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Development and Bioequivalence of 3D-Printed Medication at the Point-of-Care: Bridging the Gap Toward Personalized Medicine

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Personalized medicine is currently hampered by the lack of flexible drug formulations. Especially for pediatric patients, manual compounding of personalized drug formulations by pharmacists is required. Three-Dimensional (3D) printing of medicines, which enables small-scale manufacturing at the point-of-care, can fulfill this unmet clinical need. This study investigates the feasibility of developing a 3D-printed tablet formulation at the point-of-care which complies to quality requirements for clinical practice, including bioequivalence. Development, manufacturing, and quality control of the 3D-printed tablets was performed at the manufacturing facility and laboratory of the department of Clinical Pharmacy and Toxicology at Leiden University Medical Center. Sildenafil was used as a model drug for the tablet formulation. Along with the 3D-printed tablets a randomized, an open-label, 2-period, crossover, single-dose clinical trial to assess bioequivalence was performed in healthy adults. Bioequivalence was established if areas under the plasma concentration curve from administration to the time of the last quantifiable concentration (AUC_{0-t}) and maximum plasma concentration (C_{max}) ratios were within the limits of 80.00–125.00%. The manufacturing process provided reproducible 3D-printed tablets that adhered to quality control requirements and were consequently used in the clinical trial. The clinical trial was conducted in 12 healthy volunteers. The 90% confidence intervals (CIs) of both AUC_{0-t} and C_{max} ratios were within bioequivalence limits (AUC_{0-t} 90% CI: 87.28–104.14; C_{max} 90% CI: 80.23–109.58). For the first time, we demonstrate the development of a 3D-printed tablet formulation at the point-of-care that is bioequivalent to its marketed originator. The 3D printing of personalized formulations is a disruptive technology for compounding, bridging the gap toward personalized medicine.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Three-Dimensional (3D) printing technology has the potential to deliver personalized medicine to the individual patient. So far, preclinical research of 3D printing tablets has been promising. However, knowledge on clinical application of 3D-printed tablets at the point-of-care remains relatively unexplored.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study investigates the feasibility of developing a 3D-printed tablet formulation at the point-of-care which complies to quality requirements for use in clinical practice, including bioequivalence in healthy volunteers.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The findings of this study show that 3D-printed tablets can be developed at the point-of-care and that these tablets are bioequivalent to their marketed originator.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The 3D-printed formulations are an addition to current compounded formulations in pharmacies, enabling precision dosing at the point-of-care. Personalizing medicine can improve drug treatment, by increasing the efficacy and reducing adverse effects. For patients in whom the commercially available dosages are not suitable, such as the pediatric population, 3D-printed formulations will fulfill an unmet clinical need.

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Personalized medicine, tailoring treatment to the individual patients' needs, holds the promise of increasing efficacy and reducing adverse effects of drug treatment.[1] A cornerstone of personalized medicine is precision dosing. However, a practical limitation is the lack of flexible drug formulations to facilitate precision dosing, because commercial drug formulations, such as tablets, are only available in a limited number of fixed strengths. Under current regulations,[2,3] pharmacists are allowed to prepare personalized medication extemporaneously, such as capsules and oral liquids, if marketed drugs are unsuitable or unavailable for a patient. They use labor intensive and time-consuming manufacturing methods to meet the clinical need for individual patients, especially in pediatrics. Typically, children have an age-dependent maturation of organ functions important for drug absorption, distribution, and elimination, combined with changes in receptor expression and diseases that might interfere with the developmental changes, demanding personalized drug treatment.[4,5] In general, optimizing the drug dose based on individual pharmacokinetic and pharmacodynamic characteristics, disease state, patient specific characteristics, and drug attributes enhances the probability to improve drug treatment.[6]

To fulfill the unmet clinical need, a novel, potentially disruptive drug manufacturing technique has emerged: 3D printing of medication. The principle of 3D printing is based on building a tablet layer-by-layer using a computer model adjusted to meet the patient's requirements. The 3D printing can be digitally controlled leading to a greater ease of manufacturing than current manual compounding methods. Interestingly, 3D printing enables personalized manufacturing at the point-of-care, such as in a hospital pharmacy.[7] The use of 3D printing technology is emerging rapidly in health care and is already being used in a diversity of applications, such as prosthetics, customized implants, pre-surgery 3D modeling, and tissue and organ printing.[8,9] However, to date, the clinical application of 3D-printed medication at the point-of-care remains relatively unexplored.

