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ORIGINAL ARTICLE

3D Drug Printing by Semi-Solid Extrusion Through Reusable Cartridges: Usability Evaluation

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Abstract

Purpose Three-dimensional (3D) printing is revolutionising tablet fabrication in the field of pharmacy, offering personalised dosing through additive manufacturing techniques such as semi-solid extrusion (SSE). SSE traditionally uses disposable syringes, which pose challenges in temperature control and waste generation.

Methods This article experimentally simulates various scenarios relevant to pharmacy practice to evaluate the usability of the semi-solid extrusion approach using a first-of-its-kind reusable cartridge. The research assesses the stability of formulations under thermal stress conditions that simulate commercial settings, demonstrating the robust performance of this 3D drug printing method across multiple uses.

Results This study introduces pharmaceutical-grade stainless-steel cartridges as a sustainable alternative to disposable syringes, enhancing temperature management and reducing waste in SSE 3D printing.

Conclusion Our findings highlight the potential of reusable cartridges to improve efficiency and sustainability in pharmaceutical manufacturing, with implications for future formulation developments and stability studies. The presented 3D drug printing approach offers a promising solution for environmentally responsible practices in pharmacy.

Keywords 3D printing · Sustainability · Semi-solid extrusion

Introduction

Three-dimensional (3D) printing technology is emerging as a revolutionary approach to tablet fabrication in the pharmaceutical industry, enabling personalised dosing. 3D printing is an innovative additive manufacturing technology that can fabricate desired structures layer by layer [1]. In addition to personalised dosing, 3D printed medications offer improved compliance through precise dosing, taste and odour control, and polypharmacy [2, 3].

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Semi-solid extrusion (SSE) is a subset of material extrusion 3D printing that uses the sequential deposition of layers of gel or paste to create objects of any desired size and shape. SSE 3D printing employs low printing temperatures, making it suitable for drug delivery and biomedical applications [4]. The SSE printing process begins by generating the desired 3D model structure using Computer Aided Design (CAD) software [5]. Any modifications to the final object can be accomplished by simply adjusting the initial code. As the entire process is computer-controlled, it reduces production time, cost, and manual labour, thereby providing a significant advantage of 3D printing over traditional manufacturing processes. SSE printing thus enables pharmaceutical companies to create small batches of drugs quickly and at a lower cost, which is particularly useful for personalised medicine. By optimising the production process and reducing waste, SSE printing has the potential to revolutionise pharmaceutical manufacturing. The application of this technology to manufacturing polypharmacy, tablets, and other dosage forms has rapidly advanced [6–8].

The use of disposable syringes as cartridges in SSE 3D printers is a common practice. This approach helps meet

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the stringent quality requirements set by regulatory agencies [9–11]. However, disposable syringes have notable drawbacks. One significant issue is that heating disposable syringes may lead to imprecision of the output, due to the inability to control temperature evenly across plastic (an insulating material). Typically, the syringe is heated before printing until the formulation reaches a viscosity, low enough for extrusion through the nozzle [12]. Maintaining the appropriate printing temperature is crucial, as excessive heat can cause over-extrusion [13, 14]. Secondly, the amount of waste generated by disposable cartridges is significantly high; thirdly, the EU is moving towards sustainability, and new regulations are coming into place to prevent single-use plastics [15–17]. In our study, we address these limitations by using quality-controlled, refillable cartridges. Specifically, we utilise pharmaceutical-grade stainless-steel cartridges, which offer better control and reliability in the printing process.

To evaluate the usability of the technology, we investigate the stability of the formulations in stresses experienced in use. In practice, various thermal stresses, including heating and cooling cycles, will expectedly be applied by users; thus, evaluating their impact on the outcome is essential. In this article, we experimentally simulate several scenarios that are relevant to pharmacy practice and will evaluate the usability of the semi-solid extrusion approach using reusable cartridges.

Design of the Study

Usability Aspect 1. The Formulations Can be Reused Multiple Times

The primary advantage of 3D-printed tablets is their ability to customise dose size and volume, allowing pharmacists to produce only the exact number of tablets needed. To enhance the commercial viability of this technology, it is crucial that formulations within the cartridge can be reheated and reused multiple times. This capability minimises the waste of residual formulation post-printing.

To evaluate this, a cartridge was heated at a four-hour interval for three days, emulating a pharmacy repeatedly reusing the cartridge.

Usability Aspect 2: The Formulations are Stable Under Thermal Stress Experienced in the Commercial Context

One of the bottlenecks of the 3D printing tablets is long preheat times. This is mainly caused by the poor thermal conductivity of organic compounds. In a commercial setting, it would be ideal to print the tablets instantly. One way to solve this problem is to always keep the cartridges slightly below the printing temperature.

We designed two experiments to simulate the described scenario. The first experiment aimed to replicate a standard working schedule by preheating cartridges during typical working hours: each cartridge was heated for 8 h and subsequently maintained at ambient temperature for 16 h over a period of 3 days. This setup was intended to mimic a typical usage pattern. The second experiment evaluated a continuous heating system implemented to accommodate high throughput and assess temperature stability. In this case, cartridges were consistently kept at the desired temperature without fluctuations for the entire 3-day duration to gauge sustained operational conditions. These experiments were conducted to investigate and compare the performance of the heating methods under controlled conditions simulating practical usage scenarios.

Usability Aspect 3: The Formulations are Stable Under Rapid Cooling

Using metal cartridges enables us to heat solid formulations directly on the printer, making them semi-solid before printing. The formulations are mixed as liquids at high temperatures and poured hot into the cartridges, where they must solidify before they can be used for printing. However, due to the poor thermal characteristics of the formulations and cartridge geometry, heat dissipation is limited and slows down as it reaches the ambient, resulting in a lengthy solidification process. For commercial viability, reducing the solidification time is essential.

To emulate this situation, we devised two experiments. The first involved quenching a cartridge in cold water immediately after being poured, simulating a rapid cooling process over a period of 2 h. The second experiment replicated a more extreme scenario where a cartridge was immersed in icy cold water for the same duration, aiming to simulate prolonged exposure to harsh cooling conditions. These experiments were designed to investigate the effects of different cooling methods on cartridge durability and performance under controlled conditions. We compared the findings from the first use (internal reference) with subsequent uses to evaluate the cartridge's reusability.

