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International Journal of Pharmaceutics 603 (2021) 120694

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

3D printed furosemide and sildenafil tablets: Innovative production and quality control

I. Lafeber [a], J.M. Tichem [a], N. Ouwerkerk [b], A.D. van Unen [b], J.J.D. van Uitert [b], H.C. M. Bijleveld-Olierook [a], D.M. Kweekel [a], W.M. Zaal [a], P.P.H. Le Brun [a], H.J. Guchelaar [a], K.J. M. Schimmel [a,*]

[a] Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Albinusdreef 2, 2333ZA Leiden, the Netherlands
[b] Doser BV, Langegracht 70, 2312 NV Leiden, the Netherlands

ARTICLE INFO

Keywords:
3D printing
Quality control
Personalised medicine
Furosemide
Sildenafil
Paediatrics

ABSTRACT

Three-dimensional (3D) printing of pharmaceuticals has the potential to revolutionise personalised medicine but is as yet largely unexplored. A proof-of-concept study of a novel heated, piston-driven semi-solid extrusion 3D printer was performed by producing furosemide and sildenafil tablets for paediatric patients. The average weight of the tablets was 141.1 mg (RSD 1.26%). The acceptance values of the content uniformity were 4.2–10.6 (concentration RSD 0.41–0.63%), 4.8–8.9 (concentration RSD 0.76–0.97%) and 6.6–9.2 (concentration RSD 0.94–1.44%) for furosemide 2 mg, 10 mg and sildenafil 4 mg, respectively. The dissolution rate limiting step was the dissolving and eroding of the tablet matrix and showed an immediate release. The tablets complied to the requirements of the European Pharmacopoeia (EP) for uniformity of mass (EP 2.9.5), content uniformity (EP 2.9.40) and conventional release (EP 2.9.3). While they complied, not all of these quality tests for tablets might be suitable for 3D printed tablets due to the layering of the tablets and the small batch production. To assess adequate layer adhesion adjusted friability (EP 2.9.7) and resistance to crushing (EP 2.9.8) tests are proposed.

1. Introduction

While the three-dimensional (3D) printing technique was originally developed as a means of producing prototypes in the 1980s, it now has evolved into a technique capable of repeatedly producing accurate objects with a wide range of materials. The principle of the 3D printing technique is based on building an object in a layer-by-layer fashion from a computer model. Using computer-aided design (CAD), the object can be adjusted to meet the user's requirements. When the first multi-material 3D printer was marketed in 2006, the applicability of 3D printing increased over the years.

3D printing of pharmaceuticals has gained interest over the past decade and it provides opportunities for accessible and affordable personalised medicine [1,2]. Indeed, current techniques for producing licensed medicine are mostly incapable to fill the gap between 'one size fits all' and individualised dosing as they are designed for low-cost mass production and strict quality assurance. As a result, they cannot be easily adapted for individualised dosing.

One population for which personalised medicine is a prerequisite is the paediatric population as children mostly are dosed based on their body weight. Besides the fact that these individualised solid dosage forms are not commercially available, the size of tablets or capsules can be too large, and pharmaceutical preparations in general can contain unsuitable excipients for children [3]. One well known example of such unsuitable excipient is propylene glycol in oral liquids [4]. In addition, the taste of liquid oral dosage forms can be unpleasant. Interestingly, research has shown that children prefer small tablets over other dosage forms [5].

Furosemide [6] and sildenafil [7] are frequently used in children, but lack a suitable commercial paediatric dosage form. Extemporaneously manufactured liquid dosage forms of furosemide and sildenafil are also suboptimal as they contain solvents such as propylene glycol, have a poor taste, or, if the active pharmaceutical ingredient (API) is suspended, have the intrinsic risk of dosage errors by inhomogeneity. These problems can possibly be overcome by 3D printing of personalised solid oral dosage forms. 3D printing has the potency of producing accurate pharmaceutical preparations in terms of content uniformity [8], specific drug release profiles [9,10] and adjusted geometry [11,12].

* Corresponding author.
E-mail address: k.j.m.schimmel@lumc.nl (K.J.M. Schimmel).

https://doi.org/10.1016/j.ijpharm.2021.120694
Received 9 February 2021; Received in revised form 22 April 2021; Accepted 6 May 2021
Available online 11 May 2021

Different techniques can be used for the 3D printing of oral solid dosage forms, such as fused deposition modelling (FDM) [13–15], direct powder extrusion (DPE) [16–19], selective laser sintering (SLS) [20], vat photopolymerisation [21] and semi-solid extrusion (SSE) [22,23]. The latter technique is especially interesting for use in the clinical setting, as it allows for easy integration of a large range of APIs. Even chemically unstable drugs can be printed using this method. SSE typically uses a paste or gel, which is formed either by solvents or heat. This paste or gel is extruded through a nozzle on a printing bed.

However, for 3D printed tablets, quality requirements are not yet well established. The European Pharmacopoeia (EP) does describe quality tests for tablets [24], but it is unclear whether the current EP tests for tablets are also fully applicable to 3D printed tablets. To be able to clinically implement the 3D printing technique, the discussion on quality requirements has to be held. Therefore, the aim of this study was to perform a proof-of-concept study for a novel SSE 3D printer and to evaluate the quality requirements that are stated by the EP.

