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RESEARCH PAPER

Immediate Release 3D-Printed Tablets Produced Via Fused Deposition Modeling of a Thermo-Sensitive Drug

Wiebke Kempin[1] • Vanessa Domsta[1] • Georg Grathoff[2] • Iris Brecht[3] • Beatrice Semmling[3] • Susan Tillmann[4] • Werner Weitschies[1] • Anne Seidlitz[1]

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ABSTRACT

Purpose Dissolution speeds of tablets printed via Fused Deposition Modeling (FDM) so far are significantly lower compared to powder or granule pressed immediate release tablets. The aim of this work was to print an actual immediate release tablet by choosing suitable polymers and printing designs, also taking into account lower processing temperatures (below 100°C) owing to the used model drug pantoprazole sodium.

Methods Five different pharmaceutical grade polymers polyvinylpyrrolidone (PVP K12), polyethylene glycol 6000 (PEG 6000), Kollidon® VA64, polyethylene glycol 20,000 (PEG 20,000) and poloxamer 407 were successfully hot-melt-extruded to drug loaded filaments and printed to tablets at the required low temperatures.

Results Tablets with the polymers PEG 6000 and PVP K12 and with a proportion of 10% pantoprazole sodium (*w/w*) demonstrated a fast drug release that was completed within 29 min or 10 min, respectively. By reducing the infill rate of PVP tablets to 50% and thereby increase the tablet porosity it was even possible to reduce the mean time for total drug release to only 3 min.

Conclusions The knowledge acquired through this work might be very beneficial for future FDM applications in the field of immediate release tablets especially with respect to thermo-sensitive drugs.

KEY WORDS 3D-printing · filament extrusion · fused deposition modeling · immediate drug release · pantoprazole sodium

ABBREVIATIONS

API	Active pharmaceutical ingredient
FDM	Fused deposition modeling
HME	Hot-melt extrusion
HPC	Hydroxypropyl cellulose
PBS	Phosphate buffer solution (according to USP)
PEG	Polyethylene glycol
PEO	Polyethylene oxide
PLA	Polylactic acid
PVA	Polyvinyl alcohol
PVP	Polyvinylpyrrolidone
TEC	Triethyl citrate
XRPD	X-ray powder diffraction

INTRODUCTION

Currently, immediate release dosage forms represent the major share among orally administered drug delivery devices available [1]. One main challenge for future developments in this area will be the personalisation of therapy, e.g. by customizing the dose or using patient-individual drug combinations. Hopes are placed on new production technologies such as 3D-printing that may offer great advantages compared to classical manufacturing techniques as tableting for

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✉ Anne Seidlitz
anne.seidlitz@uni-greifswald.de

[1] Institute of Pharmacy, Center of Drug Absorption and Transport, University of Greifswald, Felix-Hausdorff-Straße 3, 17487 Greifswald, Germany

[2] Economic geology and mineralogy, University of Greifswald, 17487 Greifswald, Germany

[3] Plant Oranienburg, Takeda GmbH, 16515 Oranienburg, Germany

[4] Takeda Pharmaceuticals International AG Zürich, 8152, Glattpark, Switzerland

managing individual preparations and very small quantity productions [2–4]. The 3D-printing technique of powder binding has also demonstrated its ability to print very porous tablets as shown for Spritam®, the first FDA approved 3D-printed tablet that rapidly disintegrates within the oral cavity and releases high doses of the drug levetiracetam within seconds [5, 6]. At the same time also the extrusion-based technique of fused deposition modeling (FDM) - that utilizes the layerwise deposition of extruded material onto a build plate to form the requested object - moved into focus for the printing of oral dosage forms. FDM has already proven to offer a wide range of new possibilities for the preparation of desired drug products, e.g. dispensing of a specific dose by varying the tablet size [7, 8] or the drug load of the used filament [9], influencing drug release by printing different geometries [10] or dual extrusion FDM for a combination of different drugs or polymers in one dosage form [11–13]. However, tablets printed via FDM often show relatively slow dissolution speeds compared to powder/ granule compacted immediate release tablets, probably due to the used polymers and the compactness of the solidified melt. Polyvinyl alcohol (PVA) tablets printed by Goyanes *et al.* completed drug release no earlier than after 4 h for 5-aminosalicylic acid, even for tablets with lower infill rates of 10 or 50% [14] and no earlier than 6 h for the hydrophilic model drug fluorescein [15]. Labelled as immediate release tablets, printlets with hydroxypropyl cellulose (HPC) showed a complete theophylline release only within 120 min [7]. The fastest drug release from printed tablets that was described in literature was observed for the polymers of Eudragit® E and polyvinylpyrrolidone (PVP) with filling and plasticizing additives and was nearly finished after 30 min [16, 17].

The aim of this work was to achieve an accelerated drug release for tablets that are produced via FDM and contain the thermo-sensitive drug pantoprazole sodium by choosing suitable polymers and printing designs. Pantoprazole sodium was chosen as a model drug for this work because it represents a challenging compound which is thermo-sensitive. The drug is also acid-labile, however the point of achieving gastro-resistance e.g. by coating [18, 19] or printing an enteric shell [12] was not addressed in this work but will be subject of further research. However, the need for an enteric coating needs to be considered in the estimation of dissolution speeds. According to the dissolution performance test 1 of the USP monograph, pantoprazole sodium delayed-release tablets need to release no less than 75% of their labelled drug amount within 30 min in pH 6.8 phosphate buffer after pH change [20]. Taking lag times due to the dissolution of the coat into account, a complete drug release within 15 min for pure tablet cores was striven for in this work. In order to avoid thermal degradation of the active pharmaceutical ingredient (API) this work also focusses on polymers that could be printed at lower temperatures than the ones described in literature so far, in this specific case lower than 100°C to meet the requirements of pantoprazole sodium.