Materials and Methods

Reagents

Mexiletine Hydrochloride was purchased from ThermoFisher Scientific (Dreieich, Germany). Gelucire 48/16 was generously provided by Gattefossé (Saint-Priest, France). Glycerol and Polyethylene Glycol 35,000 (PEG35000) were obtained from Merck (Darmstadt, Germany). Monolaurin was sourced from TCI (Tokyo, Japan).

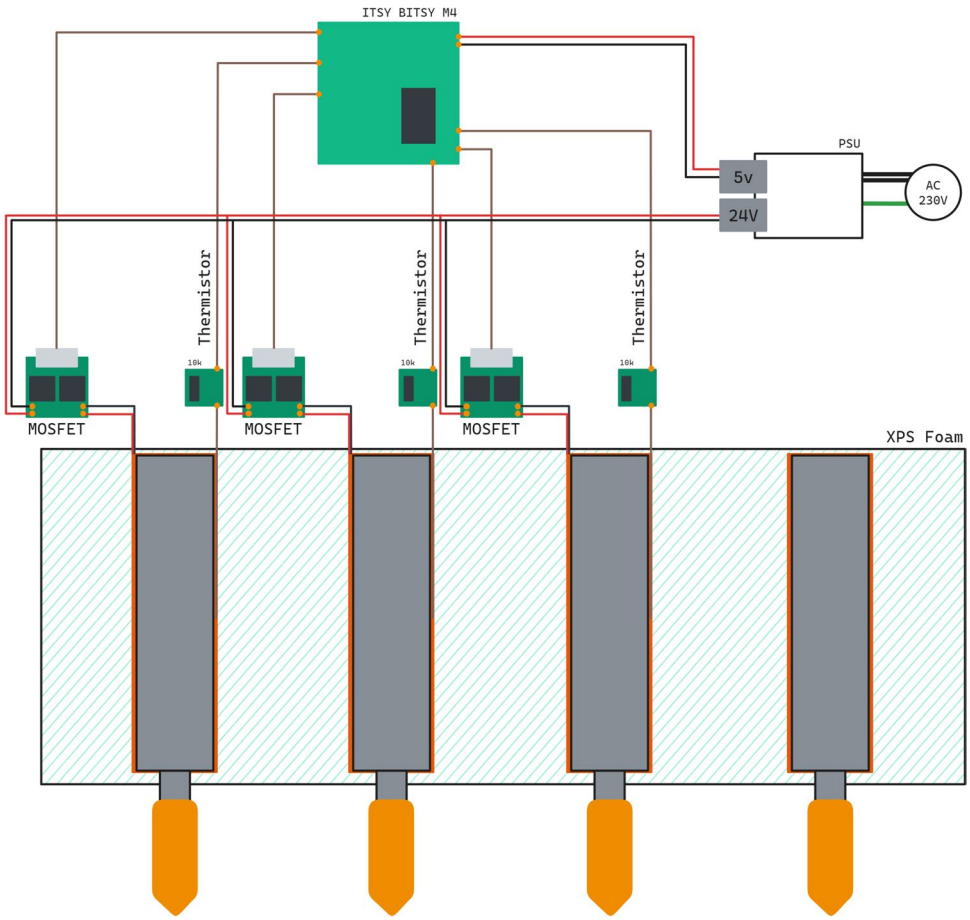

Fig. 1 Preheating setup. The setup is composed of 4 stainless steel cartridges, which are in touch with temperature sensors

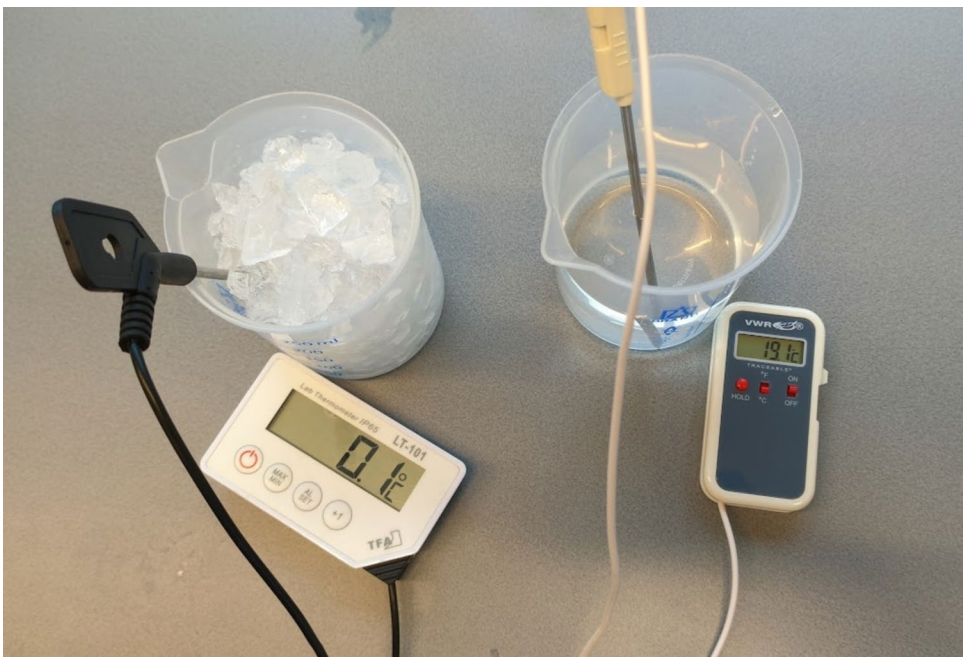

Fig. 2 The setup used for cooling cartridges

Table 1 Stress-heating intervals are used in both formulations. Formulation A consists of pure Gelucire 48/16, and formulation B includes Mexiletine HCl

Sr	Formulation	Cartridge	Regiment
1	Formulation A	H-AC	Control
2		H-A1	4 h cycles
3		H-A2	8 h cycles
4		H-A3	Continuous
5	Formulation B	H-BC	Control
6		H-B1	4 h cycles
7		H-B2	8 h cycles
8		H-B3	Continuous

Formulation Preparation

Two sets of formulations were made. Formulation A consisted only of Gelucire 48/16, while Formulation B consisted of Mexiletine Hydrochloride, Monolaurin, Glycerol, and PEG 35000. Formulation A was stirred and heated at 70 °C for 30 min to achieve a homogeneous mixture. For Formulation B, the components were melted and stirred at 80–85 °C for 60 min using a heating magnetic stirrer.