A proof-of-concept study was performed for furosemide 2 and 10 mg tablets, and sildenafil 4 mg tablets, all with Gelucire 48/16 as excipient. In previous studies Gelucire has shown favourable printing properties [25–27]. A novel 3D printer based on heated, piston-driven SSE was used. The lower dosages were chosen to be suitable for children from the age of 1 year old. Dosages of 1–4 mg/kg/day in 2–4 doses and 0.5–6 mg/kg/day in 3 doses are prescribed for furosemide and sildenafil, respectively. In our hospital with a large paediatric cardiology department, these drugs are frequently prescribed in the younger population. Multiple dosages were chosen for furosemide to show the feasibility of this technique to reliably produce a dosage range. The 10 mg furosemide was chosen to reflect the maximum needed personalised dosage, as dividable 20 mg furosemide tablets are available on the market.

The quality of the tablets was tested by assessing their weight distribution, dissolution rates and content uniformity as prescribed by the EP. In addition, the crystallinity of furosemide in the tablets was determined using X-ray powder diffraction. The quality tests that are prescribed by the EP for tablets were evaluated for their suitability for the small-batch production of 3D printed tablets.

2. Materials and methods

2.1. Materials

Furosemide, sildenafil citrate and polysorbate 80, all EP grade, were obtained from Duchefa Farma (Haarlem, The Netherlands). Gelucire 48/16 was kindly provided by Gattefossé (Saint-Priest, France). Methanol R, di-ammonium hydrogen phosphate, ammonium acetate, triethylamine, sodium hydroxide, hydrochloric acid, hydrogen peroxide and acetonitrile were purchased from Merck (Darmstadt, Germany). Potassium dihydrogen orthophosphate was obtained from Fisher Scientific UK Ltd (Loughborough, United Kingdom). The sodium hydroxide and hydrochloric acid were diluted using purified water, which was produced on site using an ELGA PURELAB Flex, Veolia Water Solutions & Technologies (Saint-Maurice, France).

2.2. Methods

2.2.1. Cartridge preparation

Furosemide tablets were produced by mixing the carrier Gelucire 48/16, furosemide respective of 2 mg or 10 mg per tablet, and polysorbate 80 was added as a plasticiser. To achieve a homogenous mixture the components were melted at 50 °C for 15 min using a Heraeus UT 6120 oven (Hanau, Germany) and then stirred vigorously. The mixture was cooled in the stainless steel cartridge with tap water. After cooling for 60 min at room temperature, the cartridge was heated in the printer to 41 °C. The nozzle temperature was also set at 41 °C.

Sildenafil tablets were produced by mixing Gelucire 48/16, sildenafil respectively of 4 mg per tablet and polysorbate 80 in a stainless steel mortar with melamine pestle over a water bath at a temperature of 50–55 °C until homogenous. The mixture was cooled in the stainless steel cartridge using tap water. After cooling for 60 min at room temperature, the cartridge was heated to 44 °C. The nozzle temperature was set at 41 °C. More detailed information can be provided upon individual request.

2.2.2. Printer settings

A modified Prusa i3 MK2 3D printer running on open source Prusa firmware version 3.1.0 was used. Improvements were made on the printhead to make it suitable for SSE. The tablets were designed using custom-build G-code generator software. Upon individual request more detailed information can be provided about the used printer and software. After optimisation the following printing parameters were found. The layer height, both first and consecutive, were set at 0.43 mm. The nozzle diameter was 0.4 mm. In total 7 layers were printed per tablet. The infill percentage for all tablets was 100%. The tablet diameter was set at 6.5 mm. For this study, the tablets were printed in double rows of each 12 tablets, resulting in 24 tablets per batch. The cartridge capacity was 8 mL, implying that approximately 40 tablets could be printed at full capacity.

2.2.3. Weight distribution

Uniformity of mass, as described in EP 2.9.5 [24], was assessed for all tablets. In addition, the quality requirement for the relative standard deviation (RSD) was set at <3%. This requirement is used by the Laboratory of Dutch Pharmacists (LNA) to assess the weight distribution of pharmacy prepared capsules [28]. This standard requires weighing ten individual units. However, for this study all tablets were weighed per batch. The tablets were weighed using a Sartorius Quintix 64-1CEU analytical balance (Goettingen, Germany).

2.2.4. Dissolution

For the furosemide tablets, a phosphate buffer solution pH = 5.8 as described in EP 5.17.1 table 3 was used. For the sildenafil tablets, a hydrochloric acid medium pH = 2.0 as described in EP 5.17.1 table 2 was used [24]. The test volumes, set at 37 °C, were 600 mL, 1000 mL and 750 mL for furosemide 2 and 10 mg tablets, and sildenafil 4 mg tablets, respectively. A Pharma Test PTWS 120D dissolution paddle apparatus (Hainburg, Germany) coupled to a Shimadzu UV-1800 UV–VIS spectrophotometer with multi cuvette unit (Kyoto, Japan) via an Ismatec IPC high-precision multi-channel pump (Wertheim, Germany) was used. The stirring speed of the paddles was set at 50 rpm [24] and samples were taken every 5 min for 140 min. The absorbance was measured at 278 nm for furosemide tablets and at 295 nm for sildenafil tablets. Three batches were tested for each preparation and six tablets per batch. The dissolution had to meet the requirement for conventional-release solid dosage forms as stated in EP 2.9.3 table 1 and EP 5.17.1 [24].

