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Research paper

# On-demand manufacturing of immediate release levetiracetam tablets using pressure-assisted microsyringe printing

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ABSTRACT

Fast and accurate manufacturing of individually tailored solid dosage forms is one of the main challenges for personalized medicine. The use of 3D printers has recently been studied to determine their suitability for personalized drug manufacturing.

In the current work, formulations free of organic solvents were developed for a pressure-assisted microsyringe printing method (PAM). The water soluble polymer polyvinyl alcohol-polyethylene glycol graft copolymer (PVA-PEG) was used as matrix, while levetiracetam (LEV) was used as model drug. Furthermore, the influence of a second polymer, polyvinylpyrrolidone-vinyl acetate copolymer (PVP-PVAc) on the properties of the printed tablets was investigated. Tablets were printed using a 3D-Bioplotter. The printed formulations were analyzed regarding mass variation, friability and thickness. Furthermore, the disintegration behavior and dissolution profile were analyzed. Investigations of the dissolution profiles of printed tablets show that an immediate release of the API could be achieved. For tablets with PVA-PEG the drug is released completely within 10 min while the additional use of PVP-PVAc leads to a slightly delay with a complete release within 20 min. The same trend is observed regarding the disintegration time of printed tablets. Tablets with PVA-PEG disintegrated within 95 ± 10 s while tablets with additional PVP-PVAc disintegrated within 130 ± 20 s.

Friability of < 0.5% indicate that the used PAM printing method provides tablets without loss of structural integrity during handling. Furthermore, it could be shown that the production of tablets with a good content uniformity using a 3D Bioplotter is suitable.

## 1. Introduction

The demands for pharmaceutical dosage forms are facing significant changes nowadays. Recent findings in the field of pharmacogenomics act as a driving force in the shift towards individualized dosage forms [1,2]. Until now, the concept of “one size fits all” is the most common way of administration of pharmaceutical drugs to patients [3]. However, this concept does not match the needs of individual patient groups or singular patients such as pediatric or geriatric age groups for whom an inappropriate therapy can lead to a higher probability of adverse effects [4]. Therefore, the administration of selected active ingredients (APIs) should be tailored to individual patients based on pharmacogenomic characteristics, weight, age and health status to achieve an optimal therapy [4]. Whereas traditional pharmaceutical manufacturing processes have been used for large-scale production of oral dosage forms for years, these processes are unsuitable for the production of patient-tailored dosage forms [5,6]. They are relatively inflexible and economically not feasible in terms of dispensing and fabricating of small batches for special patient groups. An increasing interest in flexible and adjustable manufacturing processes to match the needs of patients is observed.

Three-dimensional printing (3DP) has been reported as an alternative pharmaceutical manufacturing process for individualized dosage forms [5–12]. The United States Government Accountability Office (GAO) defines 3DP as the production of a solid 3D object using a layer-by-layer process [13]. The solid 3D object is created from a predesigned digital file. By varying the digital file, a high variation in dosage forms can be achieved using the same 3D printer [14].

3DP includes a number of different techniques for the production of 3D objects. In 2015, the Food and Drug Administration (FDA) licensed the first printed pharmaceutical drug, Spritam® (Aprecia Pharmaceuticals, USA). Spritam® is printed using the drop-on-powder printing technique, where a liquid binder solution is sprayed on a powder bed to solidify a layer. This process leads to a solid tablet containing LEV with a highly porous structure and fast disintegration. Among 3DP techniques, fused filament fabrication (FFF) has recently

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gained considerable interest for printing of individualized dosage forms. The 3DP technique requires a polymer filament as starting material, which is produced via hot melt extrusion (HME). The solid filament is molten to a viscos liquid in the print head and printed through a nozzle onto a platform, where the printed polymer solidifies. As FFF requires high temperatures during production of and printing of the filament, the technique is not suitable for thermosensitive drugs. Furthermore, HME is a versatile process where a number of parameters have a distinct influence on the final product [15]. Especially the feeding rate of powder mixture, screw speed of the extruder and extrusion temperature determine the quality of the final product decisively. Previous works on this research area have shown that these parameters needs to be optimized to obtain for printing suitable filaments [16].

Another 3DP technique of interest is printing via a pressure assisted microsyringe (PAM) [17]. This technique requires a semisolid formulation as starting material, which needs to have the property to form a 3D object without collapsing during printing. In comparison to other 3DP processes like FFF, manufacturing of solid filaments using hot melt extrusion is not necessary. A further advantage of PAM, is that the semisolid formulation is extruded by pressurized air through the nozzle during the printing process and is therefore not stressed by a gear system as the required filament in the FFF process. Since the printing material does not have to be molten but only deformable plastically, the printing process can be carried out at or even below room temperature. Thermally instable drugs can be processed with this method easily. The printability depends mainly on the formulation viscosity. If the viscosity is too high, printing is not possible due to nozzle clogging. If the viscosity is too low, the material will not support a 3D structure. Yet, due to the fact that the most printing formulations for this 3DP technique are based on solvents a drying step of the printed 3D object is required.