Demonstrating the feasibility and clinical use of 3D-printed medication at the point-of-care is paramount for the success of these novel dosage forms. When developing a novel, generic drug formulation, one of the criteria required by regulatory authorities is to show bioequivalence with the registered originator. At present, little is known about the pharmacokinetic behavior of 3D-printed tablets. The aim of this study was to investigate the feasibility of developing a 3D-printed tablet formulation at the point-of-care which complies to quality requirements for use in clinical practice, including the assessment of bioequivalence in healthy adults.

METHODS

Development of 3D-printed tablets

Development, manufacturing, and quality control of the 3D-printed tablets was performed at the Good Manufacturing Practice facility of the Department of Clinical Pharmacy and Toxicology, at Leiden University Medical Center (LUMC) using quality by design principles. Tablets were printed with a novel, validated, semi-solid extrusion 3D printer from Doser B.V. (Leiden, The Netherlands). The formulation contained Gelucire 48/16 from Gattefossé (Saint-Priest, France) as a carrier, 10% *w/w* glycerol 99.5% from Duchefa Farma (Haarlem, The Netherlands) as plasticizer, and sildenafil citrate from Spruyt Hillen (IJsselstein, The Netherlands) equal to 10 mg sildenafil per tablet. A single batch of 80 3D-printed tablets was manufactured a month prior to the start of the bioequivalence trial to allow quality control release testing.

An overview of the manufacturing process is provided in **Figure 1**. The manufacturing process consisted of two phases: the cartridge preparation and printing of the tablets. All components are first molten and mixed together, after which they are transferred to the cartridge. After complete solidification, the cartridge was inserted in the 3D printer, which is heated up to 43°C using a heating pad to allow printing. A video of the printing of the tablets is provided in the **Material S1**. Further in-depth information on the product development and quality control analysis of the 3D-printed tablets is provided in our previous study[10] and the **Material S1**.

Choice of active ingredient. As a proof of concept, a 3D-printed tablet formulation containing sildenafil was developed. Sildenafil is a phosphodiesterase type 5 (PDE5) enzyme inhibitor used in low dosages for the treatment of pulmonary arterial hypertension in young children.[11] Current treatment options for children consist of either commercially available tablets or oral suspensions. Both formulations have a relatively high strength which makes accurate administration of low dosages