2.2.5. Content uniformity

For furosemide content measurements, a 10 mM di-ammonium hydrogen phosphate pH = 8.0/methanol R 700/300 *v/v* mobile phase was prepared. Analytical reference standard solutions (n = 2) were prepared by dissolving 50 mg of furosemide in 50.0 mL of mobile phase. From this solution 0.50 mL was diluted to 50.0 mL using mobile phase. Samples of 2 mg furosemide tablets were dissolved in 60.0 mL methanol R and diluted to 200.0 mL with 10 mM di-ammonium hydrogen phosphate pH = 8.0 solution. Samples of 10 mg furosemide tablets were dissolved in 30 mL methanol R and diluted to 100.0 mL with 10 mM di-ammonium hydrogen phosphate pH = 8.0 solution. From this solution 1.00 mL was diluted to 10.0 mL using mobile phase.

For sildenafil content measurements, a mobile phase of 20 mM ammonium acetate in purified water with 0.15% triethylamine/acetonitrile 700/300 *v/v* was freshly prepared. The pH was adjusted to 4.1 with 2 M HCl. Analytical reference standard solutions (n = 2) were prepared by dissolving 30 mg of sildenafil citrate in 50.0 mL of mobile

phase. From this solution 1.00 mL was diluted to 50.0 mL with mobile phase. Samples were dissolved in 15 mL acetonitrile and diluted with 20 mM ammonium acetate in purified water with 0.15% triethylamine to 50.0 mL. From this solution 1.00 mL was diluted to 10.0 mL with mobile phase. Dissolution of the samples for both furosemide and sildenafil tablets was accelerated using an ultrasonic water bath set at 45 °C.

Of each preparation, the content uniformity of three batches was tested by analysing 10 dosage units per batch. The batches had to comply to the content uniformity requirement as described by EP 2.9.40 *Uniformity of dosage units* [24]. The contents were measured by means of high-performance liquid chromatography with ultraviolet detection using a Thermo Scientific Ultimate 3000 UHPLC (Massachusetts, United States) and equipped with a MicroSpher C18 S100 × 4.6 mm column. The flow-rate was set at 1.0 mL/min and the injection volume was 20 µL. Furosemide was detected at 278 nm and sildenafil citrate at 295 nm. Tablet contents were calculated using the Thermo Scientific Chromeleon Chromatography Data System software version 7.2. To calculate the RSD of the concentration, first the content of each individual tablet was divided by the individual tablet mass. This was followed by the calculation of the standard deviation, which was then multiplied by 100 and divided by the average concentration.

2.2.6. X-ray powder diffraction

The crystallinity of furosemide was determined using a PANalytical X'Pert PRO X-ray powder diffractometer (Almelo, The Netherlands) with a CuKα X-ray tube ($\lambda_{K\alpha1}$ = 1.54060 Å and $\lambda_{K\alpha2}$ = 1.54443 Å) powered at 45 kV and 40 mA. We measured diffraction patterns in reflection mode for 2θ between 5° and 60° with a step size of 0.008°. The data was collected using the PANalytical X'Pert Data Collector software (Almelo, The Netherlands).

Furosemide raw material, Gelucire 48/16, a placebo tablet and tablets containing 2 and 10 mg furosemide were sampled. Raw materials were processed as fine powders. Tablets were scanned as a whole. Visual observations indicated that sildenafil citrate did not dissolve in the mixture with Gelucire 48/16 and polysorbate 80. These samples were therefore not analysed with X-ray powder diffraction.

3. Results and discussion

3.1. Weight distribution

While performing the measurements for the weight distribution, it became evident that the printing route affected the weight distribution. Single row printing resulted in a lower weight of the first tablets, while double row printing resulted in a consistent weight distribution, as is shown in Fig. 1. The weight average of the single row print was 139.3 mg. The first tablet deviated 13.2% from this average and the second tablet deviated 7.5%. While they met the requirements of EP 2.9.5, they did not meet the LNA requirement as the RSD was 3.70%. The double row print met all requirements. The average weight was 141.1 mg (RSD 1.26%). The maximum found mass deviation was 2.70%. Consequently, all subsequent batches were printed as double rows.

The definitive cause of the difference in weight distribution was not determined. Theoretically it might have been caused by a loss of pressure in the nozzle. During the single row print, the nozzle was lifted from the printing bed in between layers and the extrusion was temporarily stopped. The loss of extrusion pressure could be accounted for by priming before printing the next layer, but this didn't result in a consistent weight distribution. Therefore, loss of extrusion pressure was not thought to be the cause of the lower tablet masses. The pressure in the nozzle could only be accounted for by maintaining contact with the printing bed, which was achieved by double row printing.