In 2014, Khaled et al. introduced the manufacturing of bilayer guaifenesin tablets based on hypromellose (HPMC) with sustained release profiles using PAM [18]. Later on, Khaled et al. used PAM to manufacture complex multi-drug tablets with different drug release profiles [5] and to manufacture a polypill containing five different APIs with individual release kinetics [19]. Recently, the same working group published a paper about the production of high drug loaded paracetamol tablets with immediate release properties [20]. These works showed the ability of PAM printing method as manufacturing process for oral solid dosage forms. Nevertheless, a mixture of Aceton/DMSO as solvents was used in these works to prevent clogging of the printing nozzle [5]. The use of these organic solvents results in some restrictions. Thus drug delivery systems containing e.g. DMSO can be limited used for special patient groups as example for pediatric population. The use of organic solvents leads to a residual solvent determination according to the European Pharmacopeia [21]. Another disadvantage of the above mentioned works is the time consuming production time of 24 h of the printing formulation. Additionally, the printed tablets have to be dried for 24 h [5] or 48 h [18].

A recently published work of Siyawamwaya et al. [22] describes the manufacturing of fixed dose combinations for treatment of HIV using PAM. The working group was able to produce successfully a matrix containing three different drugs. However, in this work the resolution of the printed object is poor. Furthermore, organic solvents (Methanol/Aceton) were also used in this work to produce the printing formulation, which leads to the same consequences as mentioned before. Until now, only one study has been published on PAM printing without organic solvents [20].

The aim of this work is to investigate the feasibility of producing immediate release levetiracetam tablets using an extrusion based 3D printer with only water as solvent and to examine the drying process.

Levetiracetam is used to treat epilepsy, especially partial onset, myoclonic and tonic-clonic seizures of pediatrics and adults [23]. The dosage is based on the body weight of the patient. In terms of pediatrics, dosing starts with 7 mg/kg body weight with increasing the dose after two weeks. To ensure this dosage scheme, a suitable and flexible processing method for levetiracetam should be considered. The printing process should be carried out at room temperature. Another focus of this work is the drying process. A low and efficient drying time should be achieved in order to keep the thermal load of the ingredients low and to minimize the overall production time.

## 2. Materials and methods

### 2.1. Materials

Levetiracetam (LEV, UCB, Belgium) was used as model drug. Polyvinyl alcohol-polyethylene glycol graft copolymer (PVA-PEG, Kollicoat® IR, BASF, Germany) was chosen as hydrophilic matrix with immediate release behavior. The influence of polyvinylpyrrolidone-vinyl acetate copolymer (PVP-PVAc, Kollidon VA 64 Fine, BASF, Germany) on the mechanical properties and release properties of the tablets was investigated. The salts for preparing the buffer dissolution media were purchased from Carl Roth (Germany).

### 2.2. Methods

#### 2.2.1. Preparation of the printing formulation

Three printing formulations were prepared (Fig. 1). Formulation A was prepared according to the following steps. 40 g of LEV were dissolved in 60 g of purified water and sonicated for 5 min to get a clear solution. 45 g PVA-PEG was added slowly to the clear solution while stirring for 30 min at 900 rpm. Formulation B contained additionally 4.5 g of PVP-PVAc to formulation A. Formulation C was prepared by adding additionally 4.5 g of PVA-PEG to formulation A in order to investigate the influence of the polymer content on the dissolution behavior.

#### 2.2.2. Design of the tablets

The computer aided design (CAD) software Inventor 2016 (Autodesk, USA) was used to design the templates of the tablets (Fig. 2) and exported into the 3D printer software (Perfactory 3.0, EnvisionTec, Germany) as a stereolithography file (.stl). The size of the tablets was set to 20 mm (length) × 10 mm (width) × 5 mm (height). The infill pattern was printed with 1.0 mm distance between the printed strands, which results in a porous structure which is exemplary shown in Fig. 2.