MATERIAL AND METHODS

Materials

Pantoprazole sodium sesquihydrate was provided by Takeda GmbH, Plant Oranienburg, Germany. Used polymers or additives were polyethylene glycol (PEG) 6000 (MW 6000, Fagron, Germany), PEG 20,000 (MW 20,000, Carl Roth, Germany), Poloxamer 407 (Sigma-Aldrich, Germany), polyvinylpyrrolidone (PVP, k-value 12, Carl Roth, Germany), Kollidon® VA64, Kollicoat® IR, Kollidon® CL (all BASF, Germany), triethyl citrate (TEC, Alfa Aesar, Germany) and sodium polyacrylate (Kobo Products Inc., USA). Solvents and all other substances used were of analytical grade.

Methods

Hot-Melt Extrusion (HME) of Filaments

To ensure a homogenous particle size distribution within the powder blends the components pantoprazole sodium, the polymer and possible additives were separately ground in a mortar and mixed for approximately 3 min. Liquid TEC was added and mixed in for plasticized filaments for approximately 1 min. The resulting mixtures were filled in the heatable metal sleeve of a self-constructed extruder as previously described [21] (Fig. 1). The extruder consists of a aluminium sleeve (internal M16 thread, pitch = 2 mm, $Ø_{internal}$ = 14 mm, $Ø_{external}$ = 25 mm, length = 10 cm) wrapped with 2 m resistance wire (diameter 0.3 mm, 6.93 Ω/m) over a length of 7 cm, and a stepping motor with a precisely fitting external thread (M16, brass, $Ø_{external}$ = 14 mm) that screws in the internal thread and forces the molten polymer through the terminal nozzle (diameter 2.8 mm). The temperature is adjusted by setting the current strength flowing through the resistance wire and is measured at the nozzle using a temperature sensor. A second motor with a rotating cylinder (diameter 30 mm) is winding up a string that is attached to the tip of the filament by a crocodile clip to stretch the polymer strand to a straight filament with the desired and uniform diameter of 2.85 mm. Rotation speeds of both stepping motors were identified for each filament separately and ranged from 4.5 to 7.5 rpm for the first motor (extrusion) and from 0.15 to 0.75 rpm for the second motor (stretching). The filling capacity of the heated aluminium sleeve was approximately 15 mL and extrusion was performed in a batch process yielding approximately 2 m of filament. Extrusion temperatures were measured at the nozzle. Filaments were stored at 20°C under protection from light.

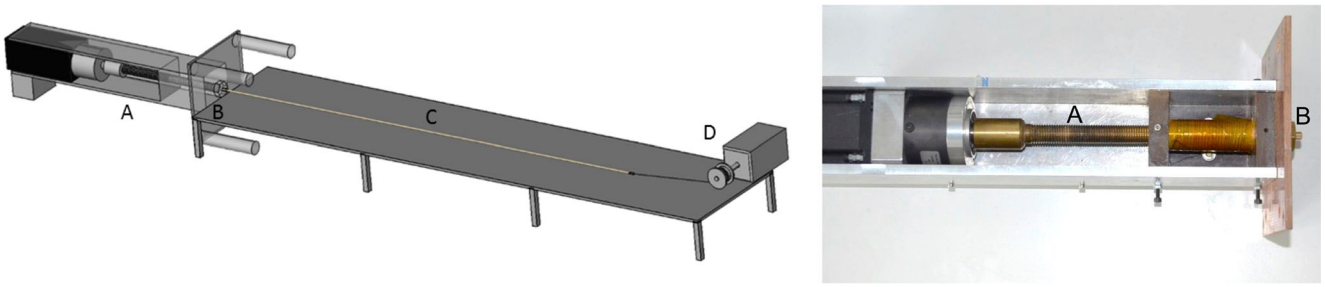

Fig. 1 Schematic design and photographic image of the used extruder including extrusion motor with an external threaded rod (**a**), a heated metal sleeve with an internal thread and a nozzle with 2.8 mm diameter (**b**), the extruded filament (**c**) and the second motor for filament stretching.

3D-Printing of Tablets

Filaments obtained from hot-melt extrusion as described above were used as the feedstock material for FDM of tablets. 3D-printing was performed with a standard FDM printer Multirap M420 (Multec GmbH, Germany) and a nozzle diameter of 0.35 mm. The tablet geometry (Ø = 8 mm, h = 3 mm) was designed with FreeCAD 0.14 and afterwards sliced with Simplify3D (version 2.2.2, Simplify3D, USA). Tablets were printed in cylindrical shape as this tablet shape is very common and easy to print. The dimensions of the tablet were chosen in such a way that printing filaments with the standard drug load of 10% (*w*/w) led to tablets with an approximate dose of 20 mg, one of the clinically applied standard doses of pantoprazole sodium [22]. The applied printing temperatures were individually determined for each filament composition. Based on prior printing-experience other printing parameters were set as follows: printing speed 360 mm/min, outline underspeed 50%, infill underspeed 80%, outline direction inside-out. Heating bed, cooling, support, raft and retraction options were inactivated. The layer height was set to 0.1 mm. First layer adhesion was improved by the application of blue painters tape on the printing table. Extruded filament segments of approximately 6 cm lengths were placed in the hot end of the FDM printer and were advanced using commercial PLA filaments which was placed behind the drug containing filament. Thus, the drug containing filament was pushed by the commercial PLA filament. This procedure was chosen in order to avoid filament fracture caused by the forces of the gear wheel during extrusion.

Apart from the standard setting of 100% infill for solid tablets, pantoprazole sodium containing PEG 6000- and PVP K12-cores were also fabricated with infill rates of 90% and 50%, respectively (without solid bottom or top layers, 2 outline shells, rectangular infill with perpendicular printing directions for every layer, infill angles 45 and - 45°). As a consequence of using the same dose in every tablet higher tablet heights of 3.2 mm (90% infill) and 4.4 mm (50% infill) resulted. Tablets were stored at 20°C under conditions protecting from light.

Imaging

Images of the extruded filaments and printed tablets were taken using a reflected-light microscope (Zeiss Stemi 2000-C with light source Zeiss CL 1500 ECO, camera Zeiss AxioCam and AxioVision software, all Carl Zeiss Microscopy GmbH, Germany).