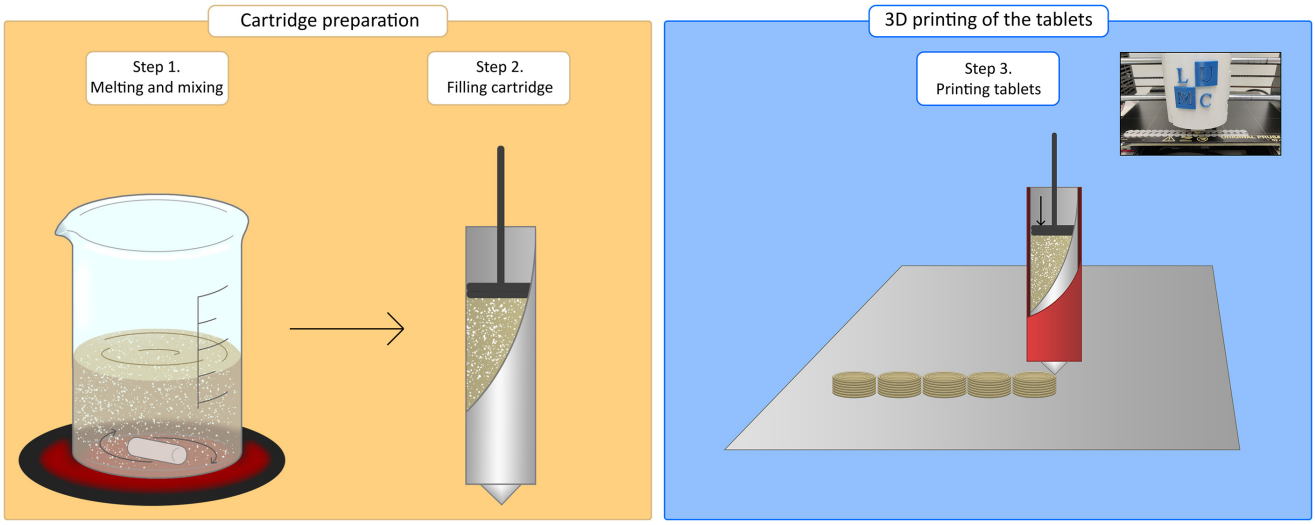

Figure 1 Overview of 3D-printed tablet manufacturing process.

difficult to achieve. Furthermore, the oral suspension has an intrinsic risk of inhomogeneity which potentially results in dosing errors. There is a clinical need for sildenafil formulations with a low and flexible strength, suitable for the treatment of young children.

Bioequivalence

Trial design and participants. The 3D-printed sildenafil tablets were used in a randomized, open-label, 2-period, crossover, single-dose study comparing the pharmacokinetic profile to the commercially available sildenafil tablets Revatio® in healthy adult volunteers. The trial was conducted at the clinical research unit of the Department of Internal Medicine of the LUMC under Good Clinical Practice conditions.

Healthy men aged 18–55 years with a body mass index of 18.5–30 kg/m^2 and a total body weight > 50 kg were eligible for this study after providing written informed consent. Participants were excluded if they had a contraindication for sildenafil, a history of alcohol or substance misuse, a positive urine drugs of abuse screening, clinically significant diseases, abnormal physical findings, cardiac or laboratory abnormalities, hypersensitivity to any of the substances of the formulations, or a history of anaphylaxis to drugs in general. Owing to the possibility of triggering changes in the pharmacokinetic profile of sildenafil, participants were not allowed to use prescription medication or consume grapefruit within 14 days of study drug administration, use non-prescription medication and supplements within 7 days of study drug administration, or use drugs that are known to be strong or moderate inhibitors or inducers of CYP3A4 and CYP2C9 within 30 days of study drug administration.

The study was performed in accordance with the Declaration of Helsinki and requirements of public registration of clinical trials. Approval was obtained from the independent local medical ethics review committee. The national competent authority gave their certificate of no objection for the trial. The study was registered as a phase I trial in EudraCT, number 2021-003072-13.

Randomization and blinding. Eligible participants were randomly assigned to either sequence A or B (1:1) using a computer-generated schedule with block sizes of two or four (Castor Electronic Data Capture System version 2021.6.2). Due to objective outcome parameters blinding was not applicable.

Procedures. The study treatment consisted of a single 20 mg dose of sildenafil provided as either 2 × 10 mg 3D-printed sildenafil tablets or 1 × 20 mg Revatio® tablets. Treatments were administered after an ≥ 8 hour overnight fast, separated by a washout period between doses of ≥ 7 days. Participants allocated to sequence A received the 3D-printed tablets in the first study period and the Revatio® tablet in the second period. Sequence B received the treatment in the opposite order. An overview of the study procedure is provided in **Figure 2**.

To standardize conditions on sampling days, participants refrained from eating food and drinking beverages other than water during the first 4 hours after dosing. Water was permitted 1 hour before and after drug intake. Participants abstained from alcohol for 48 hours prior to admission to the clinical research unit and abstained from the use of tobacco during the trial.

For each treatment period, blood samples for pharmacokinetic analysis were collected predose and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose.

Blood samples were analyzed for sildenafil at the ISO 15189 certified pharmaceutical laboratory of the Erasmus Medical Center in Rotterdam using liquid chromatography with tandem mass spectrometry validated between 2 and 1,000 µg/L in accordance with the US Food and Drug Administration (FDA) guidelines. Adverse events (AEs) were recorded throughout the study, with severity (mild, moderate, or severe) and the investigator's assessment of the causality with the study drug. Other safety assessments were vital signs, physical examination, laboratory parameters, and electrocardiogram.