#### 2.2.3. Pressure-assisted microsyringe printing

Tablets containing LEV were manufactured using a 3D Bioplotter

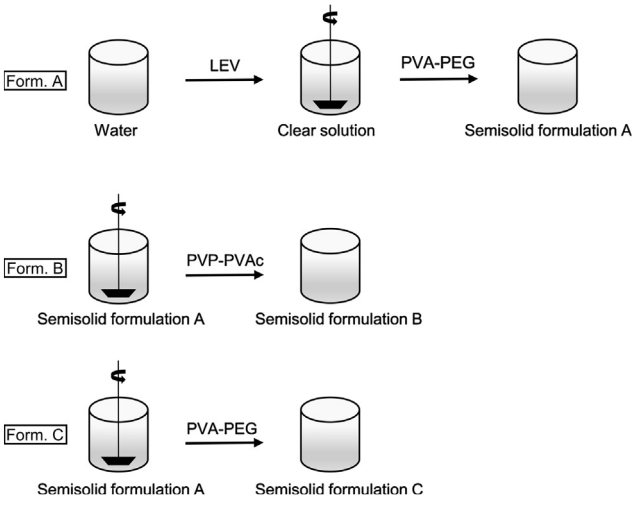


**Fig. 1.** Preparation of the semi-solid printing formulation A and B.

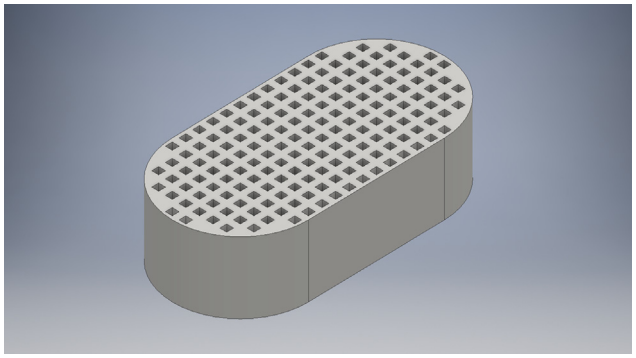

**Fig. 2.** Designed template of an exemplary tablet.

(EnvisionTec, Germany). The printer settings were chosen as follows to obtain tablets with high resolution and short printing time: print head temperature: 27 °C; building platform temperature: 27 °C; printing pressure: 4.5 bar; printing speed: 30 mm/s; travelling speed: 40 mm/s; layer thickness: 0.40 mm. For the investigations three batches containing 20 tablets per batch were printed for all developed printing formulations. For all printing trials, the same printing syringe and printing needle were always used.

*2.2.4. Differential scanning calorimetry*

DSC measurements were performed with a DSC $1^e$ (Mettler Toledo, Germany). Samples of 6 mg were weighed, sealed in pierced aluminum pans and heated at 5 °C/min to 150 °C for LEV respectively to 250 °C for starting materials, semisolid printing formulations and dried tablets. After cooling to room temperature, a second heating cycle was performed and the melting enthalpies of the second run calculated by peak integration (STARe SW 9.20, Mettler Toledo, Germany). Three tablets of each formulations was analyzed.

*2.2.5. X-ray powder diffraction*

Powder X-ray diffraction (XRPD, X'Pert Pro MPD Diffractometer, PANalytical, The Netherlands) was used to determine the solid state characteristics of materials and printed tablets. Diffractograms were recorded using Cu-Kα radiation (30 kV, 30 mA) in transmission mode from 10° to 50° 2θ with a step size of 0.033° and a scan speed of 150 s. Measurements were performed in triplicate.

*2.2.6. Microscopy*

Optical microscopy (Leica MZ 75, Leica Microsystems, Germany) and scanning electron microscopy (SEM, SU3500, Hitachi, United Kingdom) with an acceleration voltage of 5 kV were performed to examine the surface morphology of the printed tablets and the disintegration behavior of the tablets. To determine the disintegration behavior, tablets were placed in a petri dish with 50 ml water and images were taken every minute. Three tablets printed from formulation A and B were analyzed and one of these tablets were shown exemplarily in Fig. 6.

*2.2.7. Friability*

Friability was determined according to the European Pharmacopoeia (Ph. Eur.). Tablets of approximately 6.5 g were weighed, dedusted and placed into the drum of the friability apparatus (TA 120, Erweka, Germany). The drum rotated at 25 rpm for 4 min and the tablets were dedusted and weighed again. According to the Ph. Eur., the measurements were performed once [24].

*2.2.8. Uniformity of mass of single-dose preparations*

The uniformity of mass was calculated according to the Ph. Eur. 20 tablets were weighed individually and the arithmetic mean and relative standard deviation calculated. Not more than 2 of the individual masses should deviate from the average mass by more than 5%. Determination of the uniformity of the mass of single-dose preparations was carried out to assess the accuracy and variability of the printing process.

*2.2.9. Content determination for dissolution studies and content uniformity*

A high performance liquid chromatography (HPLC) method, which was validated according to the ICH guideline Q2 [25], was used to determine the concentration of released drug during dissolution studies and content of the drug. An Elite La Chrome HPLC (Hitachi-VWR, Germany) equipped with an autosampler L-2200, oven L-2300 and an UV Detector L-2400 was used. As column a 240 × 4 mm Nucleosil RP – 18 column with a particle size of 5 µm (Macherey-Nagel, Germany) was used. A water/acetonitrile (90/10) mixture was chosen as mobile phase. The flow rate was set to 1.2 ml/min, the column temperature to 40 °C and the drug was detected at a wavelength of 210 nm via UV/Vis. The autosampler injected 10 µl every 15 min. The mobile phase was degassed and filtered through a 0.45 µm membrane filter.

*2.2.10. Content uniformity*

To determine the content uniformity, the content of 10 tablets were measured. Tablets were dissolved individually in 100 ml water and filtered through a 0.45 µm membrane filter. The content was measured using HPLC as described (Section 2.2.9).

*2.2.11. Dissolution studies*

In vitro drug release studies of 3D printed tablets were performed using a United States Pharmacopeia Convention (USP) Type II apparatus (DT 700, Erweka, Germany) with a paddle speed of 50 rpm in 900 ml phosphate buffer pH 6.8 at 37.5 ± 0.5 °C according to the USP monograph. Samples were withdrawn manually during a period of 60 min, filled into HPLC glass vials and analyzed. Drug dissolution studies were performed in triplicate and the average of percentage cumulative drug release as a function of time was plotted.

*2.2.12. Disintegration time and disintegration behavior in water*

Disintegration time was measured according to Ph. Eur. using a tablet disintegration tester (PTZ AUTO 1EZ, Pharma Test Apparatebau, Germany) with an automatic endpoint detection. Six tablets per batch were analyzed.

