the operator with the drug product, improving its safety and stability.

Conclusion

The pharmaceutical 3D printer described is suitable for use at the point-of-care with specialized compounding facilities. Critical process parameters, which influence the critical quality attributes, are controlled through technical design strategies to allow processing of a wide range of feedstock into personalized 3D-printed drug products. While the regulatory landscape remains a challenge regarding 3D-printed drug products, relevant guidelines were taken into account during the design of the 3D printer. Continued development leads to incorporation of process analytical technology tools and upscaling of the feedstock development, further improving the quality, safety and accessibility of 3D-printed personalized medicine produced at the point-of-care.

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Declarations

Ethics Approval Not applicable.

Informed Consent Not applicable.

Competing Interests IL, TWJB, HJG and KJMS declare that they have no financial interests. NO, CEO and shareholder of Doser BV, and WHU, shareholder of Doser BV, declare that they have financial interests in Doser BV. The authors have no non-financial interests to declare.

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