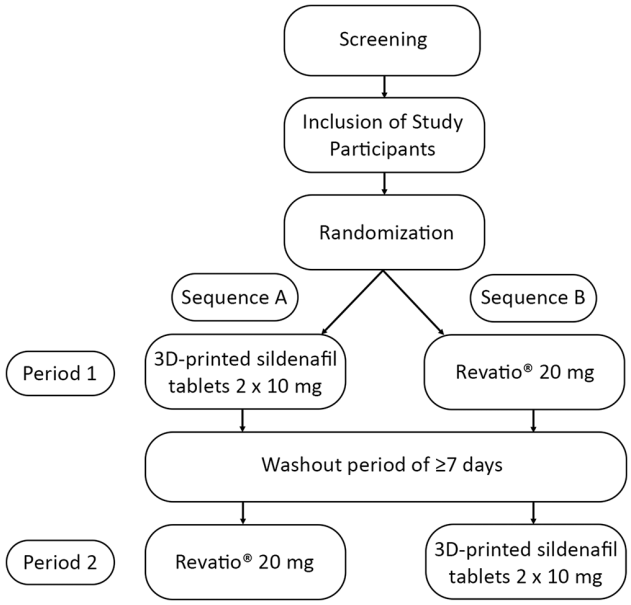

Figure 2 Study procedure. Crossover design where eligible participants were randomly assigned to either sequence A (first 3D-printed sildenafil tablets) or B (first commercial sildenafil tablet Revatio®).

Outcome measures. The primary outcome measure of the clinical trial was the bioequivalence between the 3D-printed sildenafil tablets and the commercial sildenafil tablets Revatio® based on comparison of the areas under the plasma concentration curve from administration to the time of the last quantifiable concentration ($AUC_{0\text{-}t}$) and the maximum plasma concentration (C_{max}).

Secondary outcome measures included the pharmacokinetic parameters AUC extrapolated to infinite time ($AUC_{0\text{-}\infty}$), time to maximum concentration (T_{max}), plasma concentration half-life ($t_{1/2}$), residual area, and the terminal rate constant (λ_z). Furthermore, the safety was evaluated.

Statistical analysis

According to the European Medicines Agency (EMA) guideline, bioequivalence is assumed if the 90% confidence interval (CI) of the geometric mean ratio (GMR) of test to reference treatments of $AUC_{0\text{-}t}$ and C_{max} are within the range of 80.00%–125.00%.[12] Because sildenafil improves the exercise capacity in patients with pulmonary hypertension after weeks, the total exposure is considered to be the most important pharmacokinetic parameter for the efficacy of sildenafil.[11] Therefore, the sample size calculation was based on the $AUC_{0\text{-}t}$. The sample size was calculated using R statistics (version 3.6.1) assuming a crossover design. For each number of subjects, 10,000 trials were simulated assuming within-subject standard deviations of 0.149 for the $\log_e AUC_{0\text{-}t}$.[13] The required minimum number of 12 subjects, according to the EMA guideline, provided > 95% power (± 0.4% simulation error) to show that the 90% CI of the GMR of $AUC_{0\text{-}t}$ is within the 80–125% limits. Therefore, the target for enrollment was set at 12 participants.

Sildenafil plasma concentrations below the limit of quantification were handled as missing. Actual blood sampling times were used for pharmacokinetic analysis. The pharmacokinetic parameters

were calculated with noncompartmental analysis using pharmacokinetic modeling software (PKanalix; Monolix Suite 2021R1, Lixoft, France). The AUCs were calculated by using the linear trapezoidal rule. PKanalix was also used for the test on bioequivalence to calculate the geometric least square means, the ratio of means of the test vs. the reference treatment, and the corresponding 90% CI for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max}. Wilcoxon's tests were performed on T_{max} and $t_{1/2}$ using the R function *wilcox.test*.