*2.2.13. Characterization of the drying process*

*2.2.13.1. Water activity.* To investigate the drying process, the water activity (HC2-AW, Rotronic, Germany) of the tablets was determined over a drying process of 24 h at 40 °C and 200 mbar in a vacuum dryer (Heraeus Vacutherm VT 6025, Thermo Fisher Scientific, USA). The water activity measurements were performed at a consistent temperature of 21.5 ± 0.5 °C. Three tablets of each batch were analyzed individually after 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 12 and 24 h.

*2.2.13.2. Loss on drying.* The loss on drying (LOD) of freshly printed tablets and tablets dried after defined times in a vacuum dryer (Heraeus Vacutherm VT 6025, Thermo Fisher Scientific, USA) was measured at 40 °C and 200 mbar using an infrared moisture analyzer (MA 100, Sartorius, Germany). The tablets were dried at 105 °C until the rate of change in moisture content was less than 0.1% within 60 sec. Determination of LOD was performed in triplicate with the same time scheme as describe in Section 2.2.13.1.

## 3. Results and discussion

### 3.1. Solid state characterization

*3.1.1. DSC*

To investigate potential interactions of the excipients and the API, DSC measurements of the pure substances, semisolid printing formulations and printed tablets were performed. LEV shows a sharp

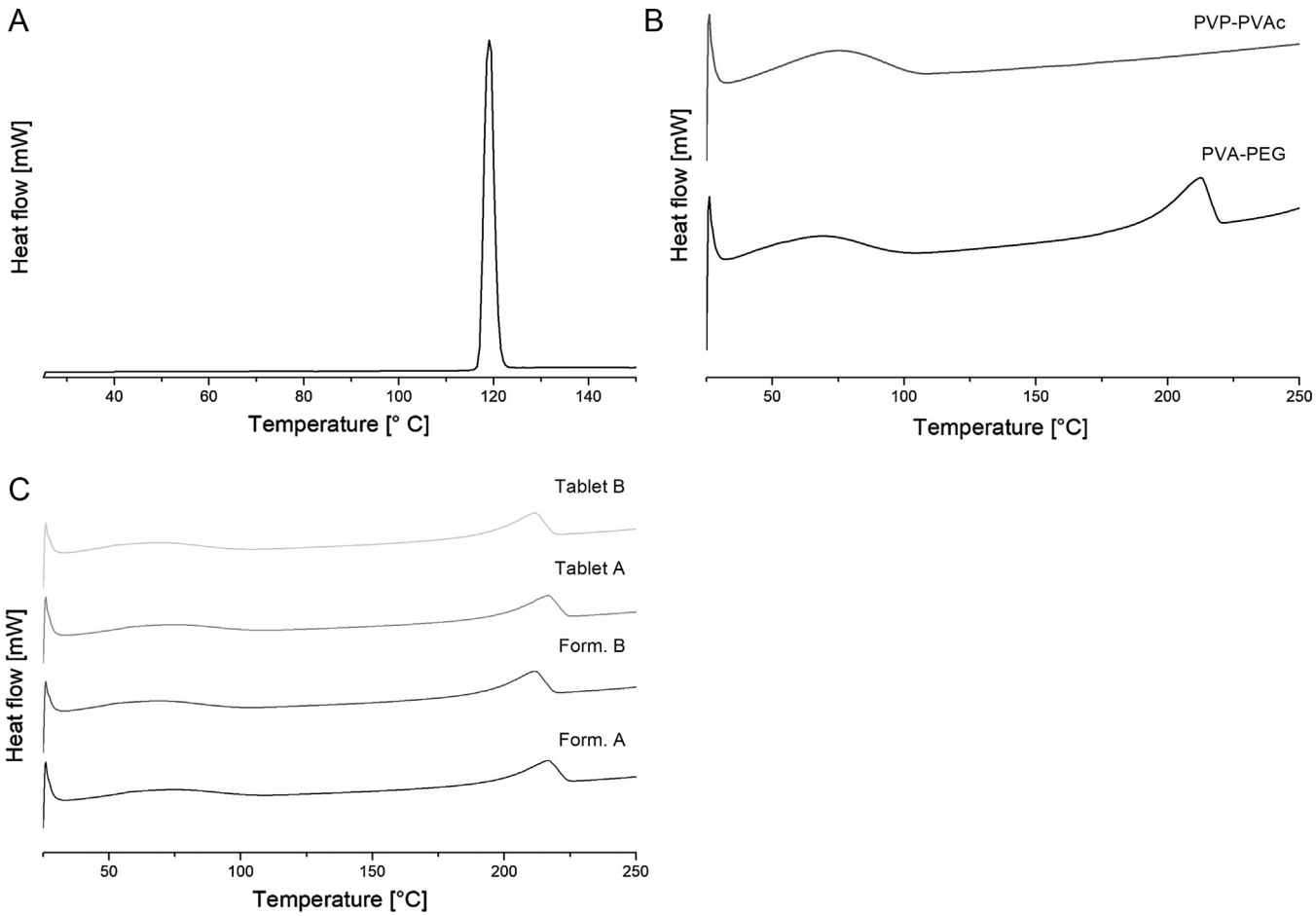


**Fig. 3.** DSC measurement; A. LEV, B. Starting material and C. Semisolid printing formulations and printed tablets.

endothermic peak at 117.29 °C (Fig. 3A) corresponding to its melting temperature, whereas PVA-PEG displays a glass transition temperature at 190.67 °C (Fig. 3B).