Setup for Preheating Cartridges

Four cartridges were filled per formulation. A temperature sensor, NTC thermistor 10 K MF52AT, was placed onto each cartridge to monitor temperatures. The cartridges were wrapped with a silicone heater mat to facilitate heating. Cartridges were placed in XPS insulating foam to minimise heat loss, providing an insulated environment for each cartridge. The heating control for the cartridges was managed using an ITSY BITSY M4 running Circuit Python v9.0.2. It was connected to four MOSFETs for individual control of the heater mats. The temperature sensors were polled at a frequency of 10 Hz.

This setup allowed for individual temperature regulation, ensuring each cartridge could be maintained at a target temperature as required by the regime (Fig. 1). The temperature for formulation A was set at 40 °C, and for formulation B was set at 47 °C.

Table 2 Stress-cooling is used in formulations A and B, including Mexiletine HCl

Sr	Formulation	Cartridge	Regiment
1	Formulation A	C-AC	Control
2		C-A1	Ice Bath
3		C-A3	Cold Water
1	Formulation B	C-BC	Control
2		C-B1	Ice Bath
3		C-B2	Cold Water

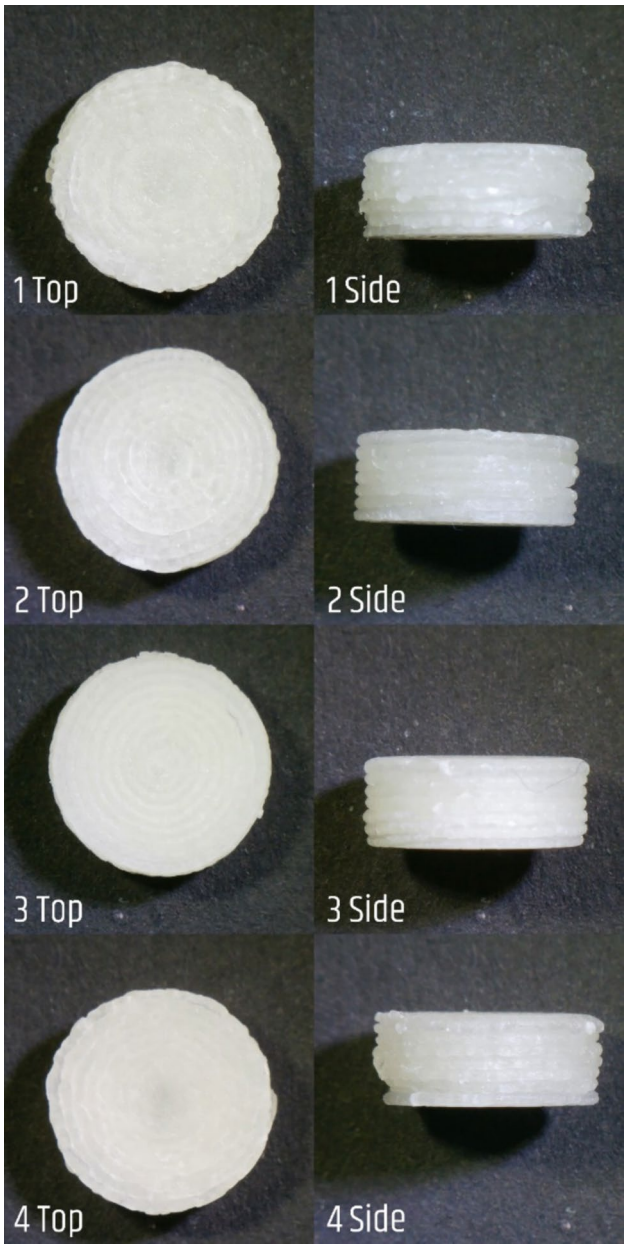

Fig. 3 Images of Gelucire 48/16 printed tablets assessed for shape, defect, and colour. 1. H-AC (Stress heating the control sample of formulation A), 2. H-A1 The 4 h of heating, 3. H-A2 (The 8 h of heating), and 4. H-A3 (the continuous heating)

Setup for Cooling Cartridges

Two beakers were prepared for the experiment. The first beaker was filled with cold water and measured at 19 °C.

The second beaker was filled with crushed ice, and its temperature was confirmed to be 0 °C (Fig. 2).

Printer Setup

For this study, we used a DoseRx1 printer (Doser B.V., Leiden, The Netherlands) with printheads designed for our sustainable approach to SSE. The tablet geometry is designed using Python v3.10 software. After optimisation, we determined the following printing parameters: the layer height was set to 0.43 mm, and the nozzle diameter was 0.4 mm. We printed a total of 7 layers per tablet. The tablets had a diameter of 7.5 mm and were printed in double rows of 5 tablets each, resulting in 10 tablets per batch, and the weight was aimed at 140 mg.

We utilised two types of printheads, each featuring different cartridge designs: one equipped with a brass nozzle and the other with a stainless-steel nozzle. While there is no change in the technical aspects or properties between the two printheads, the newer printhead, which includes the stainless-steel nozzle, offers a better to insert the cartridge into the printer.

Formulation A was printed using the brass nozzle on the older printhead, with the nozzle and cartridge maintained at 41 °C. In contrast, Formulation B was printed using the stainless-steel nozzle on the new printhead, with the cartridge set to 48 °C and the nozzle to 50 °C.

Heating Stress Application Protocol

The experiment, conducted over 72 h, involved eight cartridges subjected to different heating regimens: one control cartridge maintained at ambient temperature throughout, one on a 4-h cycle where the heater alternated on and off every 4 h, another on an 8-h cycle with the heater on for 8 h followed by 16 h off, and one cartridge continuously heated for the entire 72 h (Table 1).