Determination of the API Content in Filaments and Tablets

Six filament samples with individual length of 2–4 mm and a weight of 25–55 mg (individual weight determined) were taken at distances of 15–20 cm along the complete filament length and dissolved in phosphate buffer solution pH 6.8 (PBS pH 6.8, according to USP) yielding pantoprazole sodium concentrations between 0.005 mg/L and 0.025 mg/L. The pantoprazole sodium absorption was determined using UV/VIS-spectrophotometry at 288 nm (Cary® 50 Scan, Varian Inc., Australia) and the API contents were calculated according to the calibration function. The pantoprazole sodium content of printed tablets was determined as the cumulative release at the end of the dissolution test.

In Vitro Drug Release Studies

Drug release studies of printed tablets were carried out in 1000 mL PBS pH 6.8 using a paddle apparatus (USP apparatus 2, 37°C, 100 rpm, Pharmatest DT 70, Pharma Test Apparatebau AG, Germany). Drug release studies were discontinued when tablets had completely dissolved in PBS pH 6.8. The pantoprazole sodium release into the medium was measured by UV/VIS-spectrometry with a fiber-optics based system for on-line measurement (Cary® 50, Varian Inc., Australia and Cary® 60, Agilent Technologies, USA, both slit width 10 mm, measuring interval 10 s) at a wavelength of 286 nm in relation to calibration measurements. Absorption that was simultaneously recorded at the wavelength of 500 nm (a wavelength, at which no absorption of pantoprazole sodium occurs) was set as base-line. The released amount of the API at the last measurement point was

set to a 100% drug release for all tested tablets. Drug release tests were performed in triplicate.

X-Ray Powder Diffraction (XRPD)

XRPD analysis was utilized to determine the physical state of the pantoprazole sodium in the PEG 6000 and PVP K12 filament using a Bruker D8 θ-θ X-ray diffractometer with Lynxeye detector (Bruker, Germany) and cobalt radiation ($\lambda_{K\alpha1}$ = 1.78897 Å, $\lambda_{K\alpha2}$ = 1.79285 Å). The divergence split was 0.5 mm. The operating current and voltage were 30 mA and 40 kV. Approximately 2 weeks after extrusion, filament samples and physical mixtures were finely cut into a powder with a razor blade, placed in an aluminium sample holder and measured from 4 to 44°2Theta (2θ) with a scanning rate of 4° per minute.

RESULTS AND DISCUSSION

Filament Extrusion

Since the impregnation of pure polymer filaments in high concentrated drug solutions only resulted in very low drug loads [14, 15], HME was used in this study to produce drug loaded filaments as the feedstock material for FDM. In contrast to the previous work with this extruder [21], the preparation of drug loaded films by solvent casting was replaced with a thorough blending step of the single components prior to HME. The renunciation of organic solvents in the manufacturing chain prevents the occurrence of additional residual solvents and variation of the residual solvent amounts contained which may affect glass transition temperatures and physicochemical properties of the filaments [23].

The used model API in this work was the thermally less stable drug pantoprazole sodium with a melting point at approximately 143°C and a preceding decomposition that is visible through a colour change of the white crystals over violet to black [24]. The onset of this decomposition process was observed at 110°C (DSC data not shown, but in accordance with literature data [25]) and therefor extrusion and printing temperatures below 100°C were striven for in this work. In order to avoid local overheating at the extruder walls close to the heating element and to achieve a uniform heat distribution within the powder blend, the temperature - measured at the nozzle - was raised very slowly and kept constant for 20 min at the extrusion temperature before extrusion started. Extrusion and stretching speeds were adjusted so that all filaments exhibited a constant diameter of approximately 2.85 mm along the filament length.

API-free polymers were initially extruded to evaluate extrusion and printing temperatures and estimate their suitability for embedding pantoprazole sodium (pre-test data not shown). The flowchart for the formulation development is given in Fig. 2. With regard to a rapid drug release water-soluble polymers were selected for the filament matrix and combined with the plasticizer TEC, if required for extrusion and printing below 100°C. Some of the tested polymers such

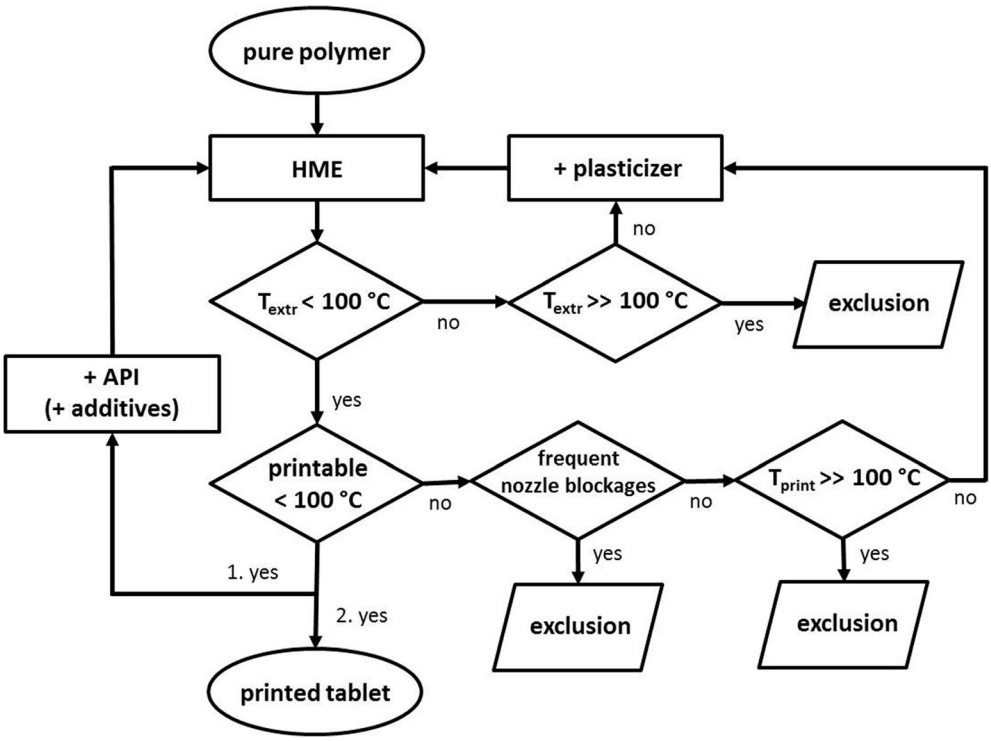

Fig. 2 Flow chart for drug loaded tablet formulations; T_{extr} = temperature required for extrusion; T_{print} = temperature required for printing; API = active pharmaceutical ingredient.