3.2. Dissolution

The obtained average dissolution profiles for all three preparations are shown in Fig. 2. All batches of the preparations were tested according to level S_1. All batches of furosemide 10 mg tablets and sildenafil 4 mg tablets complied to the standard, which means that all batches showed a minimum of 80% dissolution after 45 min of testing. The amount of dissolved furosemide was 88.8%, 87.8 and 86.3% for batches 1, 2 and 3, respectively, with a standard error of the means of 0.72%. For sildenafil, these amounts were 89.7%, 86.6% and 86.6% for batches 1, 2 and 3, respectively, with a standard error of the means of 1.06%. The batches of furosemide 2 mg did not comply to the test of level S_1, so level S_2 was applied to batch 1 as well. At this level the average dissolved amount at the 45 min timepoint had to be >75% with no tablet <60%. Dissolution data of furosemide 2 mg batch 1 at t = 45 min are shown in Fig. 3. An average dissolved amount of 76.9% (95%-CI 73.6–80.2%) was found and no sample had a dissolved amount <60%. Therefore, batch 1 of the furosemide 2 mg tablets could be considered conventional-release tablets. However, the 95% confidence interval indicates that the furosemide 2 mg tablets might not always comply to level S_2.

The difference between the furosemide 2 mg preparation and the other preparations can be explained by the medium volume. While volumes of 1000 mL and 750 mL were used for the furosemide 10 mg

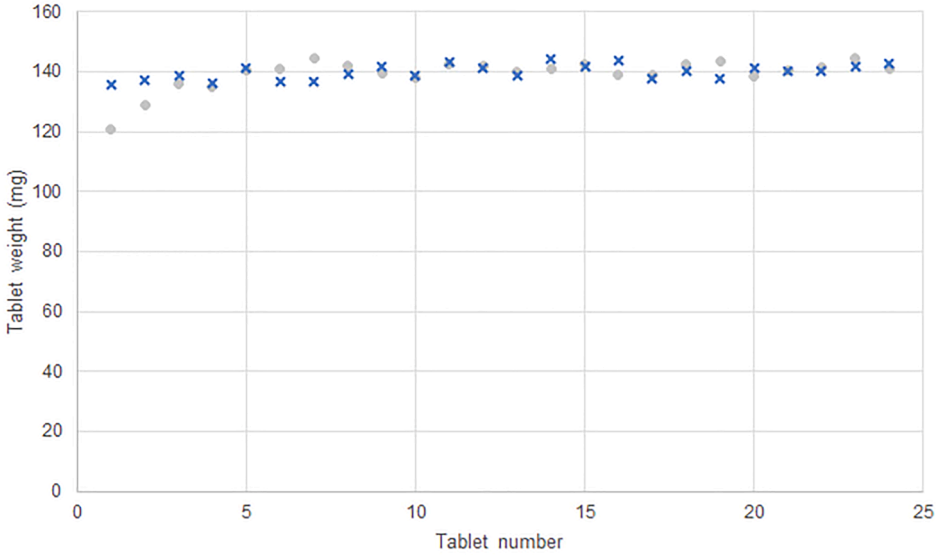

Fig. 1. Weight distribution of 24 consecutive furosemide 10 mg tablets when printed as a single row (●) or as double rows (×).