Cooling Stress Application Protocol

The experiment was conducted over 24 h, beginning with the formulation mixed on a hot plate and subsequently used to fill three cartridges. The first cartridge, assigned to the Control Group, was stored at ambient temperature overnight for cooling. The second cartridge, designated for the Ice Bath Group, was cooled in a crushed ice bath for two hours with its nozzle sealed to prevent water ingress. The third cartridge, allocated to the Cold-Water Group, underwent cooling in cold 19 °C water for 2 h with similar precautions taken to seal the nozzle against water entry (Table 2).

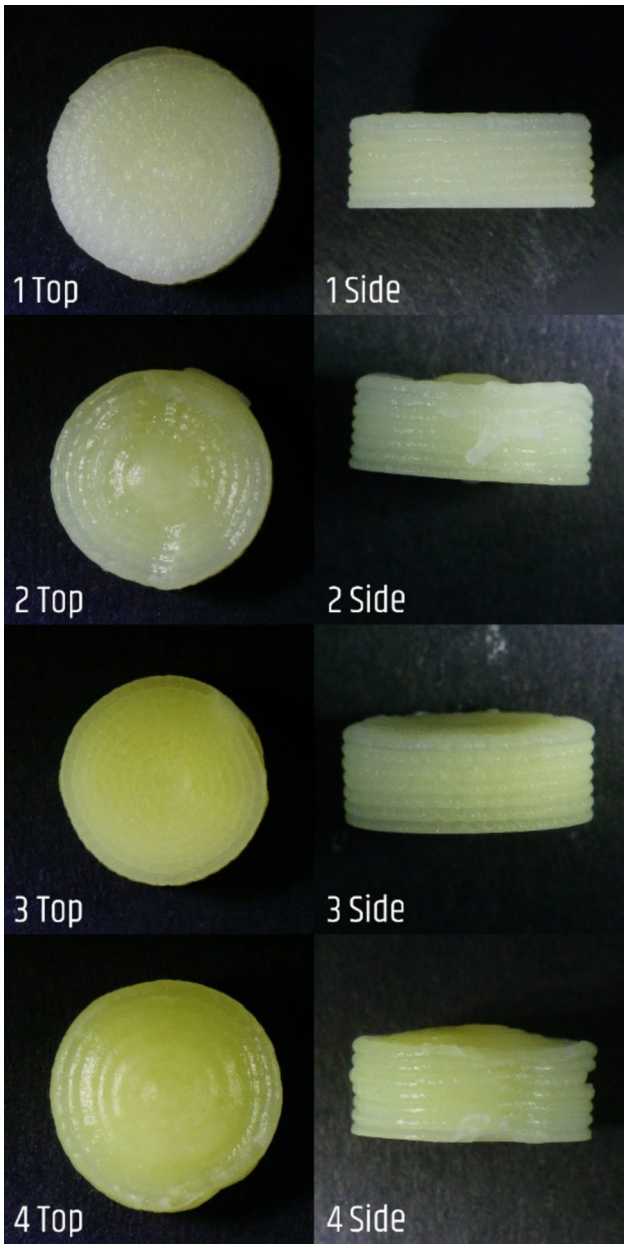

Fig. 4 Images of Mexiletine HCl printed tablets assessed for shape, defect, and colour. 1. H-BC (Stress heating the control sample of formulation B, which includes Mexiletine HCl), 2. H-B1 The 4 h of heating, 3. H-B2 (The 8 h of heating), and 4. H-B3 (the continuous heating)

Tablet Analysis

The tablets were subjected to a thorough physical and chemical analysis. Throughout the printing process, each tablet was weighed and inspected using the Andonstar AD407 Pro microscope to ensure consistency and robust layer integrity. Furthermore, the chemical composition of the tablets was analysed via