RESULTS

Development of 3D-printed tablets

The 3D printing manufacturing process was successfully implemented at the hospital pharmacy of the LUMC. An independent Good Manufacturing Practice auditing team from the National Health Inspectorate assessed the quality of the manufacturing process and deemed it sufficient. Trained pharmacy personnel were able to manufacture 3D-printed sildenafil tablets that consistently adhered to the compendial quality control requirements, as is shown in **Material S1**. The 3D-printed tablets showed an immediate release profile with an average content of 9.8 mg sildenafil.

The tablets resulting from the manufacturing process are presented in **Figure 3**.

Bioequivalence

All 12 participants completed the 2 study periods and were included in pharmacokinetic and safety analyses. The participants had a median (min-max) age of 21 (19–31) years, with a median (min-max) body mass index of 22.9 (21.1–29.0) kg/m^2. **Figure 4** shows the mean sildenafil plasma concentration-time profiles of Revatio® and the 3D-printed tablets over 12 hours following a single 20 mg dose.

The GMR of $AUC_{0\text{-}t}$ was 95.34% and the 90% CI was 87.28–104.14% (**Table 1**). The GMR of $AUC_{0\text{-}\infty}$ was 95.53% and the GMR of C_{max} was 93.77% and the corresponding 90% CIs were 88.03–103.67% and 80.23–109.58%, respectively. The 90% CI of the GMR of $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} were all within bioequivalence limits (80.00–125.00%). Additional pharmacokinetic parameter summaries are presented in **Table 2**. Median T_{max} values were comparable across both formulations ($P = 0.5946$), with a range of 0.50–2.00 hours, as was the $t_{1/2}$ ($P = 0.7540$).

Figure 3 The 3D-printed tablets containing 10 mg sildenafil.

The within-subject standard deviation of the study population was 0.12 µg*h/L for $AUC_{0\text{-}t}$, 0.21 µg/L for C_{max}, and 0.11 µg*h/L for $AUC_{0\text{-}\infty}$. For reference purposes, a *post hoc* power analysis for the C_{max} based on this within-subject standard deviation was performed, resulting in a power estimated to be 65% (± 1% simulation error). The individual concentration-time profiles are included in **Material S1**.

No serious or severe AEs or clinically relevant changes in laboratory values or vital signs occurred during this study, nor did any participant discontinue from the study due to an AE. Six participants experienced ≥ 1 AE. All AEs were temporary and of mild severity. The reported AEs were headache (5 times), flushing (3 times), and thin defecation once after finishing a study period. As all AEs were known AEs of sildenafil and occurred during or at the end of a study period, they were considered possibly related to the study treatment.

DISCUSSION

This study demonstrates for the first time the feasibility of developing and manufacturing a 3D-printed tablet drug formulation at the point-of-care that is bioequivalent to its marketed, large-scale produced originator. The 3D printing of medicines opens the possibility to serve the medical community with the manufacturing of tailor-made dosage strengths for patients for whom the commercially available dosages are not suitable. Besides small children this may also apply to patients with drug–drug interactions or gene polymorphisms in metabolizing liver enzymes that necessitate dose adjustment to lower daily doses.

Despite the clinical need, to date, 3D-printed formulations are rarely used in clinical practice. The bioequivalence of a fast-melt 3D-printed formulation containing levetiracetam has been previously shown[14] and this formulation was subsequently brought to market. This formulation was manufactured using a 3D printing technology intended for large-scale production. Wang *et al.*[15] showed the development of 3D-printed controlled release dosage forms containing pseudoephedrine hydrochloride and evaluated the *in vivo* performance in healthy adults. Both these 3D-printed formulations are not intended for personalized medicine. Goyanes *et al.*[16] showed the use of 3D printing in a hospital setting for the preparation of personalized isoleucine formulations. Although the results were promising, a small population of only 4 pediatric patients was included and this was not a comparative bioequivalence study, limiting the conclusions of the clinical utility of this 3D-printed formulation.