as polyvinylalcohol or Kollicoat® IR were also extruded to filaments but temperatures far above the intended 100°C were necessary. These polymers were excluded from further studies. Exemplarily showing the unsuitability for processing with thermo-labile drugs a discoloured black filament - resulting from the extrusion of Kollicoat® IR with 5% pantoprazole sodium at temperatures of 142–145°C that greatly exceeded the decomposition temperature of the API - is depicted in Fig. 3l.

If suitable polymer candidates were also printable below 100°C they were extruded along with pantoprazole sodium. PEG filaments were also extruded with the addition of the swelling disintegrants Kollidon® CL and sodium polyacrylate with the purpose of accelerating disintegration time. Compositions of successfully extruded drug-loaded filaments with associated extrusion temperatures are listed in Table I and reflected light microscopic images of the filaments are shown in Fig. 3.

For PVP filaments several compositions had to be extruded to find the best polymer-plasticizer-ratio for every drug load. Pure PVP K12 filaments were very brittle and fractured easily even under low loads. Filament fractures in the hot end of the printer must be avoided since extrusion speed is determined by advancement of a defined filament length per time and diameter variations, either resulting from non-uniform filament or broken strands, may lead to inaccurate dosing. On the other hand, very high TEC contents as observed for PVP + 20% TEC + 10% pantoprazole sodium resulted in very sticky filaments (Fig. 3i) that may also stick to the filament duct in the printer. When storing the filaments at 20°C over several weeks filament deformations by deliquescence were observed especially for higher plasticizer fractions. Thus an immediate printing after extrusion - as in this work - or a storage at lower temperatures is recommended for these filaments. As a standard drug load 10% pantoprazole sodium was incorporated into all polymers listed below. For PVP K12 even higher drug loads of up to 30% were successfully extruded (Fig. 3j).

In view of the microscopic images it is conspicuous that all filaments with PEG-polymers or PEG-containing polymers demonstrated a white appearance (Fig. 3a–f), whereas PVP- and PVP-containing filaments – all plasticized with TEC – showed a slightly beige coloration (Fig. 3g-k). A decisive point for consistent dosing via FDM, besides the described consistent diameter and feed rate, is a homogenous distribution of the active pharmaceutical ingredient (API) in the filament. Microscopic imaging of the filament revealed punctual agglomerations probably due to undissolved solids visible as little dots in the pantoprazole sodium filaments of PEG 6000 with sodium polyacrylate, PEG 20,000 and poloxamer 407 (Fig. 3d, e, f). If these solid clusters neither dissolve in the polymer during printing - usually at higher temperatures than