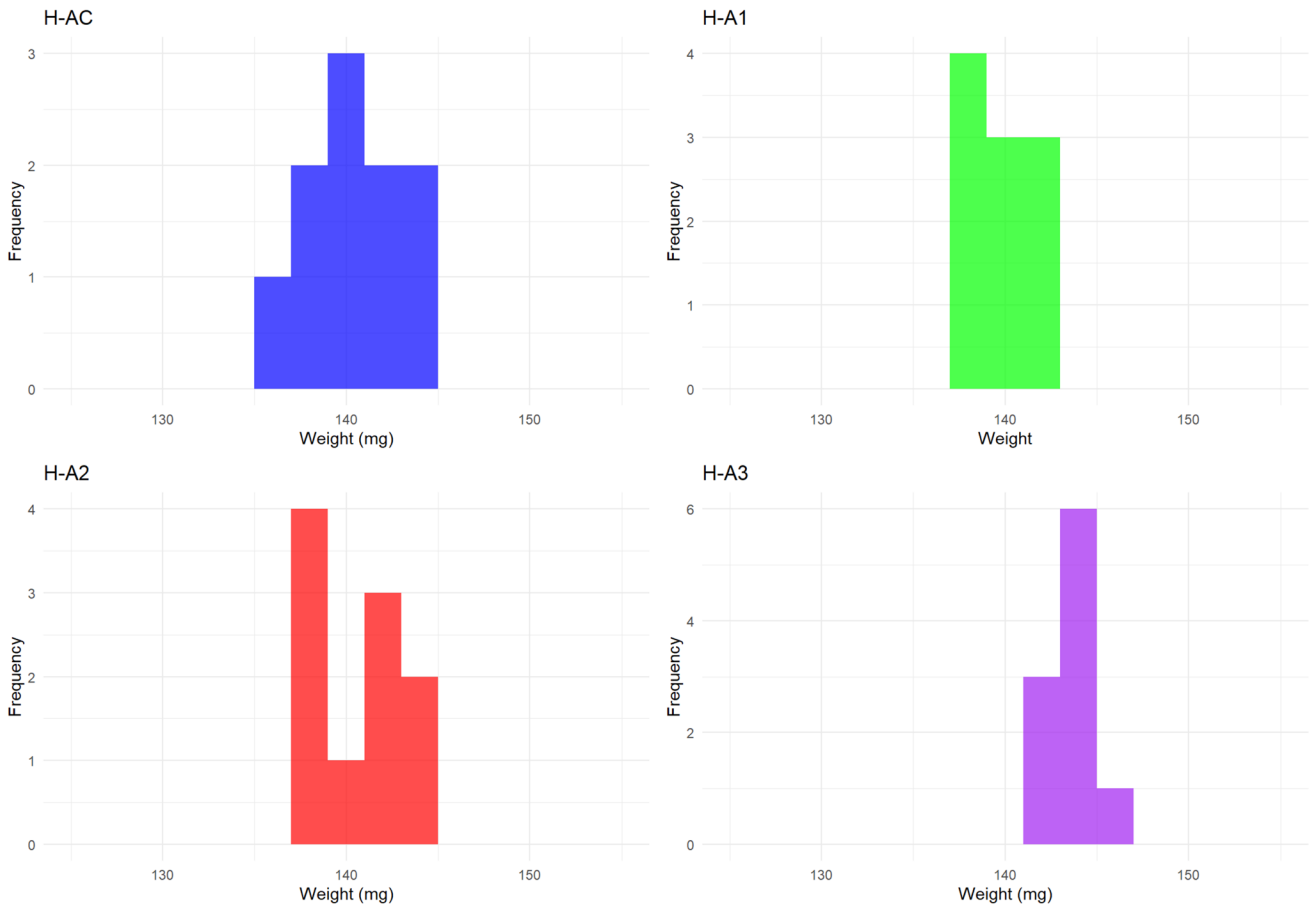

Fig. 5 Weight distributions of stress-heating Gelucire 48/16-3D printed tablets

the analytical balance and High-Performance Liquid Chromatography (HPLC). The appearance was carried out visually, the Average Weight and Weight Distribution tests were performed with the analytical balance. The assay, content uniformity, dissolution and impurity tests were performed with the HPLC. The method we used for the HPLC analysis is a USP method (USP monograph Mexiletine Hydrochloride ''Assay''; USP42—NF37—2905; USP41—NF36—2731; USP40—NF35 – 5159).

The HPLC analysis was conducted on Formulation B which contained Mexiletine HCl.

Results and Discussions

Heating Stress

Appearance

We first analysed the appearance of our tablets after printing under heating stress. The tablets were round, demonstrating exceptional quality and uniformity on their surfaces, which indicated an absence of defects and robust layer integrity. Formulation A (Fig. 3) tablets were white; in contrast, Formulation B (Fig. 4) displayed a slight yellowish tint. This discolouration was more pronounced in the tablets subjected to the 8-h and continuous cycles compared to those exposed to the 4-h cycles. The discolouration could be attributed to chemical changes in formulation B due to prolonged heat exposure or the initiation of its degradation.

Our findings highlight that continuous heating during production is inefficient and unsustainable due to degradation and waste generation. Instead, intermittent heating with pauses significantly extends production cycles, enabling over five cycles even with four hours of heating (in point-of-care scenarios, we often need less production time). Furthermore, the number of production cycles depends on both the chemistry of the formulation and the level of intermittency. While the formulation is often constrained by the active pharmaceutical ingredient (API), adjusting intermittency can enhance sustainability and prolong production. For instance, although formulation A resists heat degradation, it cannot dissolve Mexiletine HCl. By introducing intermittency, we improved the durability of formulation B, making it viable for repeated use.

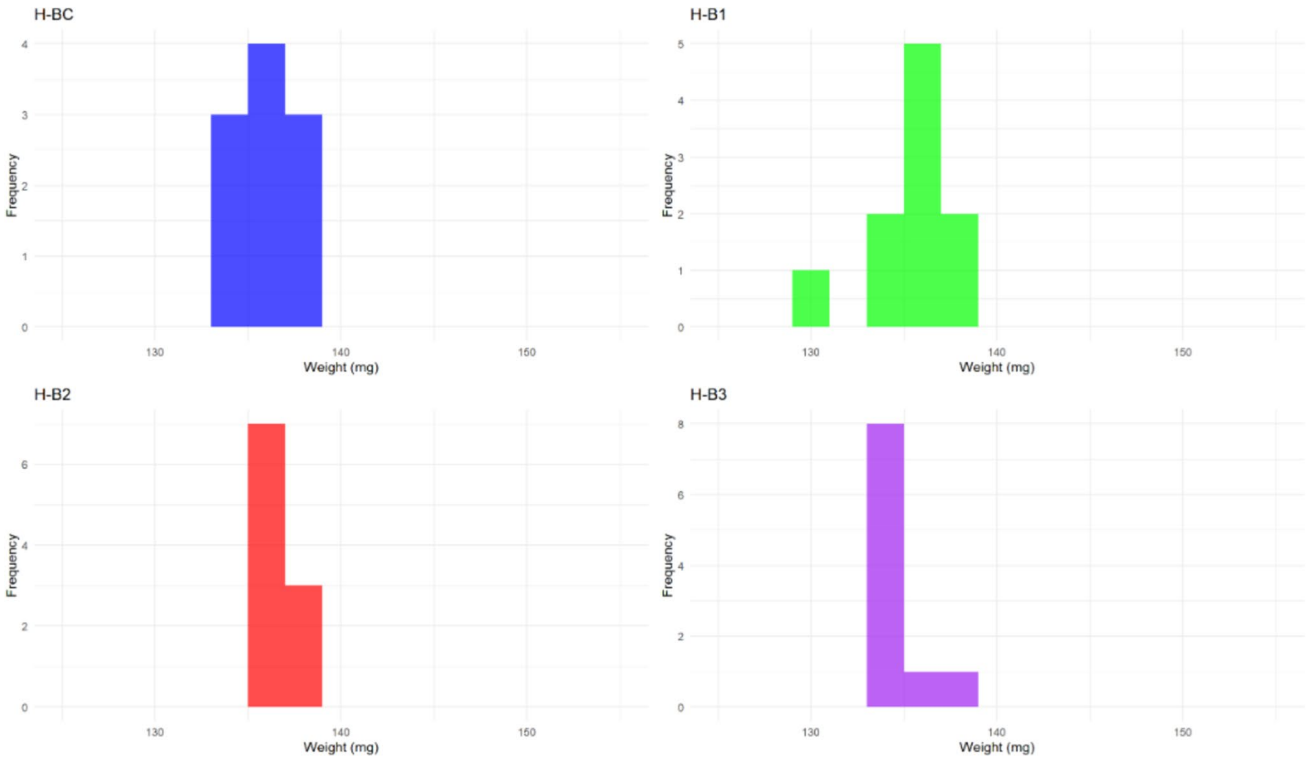

Fig. 6 Weight distributions of stress-heating Mexiletine HCl-3D printed tablets

Average Weight and Weight Distribution

Our data reveal that tablets manufactured by DoseRx1 demonstrate outstanding quality with minimal weight variability between each batch (Fig. 5 and Fig. 6). All printed tablets demonstrated a relative standard deviation (RSD) of ≤ 4.0%, thereby complying with the specified criteria (Table 3 and Table 4).