Regarding the printing formulations and printed tablets (Fig. 3C), the melting peak of the API disappears, which indicates that the drug is dissolved inside the matrix.

### 3.1.2. XRPD

Diffractograms of the raw materials and the freshly prepared printing formulations were collected to investigate changes in physical form during preparation of printing formulations and printed tablets (Fig. 4). LEV, as raw material is present in the crystalline form as demonstrated by numerous peaks in the XRPD pattern. The peak at 19.0° 2θ in the pattern of PVA-PEG indicates the presence of the semi crystalline form, while the absence of peaks in the diffractogram of PVP-PVAc denotes the amorphous form. In case of freshly prepared printing formulations, dried tablets and 3 months stored tablets, the API remain in their amorphous form (Fig. 4B). The existing peak in all cases at 18.8° 2θ is attributed to the semi crystalline form of PVA-PEG. This underlines the findings from DSC investigations.

## 3.2. SEM

In order to examine the surface structure and cross-cut sections of printed tablets, SEM images were captured (Fig. 5). Fig. 5A shows a bottom edge of a printed tablet. The movement of the printing nozzle results in overlapping of strands at the edge of the tablets. The reason is that in the pre-designed template the contour is constructed independently of the infill pattern. The top of the printed tablet is illustrated in Fig. 5B, which appears to be smooth and shows no crystals on the surface. The image demonstrates that the printer is able to print defined pore structures with high accuracy. The cross-cut of a printed tablet is shown in Fig. 5C while the close-up view of the cross section is shown in Fig. 5D. Both images indicate marginal fusion of individual layers and the creation of a highly defined porous structure.

## 3.3. Friability

The friability was determined in order to evaluate the handling properties of the printed tablets of both formulations. Both tablet batches fulfilled the requirements for friability of the Ph. Eur. (weight loss ≤ 1%) (Table 1). The additional use of 10% PVP-PVAc seems to increase the structural integrity of the printed tablets. This may be because of the plastic properties of the used PVP-PVAc, since it is also used as dry binder in tablet formulations [24,25]. To evaluate this, tablets with additionally 10% PVA-PEG instead of PVP-PVAc were printed and their friability analyzed. These tablets displays a friability of 0.25% which can be rank in between of the friability of formulation A and B. This underlines the assumption that the additionally use of PVP-PVAc increases the structural integrity.

Nevertheless, all these formulations led to tablets, which allow safe handling without the loss of structural integrity.

## 3.4. Disintegration

Tablets from formulation A disintegrate faster than tablets from formulation B. Tablets from formulation A disintegrate within 95 ± 10 s while tablets from formulation B disintegrate within

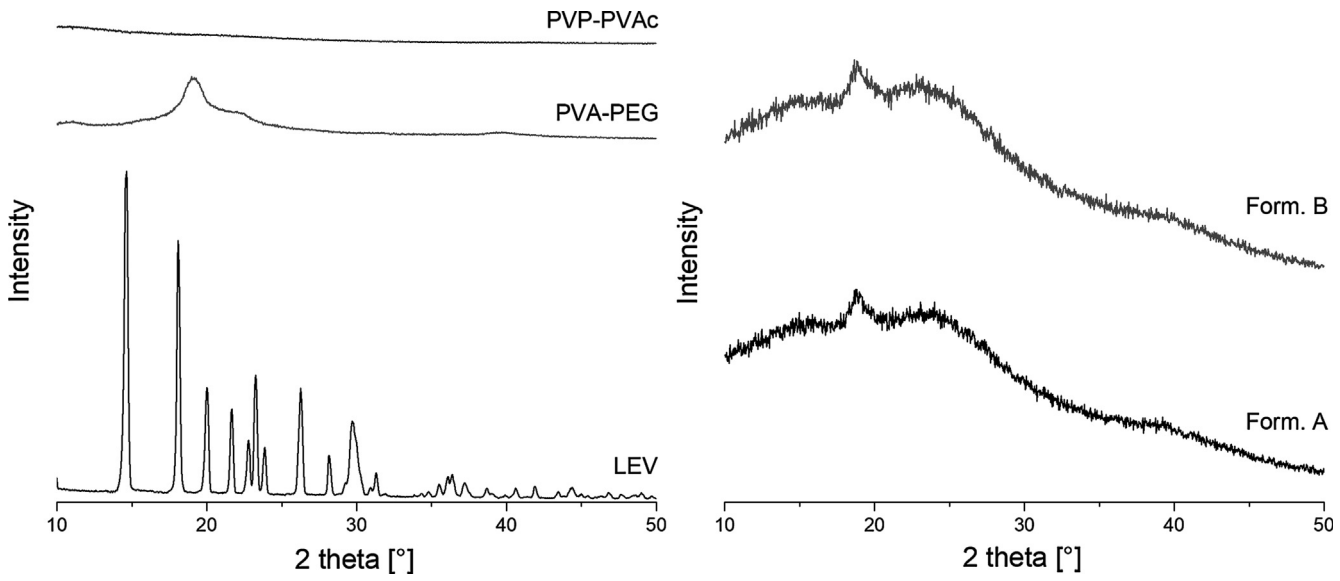


**Fig. 4.** A. Diffractograms of the starting material and B. Semisolid printing formulations, dried tablets and tablets stored for 3 months.