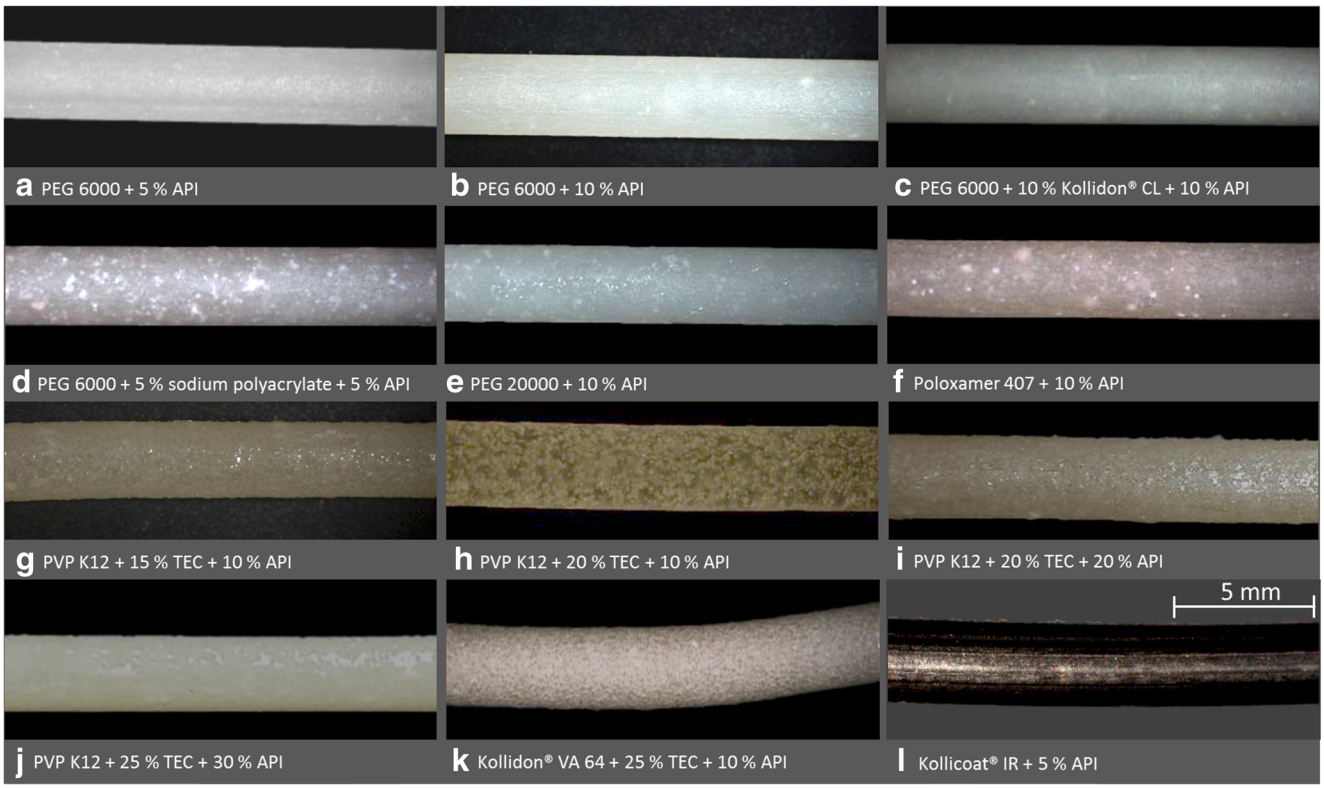

Fig. 3 Reflected light microscopic images of extruded filaments (A - L) containing the active pharmaceutical ingredient (API) pantoprazole sodium; polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), triethyl citrate (TEC); identical scale bar for all images.

Table I Filament and Tablet Compositions with Extrusion/Printing Temperatures and API Contents in Filaments and Tablets; Successfully Printed Comositions are Marked with a Tick (✓); Pantoprazole Sodium (Pantoprazole), Polyethylene Glycol (PEG), Polyvinylpyrrolidone (PVP).

			Filament		3D-printing		
Polymer	API/additives (w/w)		Temp. (extrusion) °C	Mean API content (%) $n = 6 \pm SD$	Printed	Temp. (print) °C	Mean API content (%) $n = 3 \pm SD$
PEG 6000	5%	pantoprazole	47–49	4.78 ± 0.10	✓	55	4.96 ± 0.05
	10%	pantoprazole	46–48	10.08 ± 0.28	✓	54	10.10 ± 0.51
	10%	pantoprazole	41–43	–	–	–	–
	10%	Kollidon® CL					
	5%	pantoprazole	48–50	5.09 ± 0.17	✓	58	4.77 ± 0.34
	5%	polyacrylate					
PEG 20,000	10%	pantoprazole	48–50	9.09 ± 2.00	✓	60	8.44 ± 0.17
PEO 100,000	10%	pantoprazole	41–43	10.24 ± 0.17	–	–	–
	20%	triethyl citrate					
Poloxamer 407	10%	pantoprazole	41–43	10.20 ± 0.21	✓	60	10.30 ± 0.55
PVP K12	10%	pantoprazole	58–60	9.99 ± 0.09	–	–	–
	10%	triethyl citrate					
	10%	pantoprazole	47–51	10.24 ± 0.13	✓	79	10.57 ± 0.08
	15%	triethyl citrate					
	10%	pantoprazole	48–50	9.95 ± 0.15	✓	78	–
	20%	triethyl citrate					
	20%	pantoprazole	49–51	21.04 ± 1.12	✓	86	21.25 ± 0.37
	20%	triethyl citrate					
	30%	pantoprazole	47–49	30.95 ± 1.67	✓	87	31.94 ± 0.74
	25%	triethyl citrate					
Kollidon® VA 64	10%	pantoprazole	54–56	10.04 ± 0.20	✓	85	10.50 ± 0.35
	25%	triethyl citrate					
Kollicoat® IR	5%	pantoprazole	142–145	–	–	–	–

those applied for extrusion – nor exhibit a smaller size than the 0.35 mm nozzle diameter of the printer, a blockage of the print head is very likely. Nevertheless, content measurements of six samples along the filament length showed approximately the drug load that was expected for all tested filaments (see Table I). The highest deviation was observed for the PEG 20,000 filament with a pantoprazole sodium content of 9.09 ± 2.00% and an under-dosing in the central part of the extruded filament that might be explained by an insufficient blending of the components before loading of the extruder or less likely by segregation within the feeding process. A similar trend of increasing or decreasing API contents along the filament length was not observed in any of the other filament. However, a better API distribution might be reached by using a twin screw extruder with additional mixing elements as an alternative to the used ram-extruder without considerable blending material flow during extrusion [26].

3D-Printing of Tablets

Pure polymer filaments were initially used to ascertain the printing properties of the respective polymer. Whenever printing with pure polymer filaments was promising pantoprazole sodium was added to the composition and printing was evaluated again. Polymers or compositions were excluded if the printing temperature was far too high and thus the viscosity of the melt at temperatures compatible with the API was inacceptable as observed for Kollicoat® IR or if the nozzle was frequently blocked by solids (see Fig. 2). This nozzle clogging may have occurred either due to a high solid content, an irregular distribution of particles and the formation of solid agglomerates exceeding nozzle diameters. Large particle agglomerates of Kollidon® CL that did not melt at the extrusion temperature of 41–43°C was the assumed reason for frequent nozzle blockages observed for the filament with this additive.

Polymer-API-compositions that were printed successfully are shown in Fig. 4 and are marked with a tick in Table I. PEG 6000 was printable containing pantoprazole sodium loads of 5 and 10% at nozzle temperatures of 54–55°C. These temperatures are in a good agreement with literature data for the ram-extrusion of carbamazepine with PEG 4000 at 50°C, performed in a softened but not molten state of the polymer at least 11°C below the melting point [27]. In accordance with the filaments, all PEGs or PEG-containing polymers with printing temperatures ranging from 54 to 60°C resulted in pure white tablets (Fig. 4a–e) whereas PVP-based tablets that were printed at higher temperatures and contained the plasticizer triethyl citrate resulted in tablets with a colour-shift to beige or yellow, again analogous to the filaments (Fig. 4f, g).