Content Determination and Content Uniformity

Content uniformity analysis was performed on 3D-printed tablets to ensure the API was uniformly distributed within the tablets. The solution was filtered and diluted; its absorbance was measured at 220 nm with a DAD-detector using HPLC (Agilent), and the API content, compared to the theoretical content, was determined using a calibration curve. Our HPLC analysis of the dissolved tablets revealed that tablets carried an average amount of Mexiletine HCl equal to 34.3 mg, 34.3 mg, 34.1 mg, and 34.1 mg for formulation H-BC, H-B1, H-B2, and H-B3 respectively. All tests exhibited excellent content uniformity according to USP criteria (90%−110%): 98.6%, 99.0%, 98.0%, and 99.1% (Table 5).

Cooling Stress

Appearance

The appearance of our tablets after printing under cooling stress was as expected. The tablets showed good quality and uniformity on their surfaces, and defects and robust layer

Table 3 Weight average and weight distribution of stress-heating Gelucire 48/16-3D printed tablets

Formulation A	Weight average	RSD
Cartridge H-AC	140.8 mg	1.762
Cartridge H-A1	140.3 mg	0.904
Cartridge H-A2	141 mg	1.708
Cartridge H-A3	144 mg	0.878

Table 4 Weight average and weight distribution of stress-heating Mexiletine HCl-3D printed tablets

Formulation B	Weight average	RSD
Cartridge H-BC	136.7 mg ± 0.91	1.4
Cartridge H-B1	136.1 mg ± 0.01	2.4
Cartridge H-B2	136.7 mg ± 0.49	1.4
Cartridge H-B3	135.0 mg ± 0.25	1.2

Table 5 Content uniformity. Stress-heating tablets with Mexiletine HCl batches were tested

Formulation B	Percentage (relative to Mexiletine HCl dissolved)	Amount (mg Mexiletine HCl dissolved)
Cartridge H-BC	98.6%	34.3 mg
Cartridge H-B1	99.0%	34.3 mg
Cartridge H-B2	98.0%	34.1 mg
Cartridge H-B3	99.1%	34.1 mg

integrity were absent. Both the formulations A and B tablets were visually indistinguishable from the control (Fig. 7 and Fig. 8).

Average Weight and Weight Distribution

Similar to heat stress, all the printed tablets exhibit a high degree of precision. There is minimal weight variability between the prints and the relative standard deviation (RSD) of the tablets is $\leq 4.0\%$.

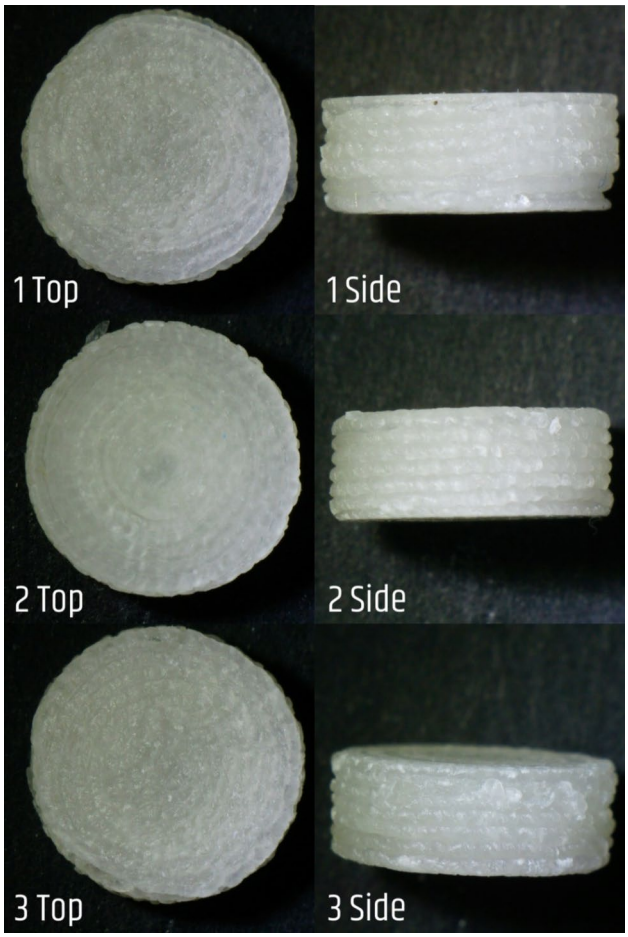

Fig. 7 Images of Gelucire printed tablets assessed for shape, defect, and colour. 1. C-AC (Stress cooling the control sample of formulation A), 2. C-A1 Ice Bath, and 3. C-A2 Cold Water Bath