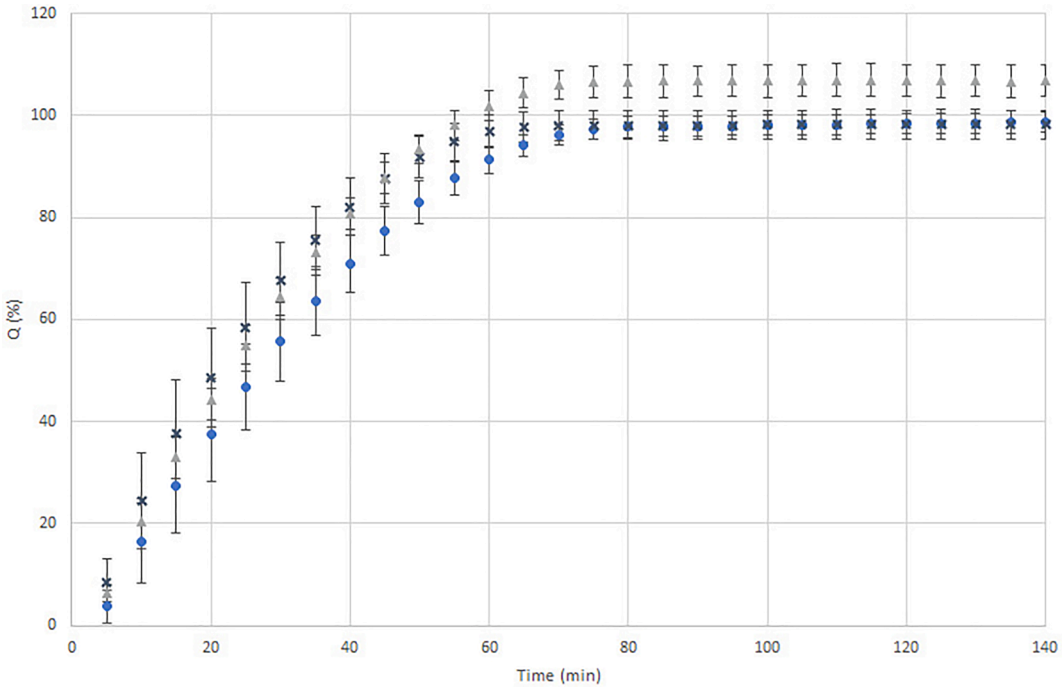

Fig. 2. Dissolution data of furosemide 2 mg tablets (●), furosemide 10 mg tablets (×) and sildenafil 4 mg tablets (Δ), including the requirement limit of level S_1 at the 45 min mark (solid line). Q = amount of dissolved active substance, expressed as a percentage of the declared amount.

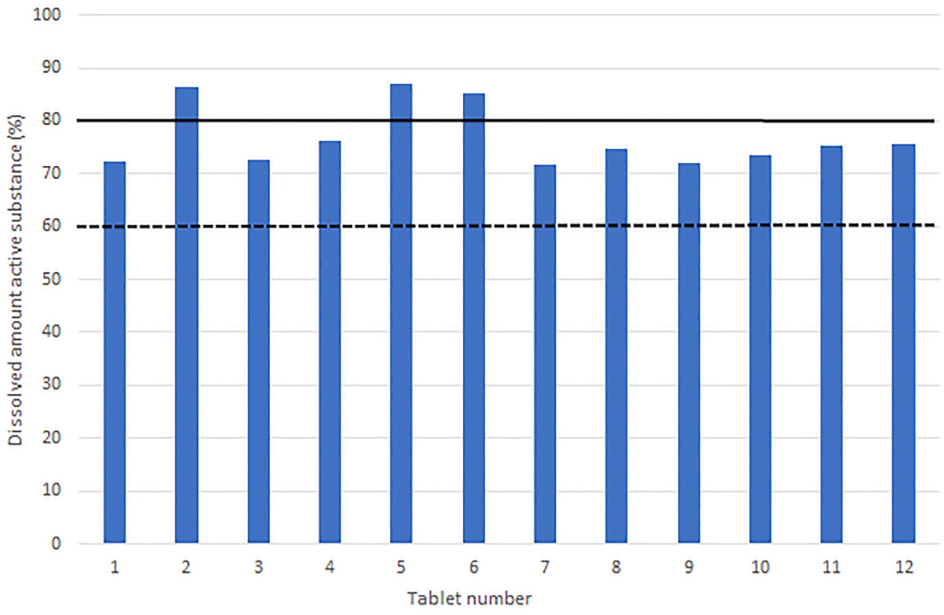

Fig. 3. Dissolution data of furosemide 2 mg tablets batch 1 at timepoint 45 min, including the requirement limits of level S_1 (solid line) and level S_2 (dashed line) for individual tablets. Q = amount of dissolved active substance, expressed as a percentage of the declared amount.

tablets and sildenafil 4 mg tablets, respectively, only 600 mL was used for the furosemide 2 mg tablets. The lower medium volume was justified due to the resulting furosemide concentration within the medium after dissolution. While a larger testing volume showed dissolution data that did comply to level S_1 testing, the analytical measurement error also increased. This indicates that eroding or dissolving of the tablet matrix is the dissolution rate limiting factor, making this matrix a suitable candidate standard matrix for the production of immediate release tablets.

The amount of active substance in the tablets could also have an influence on the dissolution rate. However, as no apparent difference in dissolution between the furosemide 10 mg and sildenafil 4 mg was seen, this influence might be of inferior importance in our case. The geometry of the tablets was identical for all preparations as can be seen in Fig. 4. Therefore it should not be considered of possible influence on the dissolution rate. While all preparations hold the potential to conform to the standards for conventional-release tablets, they barely comply. Further formulation development, such as usage of a disintegration agent [29], might improve the dissolution rate. Also, adjustment of the geometry, for instance lowering the infill percentage [27,30], increasing the surface area by different form [25,31] or reducing the tablet diameter [32], might increase the dissolution rate.

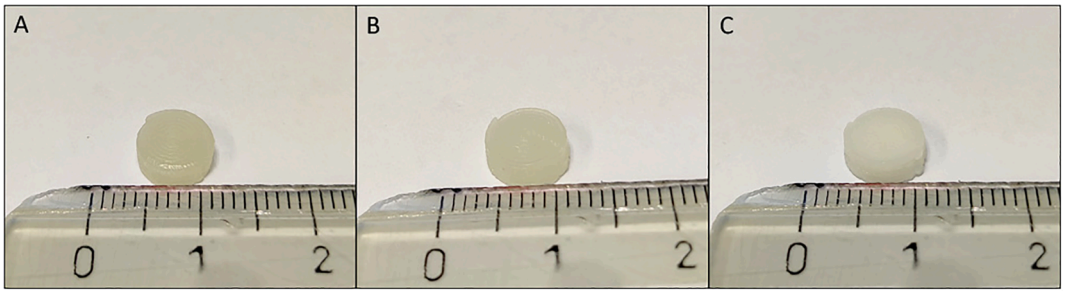

Fig. 4. Images of A. a furosemide 2 mg tablet; B. a furosemide 10 mg tablet; C. a sildenafil 4 mg tablet.