130 ± 20 s. The structural integrity of tablets from formulation B seems to be higher due to the addition of PVP-PVAc. This leads to longer disintegration times compared to tablets without the addition of PVP-PVAc. This correlates with the determined results of friability and can also be observed in the disintegration behavior of printed tablets in water as shown exemplarily in Fig. 6.

Both formulations start swelling after contact with water and the swelling continues with further water uptake, until the tablet shells rupture. For tablets printed from formulation A, the structure ruptures within 2 min. Further water uptake causes the structure to be pushed apart after 3 min and the tablets completely disintegrates after 10 min. In comparison, tablets printed from formulation B rupture after 3 min, however the structure of these tablets does not change for another 3 min. After 10 min tablets lose their structural integrity. The studied tablet shows complete disintegration after 15 min. The contained PVP-PVAc in formulation B (Fig. 1) appears to have a distinct influence on the disintegration behavior of the tablets. PVP-PVAc is often used as a dry binder in tableting formulations [26,27] and seems to increase the structural integrity in tablets printed from formulation B and thereby, the disintegration time of these tablets.

**Table 1**
Friability of printed tablets; n = 1.

| A | B |
|---|---|
| 0.31% | 0.19% |

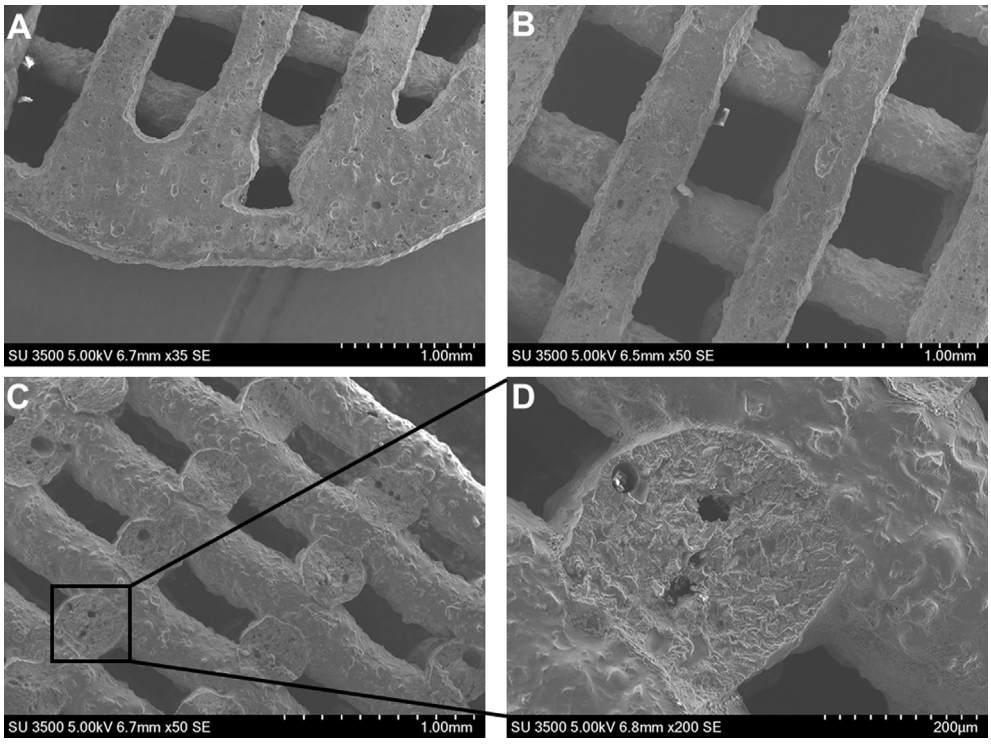


**Fig. 5.** SEM images; A. Edge of the bottom of a printed tablet, B. Surface of a printed tablet, C. Cross section of a printed tablet and D. Close-up view of the cross cut.