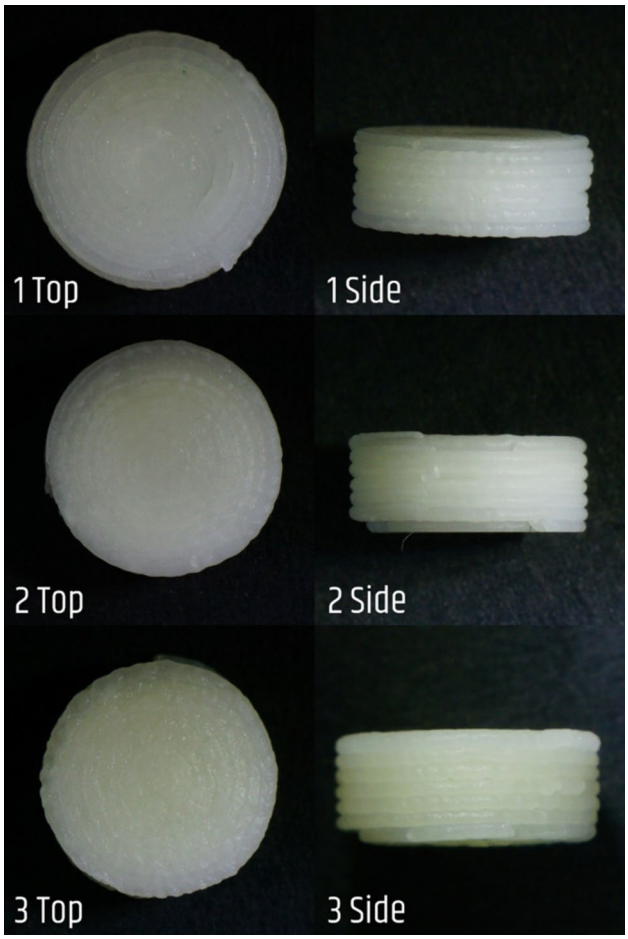

Fig. 8 Images of Mexiletine HCl printed tablets assessed for shape, defect, and colour. 1. C-BC (Stress cooling the control sample of formulation B), 2. C-B1 Ice Bath, and 3. C-B2 Cold Water Bath

The tablets formulated with Mexiletine HCl (B) exhibit a slight weight reduction compared to those formulated with Gelucire 48/16 (A) (Fig. 9). Despite using identical extrusion parameters for both formulations, formulation B displays a reduced weight, which can be partially attributed to differences in density.

Based on our findings, the formulation retains its printability and forms a robust structure, even after experiencing rapid solidification in cold water and an ice bath. Additionally, the results indicate that cold water enables the tablets to achieve the target weight more effectively than freezing conditions (Fig. 10) (Tables 6 and 7).

Content Determination and Content Uniformity

In HPLC analysis of the dissolved tablets, it was found that tablets contained an average Mexiletine HCl content of 35.9 mg, 35.3 mg, and 35.7 mg for formulations

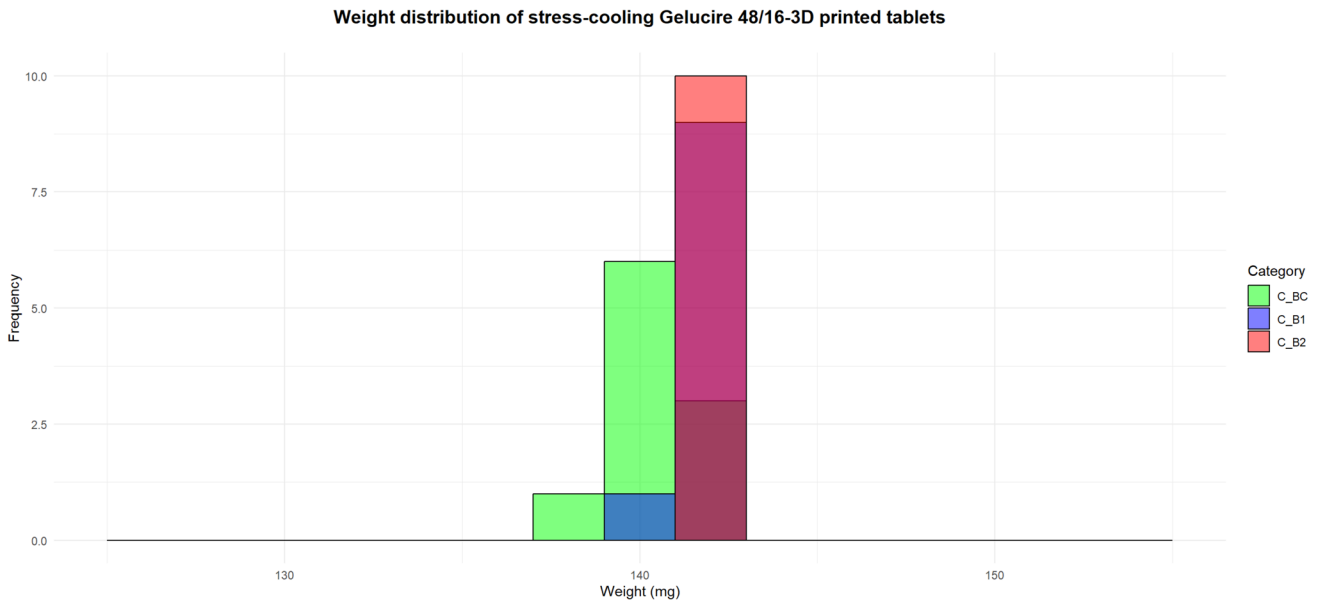

Fig. 9 Overlaid weight distributions of stress-cooling Gelucire 48/16-3D printed tablets

Fig. 10 Overlaid weight distributions of stress-cooling Mexiletine HCl-3D printed tablets