The influence of the tablet geometry on the dissolution rate has been demonstrated by Real et al. [27], who used a similar printing technique. They demonstrated that a lower tablet density resulted in a higher dissolution rate. In addition, while they used a different type of Gelucire, they found that erosion or dissolution of the tablet matrix was the main mechanism of drug release. Irrespective of the difference in tablet matrix, while preparing the pharmaceutical mixture, the active pharmaceutical ingredient is dispersed within the tablet matrix. Therefore, release of the active pharmaceutical ingredient is only possible if the tablet matrix dissolves.

3.3. Content uniformity

The results for the content uniformity analysis are shown in Table 1. All batches of the three preparations complied to the quality requirements for the content uniformity (EP 2.9.40) [24]. It shows that the printing technique is capable of accurately printing small dosages. For these small dosages the acceptance value does seem suitable to detect slight preparation or measurement errors, as is evident for the furosemide 2 mg tablets batch 3. The small standard deviation allows for the acceptance value to remain within the compendial limits. For the furosemide preparations, the small standard deviation is due to the homogenous pharmaceutical mixture. This mitigates the error introduced by the preparation. Sildenafil citrate does not dissolve in the matrix, and has therefore a higher risk for inhomogeneity. However, even for the sildenafil batches, the standard deviation remained small. This indicates that the sildenafil citrate crystals were homogenously dispersed over the tablet matrix. Any slight inhomogeneity caused by settling of the crystals could also have been corrected by the circular printing path. In addition, the RSD of the concentration is an indication of the distribution of active substance per mass unit. The lower the RSD is, the smaller the distribution is. This further supports the presumption that all preparations were more or less homogenously dispersed.

Table 1
Content uniformity analysis results.

Batch	Mean content relative to declared content (%) N = 10	Standard deviation (%)	Concentration relative standard deviation (%)	Acceptance value (EP 2.9.40)
	Furosemide 2 mg			
1	97.56	1.34	0.41	4.2
2	100.76	1.74	0.45	4.2
3	96.10	3.42	0.63	10.6
	Furosemide 10 mg			
1	95.96	0.93	0.97	4.8
2	93.92	1.80	0.88	8.9
3	95.69	2.02	0.76	7.6
	Sildenafil 4 mg			
1	103.80	2.87	1.16	9.2
2	101.67	2.66	1.44	6.6
3	99.95	2.78	0.94	6.7

3.4. Active substance crystallinity

Diffractograms were only obtained for furosemide and the carrier material, both as raw material and as tablet samples, as is shown in Fig. 5. Sildenafil showed poor solubility in the molten mixture of Gelucire 48/16 and polysorbate 80. While the molten mixture with furosemide in any concentration was clear, the mixture with sildenafil was cloudy. It was not likely that the solubility would improve during the printing process, as the printing temperature was lower than the preparation temperature. As sildenafil did not dissolve in the tablet matrix, diffractometric analysis would have been redundant.

The diffractogram of furosemide raw material gave distinctive peaks at diffraction angles 6° and 25° 2θ. These peaks were not visible in the diffractograms of the tablets with both 2 mg and 10 mg furosemide. While this indicated the absence of clear crystalline particles of furosemide in the tablets, it did not definitively indicate amorphous furosemide. Diffractometric analysis cannot distinguish nanocrystals, therefore this possibility could not be completely ruled out. However, it could be concluded that furosemide was at least molecularly dispersed in the tablet matrix and these tablets should be considered solid dispersions.

A solid dispersion may implicate an increased bioavailability of furosemide. Especially since furosemide is considered a class IV drug according to the Biopharmaceutics Classification System (BCS) [33], which means furosemide has a poor solubility and permeability. In addition, the tablet excipient polysorbate 80 might improve the permeability of furosemide [33]. A bioequivalence study should demonstrate whether this formulation indeed leads to an increased furosemide exposure.

Sildenafil citrate did not dissolve in the tablet matrix and consequently cannot be considered a solid dispersion. Sildenafil citrate is considered a BCS class II drug. The solubility is pH dependent and does not comply with the definition of high permeability as stated by the World Health Organization criteria [34]. As sildenafil citrate remains a crystalline substance in the 3D printed tablet, theoretically the solubility and consequently the bioavailability of sildenafil citrate will not be affected. Still, a bioequivalence study is needed to confirm this.