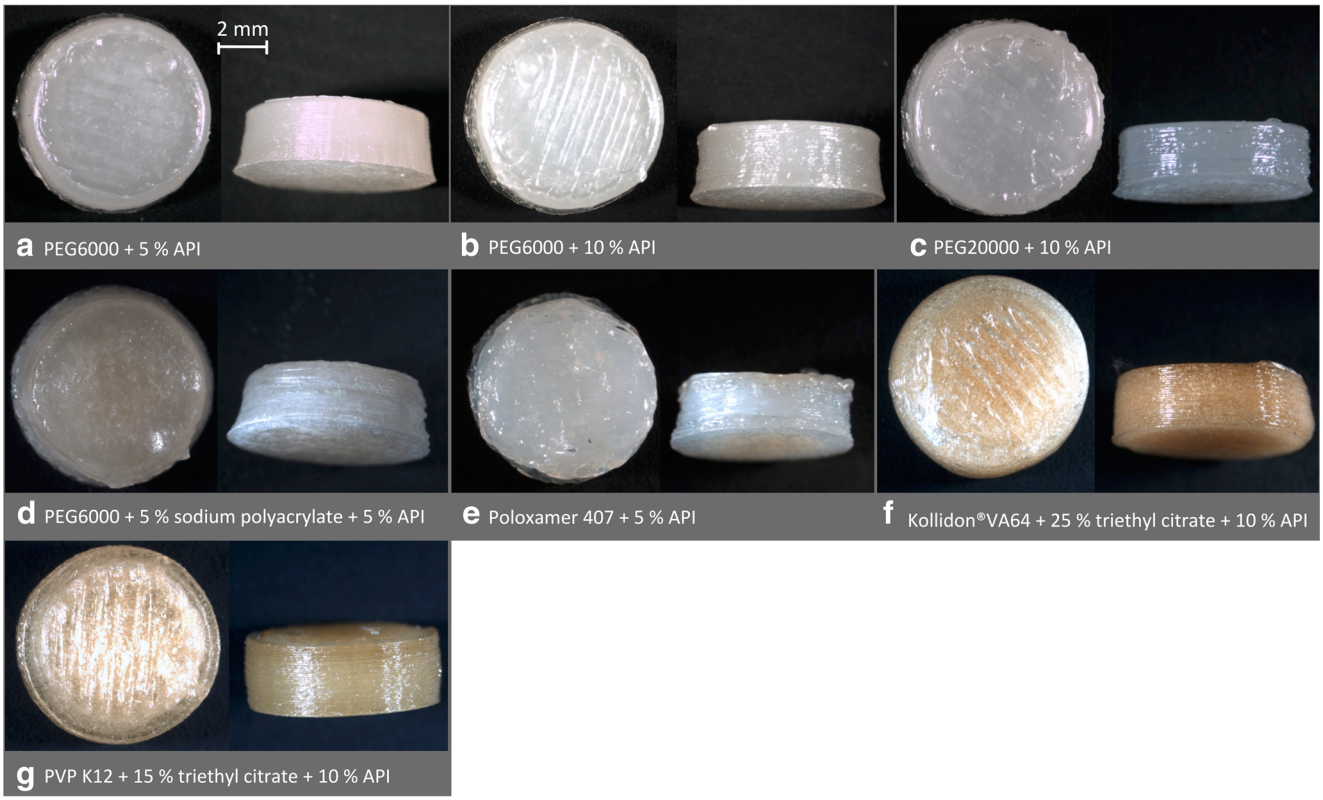

Fig. 4 Reflected light microscopic images in top view (left) and side view (right) of printed tablets containing pantoprazole sodium as the active pharmaceutical ingredient (API) and – if necessary - the plasticizer triethyl citrate; polyethylene glycol (PEG), polyvinylpyrrolidone (PVP); identical scale bar for all images.

PEG filaments with a higher degree of polymerisation were successfully printed for a molecular weight of 20,000 (Fig. 4c) but not for polyethylene oxide (PEO) with a molecular weight of 100,000 due to the temperature limit of 100°C. The extrusion force during printing was not sufficient for pushing the highly viscous PEO melt through the nozzle that is nearly ten times smaller than the one used for extrusion. To achieve a pressure drop in the melt flow channel and to enable extrusion of higher viscous polymer melts at lower temperatures the use of a larger nozzle might be reasonable if lower printing resolutions are acceptable [28]. Temperatures close to API decomposition temperature were also necessary for the brittle PVP filament with a 10% API load and only 10% TEC that showed a dark discolouration during printing experiments at 97°C indicating drug degradation processes (not shown). The same PVP filament with a TEC proportion of 20% was printable but tablets were not inherently stable. The high amount of the plasticizer lead to an outward bulging of resulting tablets directly after printing and a considerable deliquescence of the tablet shape within few days (images not shown). The best printing results for PVP with 10% API were obtained with a TEC percentage of 15% (Fig. 4g). With increasing drug loads up to 30% pantoprazole sodium higher temperatures were needed to print PVP-tablets. Literature data showed that PVP printing with even higher solid contents of 27.5% talc plus 10% of the APIs theophylline or dipyridamole required printing temperatures of 110°C and are thus unsuitable for drugs as pantoprazole sodium [17]. PVPs with higher k-values and therewith higher mean molecular weights have been reported to need higher extrusion temperatures as measured for pure PVP K25 (T_{extr} = 132–134°C) or are not extrudable [29, 30] and consequently were excluded from this study. For future investigations consideration should also be given to other plasticizers [31] or a combination of PVP and PEG-based polymers: For lansoprazole that is also sensitive to heat a successful extrusion with PVP K12 was described using 30% poloxamer 188 as a plasticizer to decrease the extrusion temperature to 65°C [32].