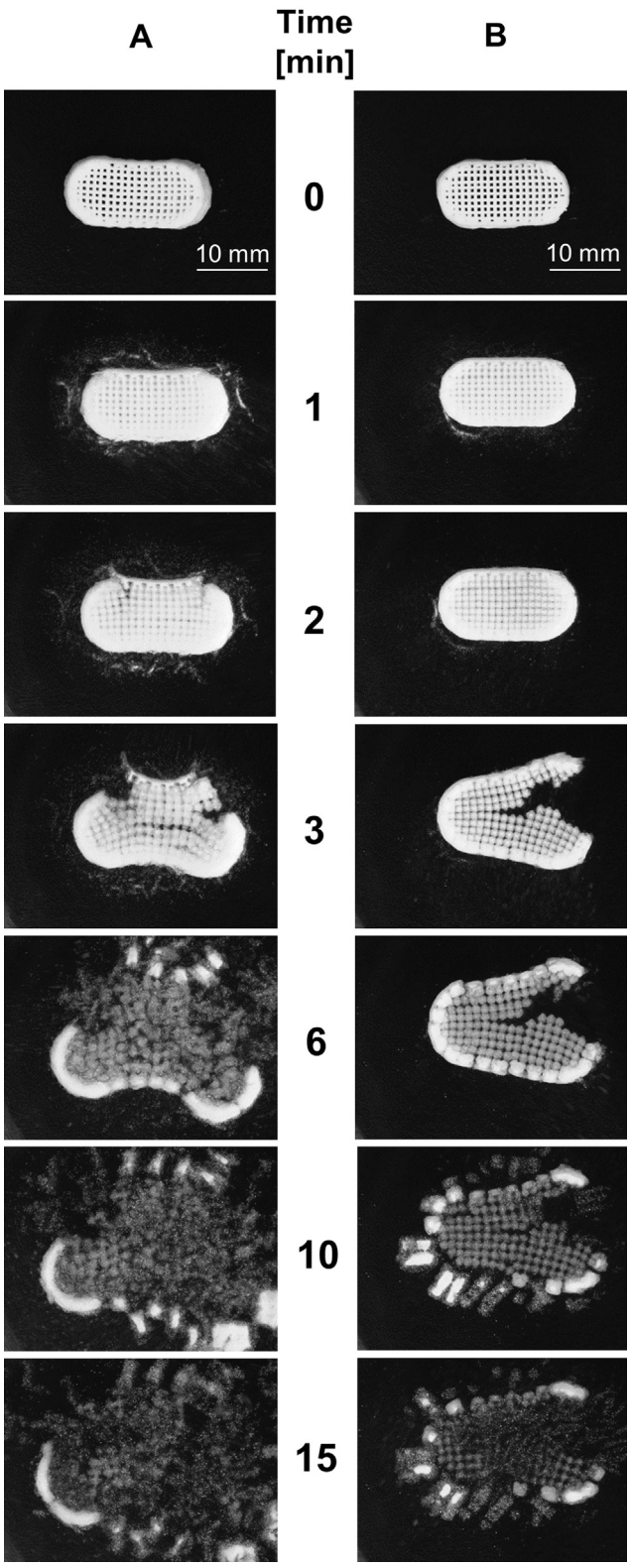


**Fig. 6.** Disintegration behavior of printed tablets in water without stirring at 25 °C, A: formulation A, B: formulation B.

### 3.5. Uniformity of mass of single-dose preparations

The determined dimensions and masses of Tablets are summarized in Table 2. Tablets were designed according to Section 2.2.2 with the dimensions of 20 × 10 × 5 mm (length, width and height). The dimensions of the printed and dried tablets are in every direction smaller then designed (Table 2). The shrinkage of the printed tablets can be explained by the drying step and the associated loss of water. Nevertheless, the structure of the tablets did not collapse due to the loss of water.

**Table 2**
Dimensions and mass of printed tablets; n = 20, for mass n = 60, mean ± SD.

| Form. | Length [mm] | Width [mm] | Height [mm] | Mass [mg] |
|---|---|---|---|---|
| A | 18.7 ± 0.4 | 9.3 ± 0.3 | 4.8 ± 0.1 | 361.1 ± 1.7 |
| B | 18.6 ± 0.3 | 9.2 ± 0.1 | 4.8 ± 0.1 | 353.8 ± 6.4 |

The mass variation data of printed tablets of both formulations are presented in Table 2. In case of the printed tablets for formulation A, all analyzed batches are uniform regarding the mass of the tablets. The relative standard deviation for all 3 batches is < 5% (Batch 1: 4.20%; Batch 2: 2.25%; Batch 3: 1.32%) and fulfill therefore the requirements of the Ph. Eur. The determined mass for tablets of formulation B seems also to be uniform, just in case of Batch 1. Here the relative standard deviation is 7.2% and fulfill therefore not the requirements of the Ph. Eur. This may occur due to the presence of air in the printing syringe at the beginning of the printing process. The printing formulation inside of the printing syringe is compressed because of the applied pressure which can cause an escape of air. This may result in structural errors during the process and a lower weight. The relative standard deviation for batch 2 and 3 is < 5% (Batch 2: 1.26%; Batch 3: 1.54%) and fulfill the requirements of the Ph. Eur. In comparison, the achieved weight for tablets of formulation A is a bit higher than the weight of tablets of formulation B. The polymer content in formulation B is higher compared to formulation A. Due to the fact that the used printing pressure was kept the same for all printing trials, the resulting printed strands of formulation B are likely thinner compared to strands of formulation A. Therefore the weight of tablets of formulation B is lower compared to tablets of formulation A. The results achieved for the uniformity of the mass show that the 3D-Bioplotter used for this study is capable to print dosage forms precisely and with a small in-batch weight variation.

### 3.6. Drying process

The water activity ($A_w$) was determined to give an indication of the microbial stability of the printed tablets. The assessment of the water activity of pharmaceutical and food products is of microbiological importance [28]. It is reported that higher water activities promote growth of microorganisms. An $A_w$ of > 0.91 is needed to support bacterial growth, whereas an $A_w$ of > 0.7 is needed to support fungal growth. An $A_w$ of < 0.6 inhibits the growth of bacteria, yeast and moulds [28]. Printed tablets form both formulations A & B were dried for 24 h at 40 °C and 200 mbar and the water activity determined after defined time intervals. The results of the water activity and LOD measurements are represented in Fig. 7. The 24 h value is not included in Fig. 7 as the values do not change anymore after 12 h.

As expected, the water activity of freshly printed tablets is very high in both cases ($A_w$ > 0.85). A drying time of 3 h in a vacuum dryer at 40 °C and 200 mbar is sufficient to reach a water activity value of about 0.25 in both cases. This indicates that the microbial stability is given after 3 h drying.