3.5. EP quality requirements evaluation

While the results of the quality analyses performed indicate a sufficient tablet quality for a successful proof-of-concept study, the applicability and practicality of the requirements need to be assessed. To evaluate the quality requirements, first the definition of “tablets” according to the EP was evaluated. The EP states: “Tablets are solid preparations each containing a single dose of one or more active substances. They are obtained by compressing uniform volumes of particles or by another suitable manufacturing technique, such as extrusion, moulding or freeze-drying (lyophilisation).” [24]. Therefore, it is undisputed that 3D printed oral solid dosage forms should be considered tablets and should generally comply with the quality requirements as stated by compendial standard. However, 3D printed tablets are

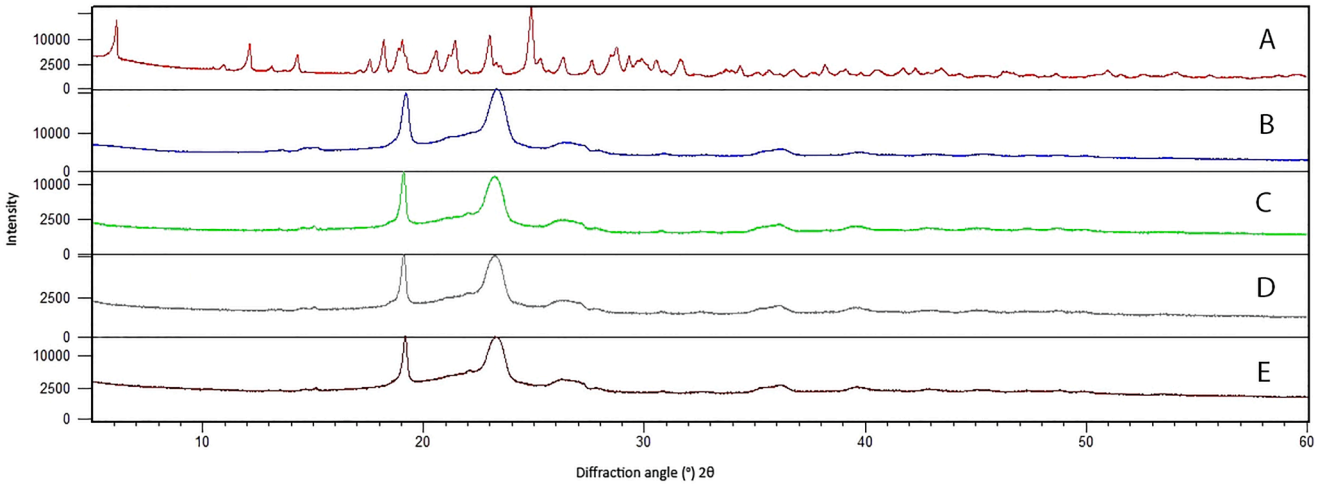

Fig. 5. Diffractograms of A. furosemide raw material; B. Gelucire 48/16 raw material; C. a placebo tablet; D. furosemide 2 mg tablet; and E. furosemide 10 mg tablet.

produced for individual patients and therefore usually have a smaller batch size. This might give challenges when executing all necessary tests.

The EP monograph for tablets states tablets comply with EP 2.9.40 *Uniformity of dosage units* or, where justified and authorised, with EP 2.9.6 *Uniformity of content* and/or EP 2.9.5 *Uniformity of mass,* and with EP 2.9.3 *Dissolution*. In addition, the tablets should uphold sufficient mechanical strength to avoid breaking by handling, for instance by the patient, and the microbiological quality should be ensured. The mechanical strength of the tablets can be demonstrated by EP 2.9.7 *Friability of uncoated tablets* and EP 2.9.8 *Resistance to crushing of tablets*. Recommendations on testing of the microbiological quality are provided by EP 5.1.4 *Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use*. These tests should, according to the definition of the EP, also apply to 3D printed tablets, irrespective of their production technique. The tablets of this study are considered uncoated tablets, as no coating had been printed around the active substance containing matrix. However, it should be noted that the EP definition of uncoated tablets refers to compressed tablets. The definition states an additional test for uncoated tablets, namely EP 2.9.1 *Disintegration of tablets and capsules*. A disintegration test may not be required where a dissolution test is prescribed [24]. All applicable tests for uncoated tablets are mentioned in Table 2, as well as the suitability of the tests for 3D printed tablets in general.

Suitability of testing of dissolution, uniformity of mass and uniformity of dosage units have been demonstrated in this study. These tests ensure the declared amount of active substance and the aimed dissolution profile as is stated by the quality target product profile. It should be noted that EP 2.9.5 *Uniformity of mass* might be redundant if EP 2.9.40 *Uniformity of dosage units* has been performed, as a deviation in tablet mass is only indicative of a deviation in tablet content. While the microbiological quality has not been demonstrated, it does also apply to 3D printed tablets.

Unsuitable tests for 3D printed tablets are EP 2.9.7 *Friability of uncoated tablets* and EP 2.9.8 *Resistance to crushing*. As EP 2.9.7 is a quite rigorous test, tablets other than compressed tablets might fail due to less compaction. EP 2.9.8 might give the unintended result of simply compressing the 3D printed tablet. The tablet matrix might soften as a result of the applied stress. In addition, splitting of individual layers will happen rather than breaking the tablet. This emphasises that the mechanical strength of 3D printed tablets should be ensured, but adjusted tests need to be proposed. The rigorousness of EP 2.9.7 can be reduced by using a small, round container which can be put inside the friability tester. EP 2.9.8 can be adjusted so that the strength which binds the layers of the tablets is defined. For instance, the lower half of the tablet will be held by a container, while a certain mass pushes against the upper half of the tablet in a horizontal way. As all 3D printed tablets are build up by individual layers, irrespective of their production technique, the strength between layers should be ascertained to be suitable for handling. It is recommended to further develop suitable validated quality tests to ensure mechanical strength of 3D printed tablets, such as is proposed here.