In the current study, bioequivalence with the 3D-printed sildenafil tablets was tested as a proof-of-concept for the clinical utility of 3D-printed medicines. Standard bioequivalence testing

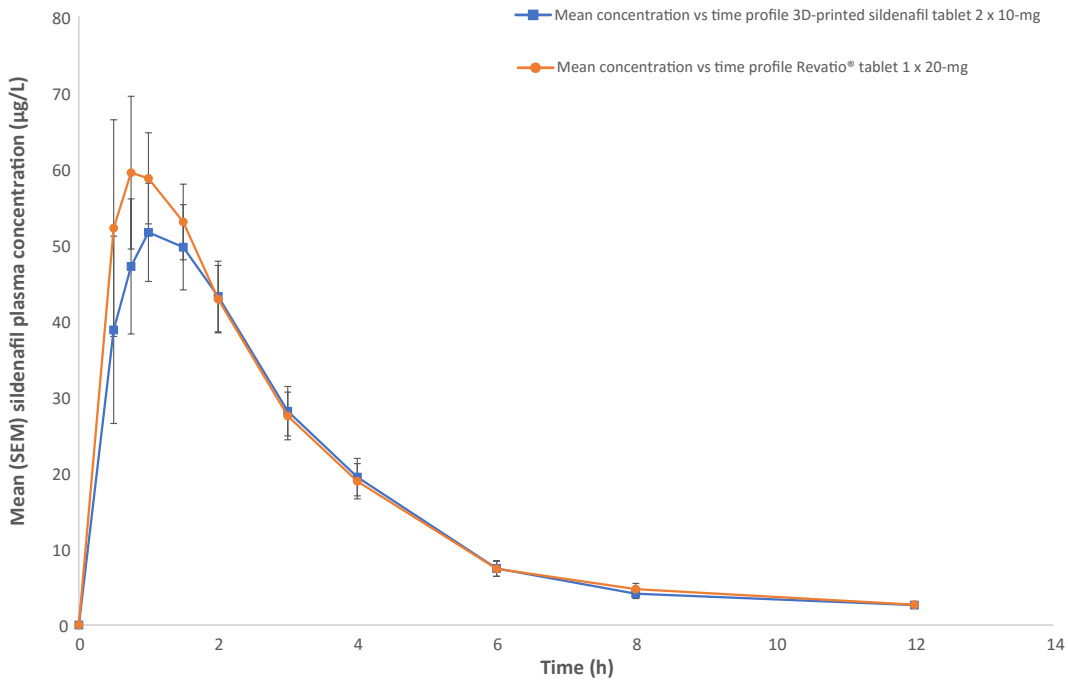

Figure 4 Mean plasma sildenafil concentration-time profiles (n = 12) of Revatio® and the 3D-printed tablets over 12 hours following a single 20 mg dose. Error bar represents standard error of the mean.

accepts a 90% CI of the GMR of the $AUC_{0\text{-}t}$ and C_{max} within 80–125% limits. In precision dosing, differences in exposure of this size are acceptable. Bioequivalence was studied in healthy adults, whereas the 3D-printed tablets were developed for the pediatric population. According to the EMA Guideline on the Investigation of Bioequivalence,[12] extrapolation of the results to other populations for whom the reference product is marketed (e.g., the pediatric population) is allowed. Non-therapeutic bioequivalence studies in vulnerable pediatric study subjects cause an ethical dilemma. Healthy volunteers are considered to be adequate to detect pharmacokinetic differences caused by the drug formulation. To be able to compare both study treatments in equal doses during the bioequivalence study, two 3D-printed sildenafil 10 mg tablets were compared to one Revatio® 20 mg tablet. The Revatio® 20 mg tablets are the lowest commercially available sildenafil tablet strength and these tablets have no break-mark. This also shows that 3D printing of medicines avoids splitting of tablets by patients to reach the right dose, or using oral suspensions which are notorious for making dosing mistakes.