In addition to the solid and completely filled cylindrical-shape-tablets, tablets with a lower infill-rate and thus a more porous structure were printed using the most promising compositions of PEG 6000 and PVP K12 (Fig. 5). An infill-rate of 50% in this work is synonymous with the printing of only every second infill line per layer and a change of the direction crosswise after every layer. In order to ensure tablet stability two outline shells remained in the G-code and to achieve the same API content the height of the tablet was increased. As the melt of PEG 6000 was more liquid, the layers partly flowed together and the printing of a grid structure was hardly possible. Hence perforations of the tablet occurred mainly in vertical and less in horizontal direction. The PVP K12 melt was more viscous and strands were deposited more easily onto each

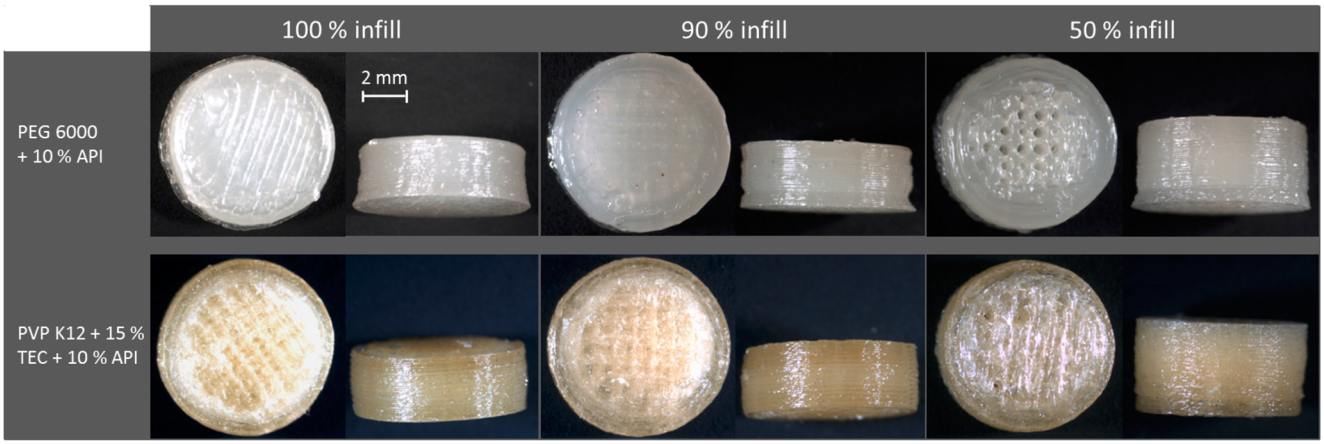

Fig. 5 Reflected light microscopic images in top view (left) and side view (right) of printed tablets with different infill rates and the active pharmaceutical ingredient (API) pantoprazole sodium 3D-printed by using PEG 6000 and PVP K12 and triethyl citrate; identical scale bar for all images.

other in a crosswise style and formed a network structure. The higher temperature difference between nozzle and ambient temperature also facilitated a fast solidification of PVP-lines.

X-Ray Powder Diffraction

XRPD analysis of an API-containing PEG 6000 filament and its components revealed an almost complete agreement of the diffraction pattern of the filament and the pure semi-crystalline polymer PEG 6000 (Fig. 6). Diffraction peaks of pantoprazole sodium in the filament diffraction pattern e.g. at 6.1, 19.2, 19.5 and 23.8°2θ with corresponding d-values of 16.84, 5.35, 5.28 and 4.33 Å can only be suspected very slightly. This almost complete absence of typical pantoprazole sodium peaks, especially in comparison with the physical mixture, indicates that the major part of the API in the filament is not present in its crystalline state after extrusion but presumably dissolved in the PEG matrix. This loss of drug crystallinity has already been shown for nifedipine in the long-chain PEO 200,000 extruded at 120°C [33].

The X-ray diffraction pattern of pure PVP K12 depicted in Fig. 7 shows characteristic amorphous halos underlining the amorphous nature of this polymer. Crystalline pantoprazole sodium peaks e.g. at 6.1, 23.7 and 25.7°2θ with corresponding

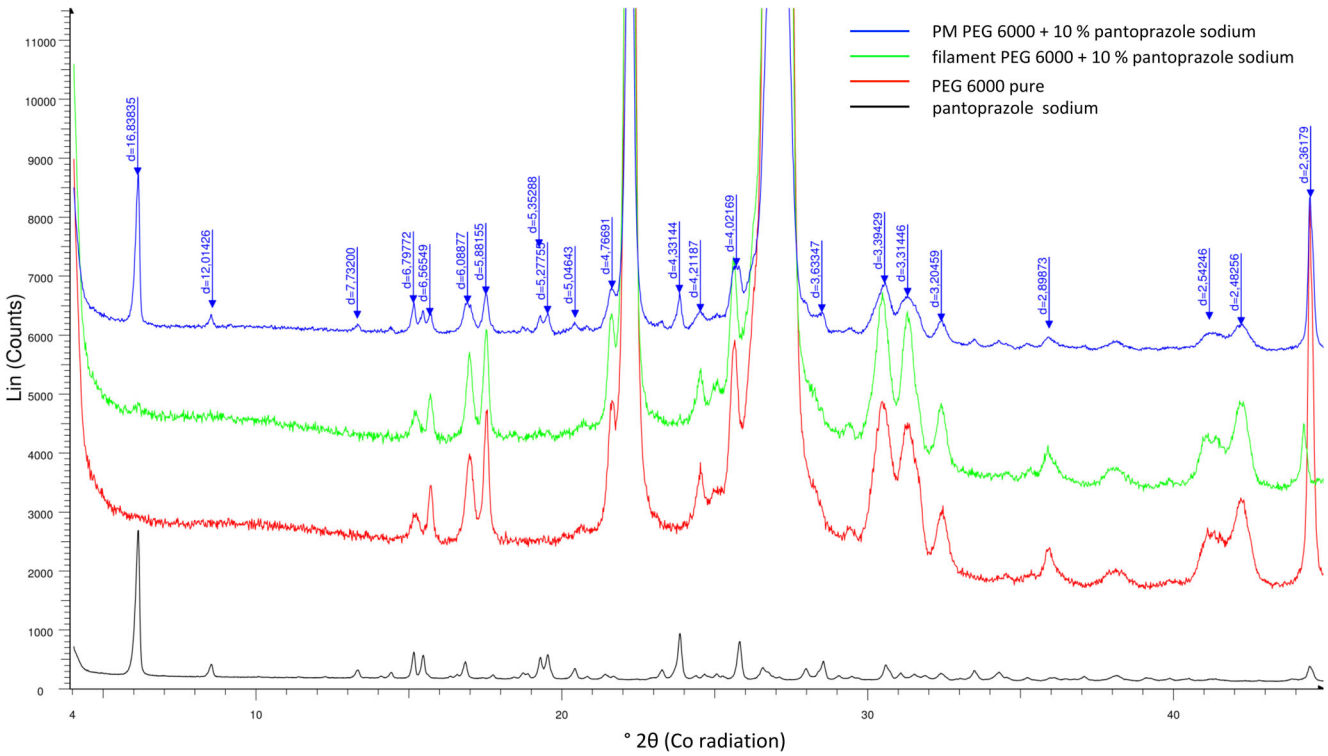

Fig. 6 Fig. 4 X-ray diffractograms of PEG 6000 filaments containing 10% pantoprazole sodium, the physical mixture (PM) of the filament components, the pure polymer and the pure drug pantoprazole sodium.