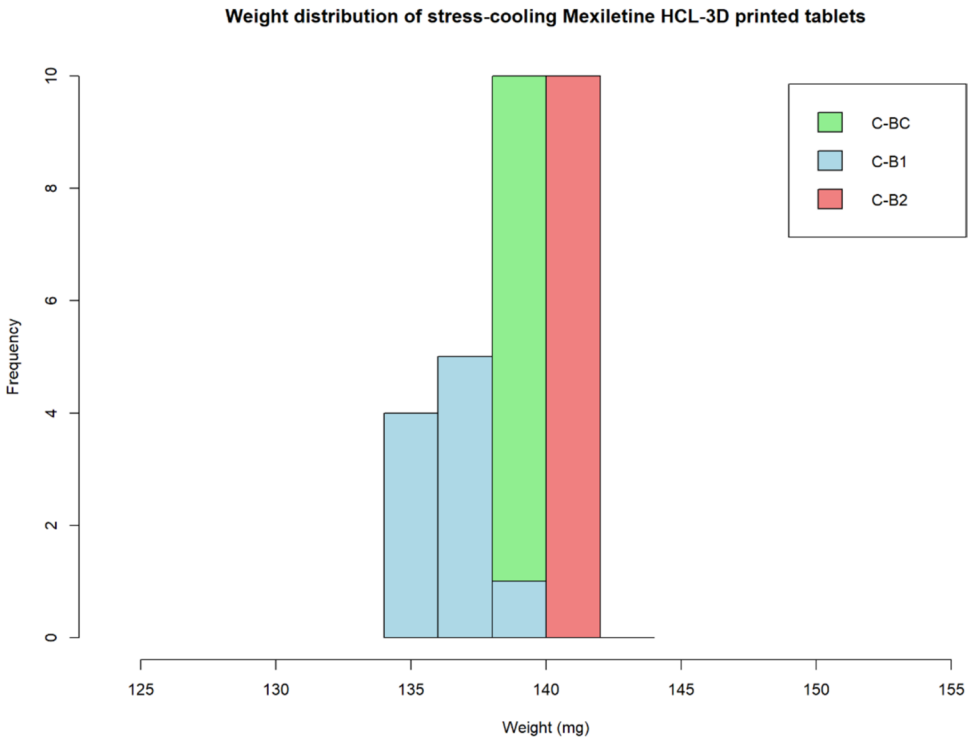

Table 6 Weight average and weight distribution of stress-cooling Gelucire 48/16-3D printed tablets

Formulation A	Weight average	RSD
Cartridge C-AC	141,10	0,87
Cartridge C-A1	142,40	0,47
Cartridge C-A2	142,70	0,32

Table 7 Weight average and weight distribution of stress-cooling Mexiletine HCl-3D printed tablets

Formulation B	Weight average	RSD
Cartridge C-BC	138.3 mg ± 0.22	0.33
Cartridge C-B1	136.5 mg ± 0.25	1.28
Cartridge C-B2	140.5 mg ± 0.19	0.48

Table 8 Content uniformity. Stress-cooling tablets with Mexiletine HCl batches were tested

Formulation B	Percentage (relative to Mexiletine HCl dissolved)	Amount (mg Mexiletine HCl dissolved)
Cartridge C-BC	102.1%	35.9 mg
Cartridge C-B1	98.7%	35.3 mg
Cartridge C-B2	102.9%	35.7 mg

Table 9 Impurity result of Mexiletine HCl 3D-printed tablets

Compound	Concentration	Precision (RSD%)
Mexiletine HCl	0.2 mg/ml	0.1

C-BC, C-B1, and C-B2, respectively. These results indicate excellent content uniformity according to USP criteria (90%−110%), with values of 102.1%, 98.7%, and 102.9% observed, respectively (Table 8).

Impurity and Substance-related Result

The analysis of impurity levels confirmed the quality of the preparation protocol. Individually, impurities were found to be consistently below 1% for tablets, highlighting adherence to stringent purity standards. Moreover, when considering the cumulative impurity levels, the total was determined to be less than 1.5%. These results meet the requirements of the USP method and highlight the effectiveness of quality control measures in maintaining low impurity levels during the production of Mexiletine HCl 3D printed tablets.

The tablets have now been measured at a concentration of 3,4 mg/ml based on the amount of API in the tablets. These results underscore the effectiveness of quality control measures in maintaining low impurity levels throughout 140 mg Mexiletine HCl 3D-printed tablet manufacturing (Table 9).

Dissolution Result

Mexiletine HCl 3D-printed tablets comply with the dissolution requirement for immediate-release tablets (EP, 2.9.3). Specifications for immediate requirements are more than 80% dissolution within 45 min. in this case, we can conclude that the release is complete (100%) at 45 min and passes the criterion. The release profile analysis shows that Mexiletine HCl formulations provide 100% dissolution reached at 40 min, signifying their potential for rapid therapeutic effects (Supplementary Fig. 1).

Conclusion and Future Outlook

3D drug printing is an innovative additive manufacturing technology in the pharmaceutical field that enables the engineering and design of personalised medications, utilising patient-specific information such as genetics, gender, and age. It optimises treatment benefits and minimises the risks of medical interventions on an individual basis. This study presented an innovation in 3D drug printing technology by introducing reusable cartridges which provides significant advancement in addressing the sustainability challenges of single-use syringes. The study demonstrates several notable benefits: effective temperature control during the printing process, minimising cartridge deformation, reduced waste generation, and alignment with the new EU sustainability regulations. By replacing disposable cartridges, the reusable design successfully resolves sustainability issues previously encountered. Importantly, stainless steel is widely used in the medical and pharmaceutical fields, particularly in conventional manufacturing processes. Established protocols for cleaning and decontamination are already in place. Therefore, while reusable cartridges are more sustainable, we believe that the advantages of disposable cartridges, such as eliminating cross-contamination, can also be achieved with reusable cartridge systems. We will investigate this point further in future studies.

Our study primarily aimed to validate the presented technological advancement. We investigated the impact of heating and cooling cycles applied to cartridges on the quality of the final printed product. Our findings indicate that these cycles do not adversely affect product quality, for the proposed heat-resistant formulations. The formulations contained within the cartridges demonstrate robustness, allowing for multiple reuses and maintaining stability even under the thermal stresses commonly encountered in commercial applications, including rapid cooling scenarios.

Our stress study specifically examined Mexiletine HCl as an API and a specific formulation, demonstrating high thermal resistance. This study can be readily extended to other APIs and formulations, to characterize the technology's broad applicability across other heat-resistant pharmaceutical formulations. Future developments may encompass stability analysis and synthesis of tablets containing sensitive APIs. Finally, the proposed approach is highly scalable, allowing the installation of multiple reusable stainless steel cartridges that are an order of magnitude larger than those presented in this study. In conclusion, introducing reusable cartridges addresses environmental concerns associated with disposable counterparts and enhances the efficiency and sustainability of 3D printing processes in various industrial applications.

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Author Contributions Conceived and Designed Research: F.S., T.M., N.O. Performed experiments and analysed data: R.R., F.S., S.V., A.A.H. Resources: N.O., A.R. Wrote the first draft: F.S., R.R. Writing and editing the manuscript: All authors.

Data Availability Data sets generated during the current study are available from Doser B.V. upon reasonable request.

Declarations

Conflict of Interests All authors R.R., T.M., S. V., N. O., and F. S. were employees of Doser B.V. during this research. Doser B.V. markets the DoseRx1. N.O. is a shareholder of Doser BV.

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