The composition of the formulation can influence the printability[17] as well as the bioavailability and therefore the therapeutic efficacy and safety. When changing the formulation (i.e., excipients or active pharmaceutical ingredient(s)), the release profile should be reasoned. In this proof-of-concept study, sildenafil was formulated in a suitable tablet matrix with an immediate release profile. Interestingly, research shows the possibility of manufacturing modified release tablets with a 3D printer.[18,19] Changing the release profile, as compared to the originator, makes it challenging to predict the bioavailability. Reasoning the bioavailability is even more important for 3D-printed tablets, as it is not feasible to clinically assess personalized medicines prior to use in the intended patient, due to individual dosing strengths and release profiles.

Continued development of 3D printable formulations can stimulate the implementation in clinical practice. The 3D

Table 1 Comparison between the test and reference treatment

	Geometric least square mean[a]			
PK parameter	Test (3D-printed sildenafil 2 × 10-mg tablets)	Reference (Revatio® 20 mg tablet)	GMR (test/reference) %	90% CI for GMR
$AUC_{0\text{-}t}$ (µg*h/L)	163.64 (1.63)	171.64 (1.62)	95.34	(87.28–104.14)
$AUC_{0\text{-}\infty}$ (µg*h/L)	172.87 (1.58)	180.96 (1.58)	95.53	(88.03–103.67)
C_{max} (µg/L)	62.33 (1.58)	66.48 (1.50)	93.77	(80.23–109.58)

$AUC_{0\text{-}t}$, areas under the plasma concentration curve from administration to the time of the last quantifiable concentration; $AUC_{0\text{-}\infty}$, areas under the plasma concentration curve from administration extrapolated to infinite time; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric least square mean ratio.

[a]Geometric mean (geometric standard deviation).

Table 2 Additional PK parameter values for sildenafil following a single oral dose of 20 mg

PK parameter	Test: 3D-printed sildenafil 2 × 10-mg tablets	Reference: Revatio® 20 mg tablet	*P* value
T_{max} (h)	1.00 (0.50–2.00)	1.00 (0.50–1.65)	0.5946
$t_{½}$ (h)	1.72 (1.37)	1.63 (1.38)	0.7540
k_e (h^{-1})	0.40 (1.37)	0.42 (1.38)	–
Residual area (%)	4.57 (1.60)	4.57 (1.57)	–

PK, pharmacokinetic; $t_{½}$, plasma concentration half-life; T_{max}, time to maximum concentration.
Geometric mean (geometric standard deviation) for all but T_{max} (median (range)).

printing is a variation upon extemporaneous preparation necessitating rigid quality assurance and validation. Standardizing formulations (e.g., cartridges as a stock product), can enable the use of this technique outside of experienced compounding centers and further ensure the quality and safety of 3D-printed tablets. Quality control can be performed on the cartridges, and in-process controls, such as near-infrared spectroscopy, can be used for the analysis of 3D-printed tablets at the point-of-care.[20] Furthermore, especially for pediatrics, these standardized formulations should be suitable for printing a dosing range and the tablets need to be small enough to be swallowable.[21–23] Previous studies have been performed on the perceptions and preferences toward the acceptability of 3D-printed formulations. They are generally positive, and the shape, size, color, taste, and swallowability are important parameters to be taken into account when developing a new 3D-printed formulation.[24–26] In addition, more clinical experience with a variety or even a combination of drugs can help build trust in this novel type of formulations, including clinical experience with precision dosing. For example, the interindividual suggestive differences in exposure shown in this study may add an additional argument for precision dosing. Proving the real-world clinical value of precision dosing by reducing the incidence of adverse drug reactions while maintaining therapeutic efficacy, further supports the need for individualized dosage forms, such as 3D-printed tablets. This has been investigated in the PREPARE study.[27]

We have shown in this study that developing 3D-printed sildenafil tablets at the point-of-care with an easily implementable technique is possible, and that these tablets are bioequivalent to commercially available sildenafil tablets. Personalized 3D-printed tablets are a novel and disruptive technology with added value to current compounded formulations in pharmacies, bridging the gap toward precision dosing.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declare no competing interest for this work.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. M.L., I.L., D.J.A.R.M., H.J.G., and K.J.M.S. designed the research. M.L. and I.L. performed the research. M.L., I.L., D.M.K., B.C.M.W., and D.J.A.R.M. analyzed the data.

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