Table 2
Quality requirements as stated by the general monograph for tablets by the EP with respect to their suitability to 3D printed tablets.

Quality test as stated by EP	Purpose of the quality test	Suitability for 3D printed tablets
2.9.1 Disintegration	Testing the prescribed time needed to disintegrate	Suitable when no dissolution test is performed
2.9.3 Dissolution	Reflect the measured dissolution rate to the intended dissolution rate	Suitable (this article)
2.9.5 Uniformity of mass	Identify individual deviation of average tablet mass	Suitable when no EP 2.9.40 test is performed (this article)
2.9.6 Uniformity of content	Testing the individual tablet content limits	Suitable when no EP 2.9.40 test is performed
2.9.7 Friability of uncoated tablets	Ensure sufficient mechanical strength	Not suitable, test is intended for compressed tablets
2.9.8 Resistance to crushing	Ensure sufficient mechanical strength	Not suitable, test is more likely to fail due to layering of the tablet or of softened matrix
2.9.40 Uniformity of dosage units	Testing the consistency of the measured tablet content as reflected to the declared content	Suitable (this article)
5.4.1 Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use	Ensure microbiological quality	Suitable

The appearance of 3D printed tablets is also thought to be of importance. Especially for tablets produced using SSE, the resolution can be poor [35]. This can also be seen in Fig. 4 for the tablets produced in this study. The resolution of tablets produced with SSE can still be improved for instance by using a smaller nozzle diameter. However, the

goal of developing this technique is first and foremost to enable accessible personalised therapy. As long as these tablets can adhere to quality control standards, the appearance may be of inferior importance. It can be reasoned that the appearance might affect the acceptance of the tablets. However, a study by Januskaite et al. indicates that children prefer 3D printed tablets produced using SSE [36].

In the EP monograph for pharmaceutical preparations it is noted that pharmaceutical preparations should comply with the General Notices, relevant general chapters and the relevant dosage form monograph. Studies on 3D printed tablets often refer and comply with the used compendial standard and the respective quality requirements [32,37–39]. However, as 3D printed tablets might be used as personalised medicine, they are likely to be unlicensed medicine and produced in small batch sizes. In addition, not all community and hospital pharmacies might have the necessary technical background [40]. Therefore, carrying out all above-mentioned tests might not be feasible. The EP monograph notes that for unlicensed pharmaceutical preparations, where it is not practical to carry out the tests, other suitable methods may be implemented to ensure the appropriate quality of the preparation. Though it should also be considered that 3D printing of tablets might lead to a larger production of individual preparations and therefor puts a larger patient population at risk if the quality requirements are not well defined.

Personalised medicine would benefit from limited sampling, as this usually concerns small batches. Moreover short throughput time between production and dispensing of the tablets is desirable. To still ensure the quality of 3D printed tablets, it is thought that performing EP 2.9.5 *Uniformity of mass* might be sufficient. This thought is based on the results of the RSD of the concentration as shown in Table 1. A RSD lower than 2% indicates a small distribution of the active substance per mass unit [16]. It indicates that the content per mass unit is so consistent, that the tablet mass reflects the tablet content. While process validation and development data are essential to validate the use of EP 2.9.5 *Uniformity of mass*, it may be a suitable method to ensure the quality of small batches of 3D printed tablets.

4. Conclusion

This novel printing technique has proven to be able to accurately print furosemide and sildenafil tablets with dosages that are necessary to treat the paediatric population. While the EP per definition states that 3D printed tablets should be considered tablets and therefore should comply with the compendial standard quality tests, a critical view on these tests has been given in this study. Especially the smaller batch sizes that are necessary to target personalised medicine requires a different view with respect to the implementation of the quality standards. As this was an exploratory study, further studies should be performed to assess the robustness of the suggestions made. In addition, pharmacokinetic studies should be done to explore the implications of 3D printed tablets on biopharmaceutical parameters.

CRediT authorship contribution statement

I. Lafeber: Investigation, Writing - original draft. **J.M. Tichem:** Investigation. **N. Ouwerkerk:** Conceptualization. **A.D. Unen:** Conceptualization. **J.J.D. Uitert:** Software. **H.C.M. Bijleveld-Olierook:** Writing - review & editing. **D.M. Kweekel:** Writing - review & editing. **W.M. Zaal:** Investigation. **P.P.H. Le Brun:** Writing - review & editing. **H.J. Guchelaar:** Writing - review & editing. **K.J.M. Schimmel:** Supervision, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors are grateful to Gattefossé (France) for the donation of raw material.

Funding

This research did not receive any specific grants from funding agencies in the public, commercial or not-for-profit sectors.

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