The determined LOD of printed tablets over a drying time of 12 h is also represented in Fig. 7. The freshly printed formulations display a high LOD due to excessive water. In all analyzed batches of both formulations, the loss on drying is above 30%. During the drying of the printed tablets, water evaporation can cause a shell formation on the surface of the tablets, which might lead to inefficient drying of the tablets. The formation of such a shell could further influence the resulting mechanical properties. A fragile outer shell might increase abrasion, which may affects the friability and hardness of tablets. Yet, drying in a vacuum dryer for 3 h leads to a LOD of < 1% in all analyzed batches of

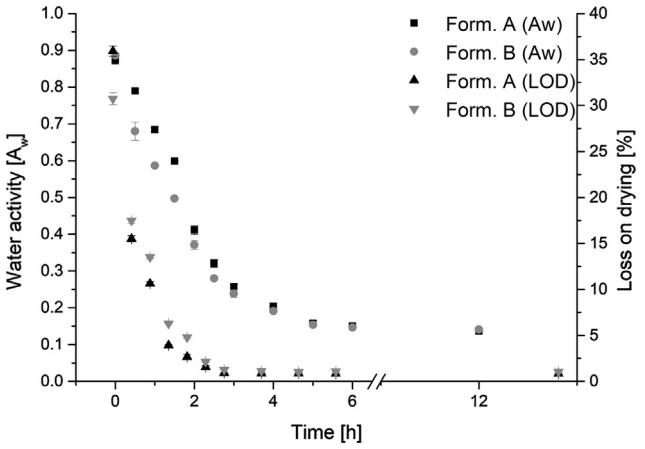


**Fig. 7.** Water activity and Loss on drying measurements of printed tablets; n = 3, mean ± SD.

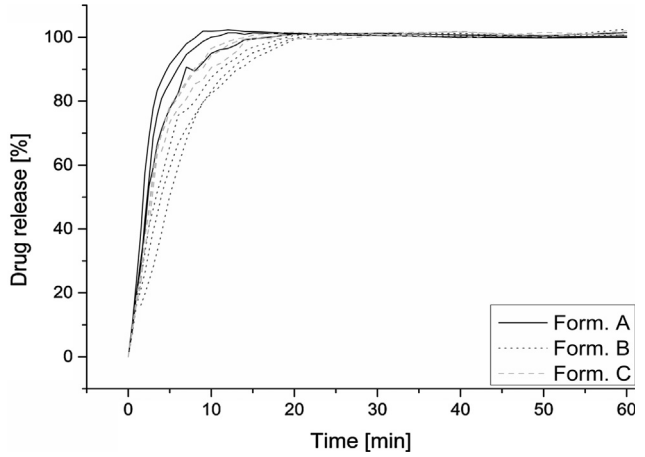


**Fig. 8.** Dissolution studies of printed tablets.

both formulations.

The obtained results for the drying process show that the drying of printed tablets follows a first-order kinetic. Due to the low LOD after drying, it can be assumed that there is no shell formation.

### 3.7. Content uniformity & dissolution studies

Content uniformity determinations depicted a content of 169.2 ± 5.4 mg for tablets of formulation A and a content of 156.5 mg ± 2.6 mg for tablets of formulation B. In both cases the relative standard deviation is below 5% and hence in compliance with the Ph. Eur.

The dissolution profiles of the 3D printed tablets are illustrated in Fig. 8. The dissolution results for formulation A show that 100% of the incorporated drug is released completely within 10 min. The drug release profile changes by adding 10% PVP-PVAc (formulation B). Compared to the dissolution profile of formulation A, the drug release is slightly delayed and shows a complete release within 20 min. These results coincide with the results from the disintegration study.

Compared to tablets printed from formulation A, tablets printed from formulation B disintegrated distinctly slower. The addition of 10% PVP-PVAc in formulation B seems to increase the structural integrity and therefore leads to a delay in drug release. In addition, printed tablets with additional 10% PVA-PEG instead of PVP-PVAc were also investigated regarding their dissolution behavior (formulation C) to determine whether the absolute polymer content it the sole influence on the disintegration time or whether the polymer type also has an impact. Tablets with the additional PVA-PEG show no discernable differences compared to the dissolution profile of tablets from formulation A. These findings underline the assumption that the plastic properties of PVP-PVAc might increase the structured integrity of tablets from formulation B and lead therefore to a delay of drug release. Nevertheless, all tablets show an immediate release of the incorporated drug according to USP monograph.

## 4. Conclusion

This study demonstrates the possibility of on-demand manufacturing of levetiracetam tablets with immediate release profile using PAM printing. Semisolid printing formulations were developed without the use of organic solvents and printing trials were carried out without the use of organic solvents to avoid nozzle clogging. The printing formulations were able to form a 3D object, which did not collapse during printing. The amorphous form of the API in the tablet is stable for at least 3 months, as demonstrated by DSC and XRPD measurements. Furthermore, the drying process was investigated. Compared to previous work, the drying time could be by shortened significantly to 3 h in total. The produced tablets obtained sufficient mechanical properties for daily use. The results of this work indicate that the use of 3D printing technique is suited for production of individualized drug delivery systems. Especially, the uniformity of mass and content achieved with the used 3D printer exhibit the suitability of this manufacturing process.

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