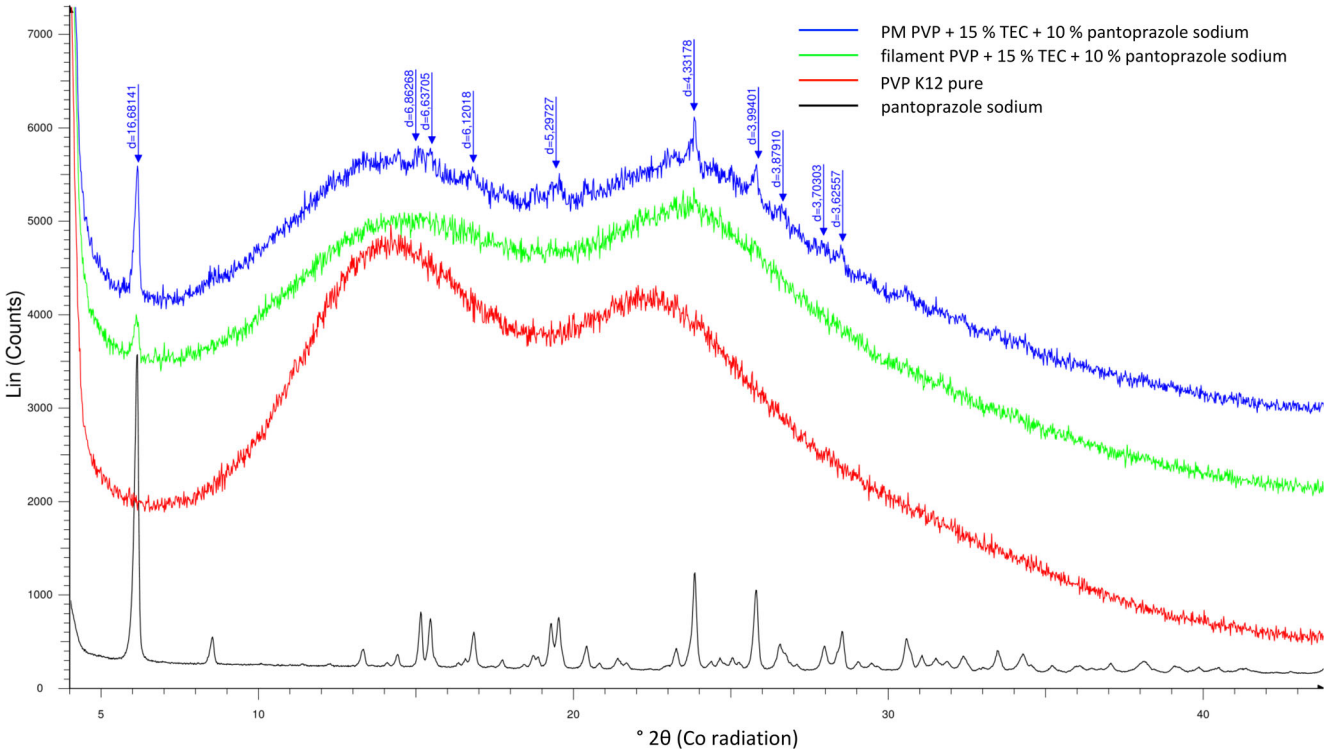

Fig. 7 X-ray diffractograms of PVP K12 filaments containing 10% pantoprazole sodium, the physical mixture (PM) of the filament components, the pure polymer and the pure drug pantoprazole sodium.

d-values of 16.68, 4.33 and 3.99 Å are clearly detectable for the physical mixture of PVP K12, triethyl citrate and pantoprazole sodium. The diffractogram of the extruded PVP filament exhibits only the most intense API peak with a d-value of 16.68 Å, but with a considerably smaller peak height compared to the physical mixture. This suggests a partly dissolution of pantoprazole sodium in PVP during HME alongside with the presence of crystalline API traces in the filament. The formation of amorphous solid dispersions was also observed for extrudates of albendazole in PVP K12 [34] and olanzapine in PVP K30 [35].

In Vitro Drug Release

Tablets Composed of Different Polymers

The drug release from printed tablets was tested using the paddle apparatus (phosphate buffered solution pH 6.8, 37°C, 100 rpm) along with 20 mg of powdered pantoprazole sodium (Fig. 8). Dissolution tests with a prior acidic stage were not performed as the acid-labile pantoprazole sodium was only used as a model substance for thermo-sensitive drugs and the required enteric coating was not focused in this work. The freely water-soluble pantoprazole sodium sesquihydrate [25, 36] completely dissolved within 1.5 min. The hydrophilic surfactant poloxamer 407, a copolymer with one polypropylene glycol block and two blocks of polyethylene glycol, is pharmaceutically used as a polymeric solubilizer, emulsifier or gel forming agent [37] but its application in HME is mainly confined to its addition as a plasticizer [38]. Used as the polymeric matrix in this work the pantoprazole sodium release from the printed poloxamer tablets was relatively slow and completely finished after approximately 2 h. The slow drug release from this water soluble poloxamer might be explained by the formation of a poloxamer gel layer around the tablet that possibly slowed down drug release before being sheared off by stirring. A gelation of poloxamer in concentrations above 15% (*w*/w) at temperatures of 36.3°C and below is described in literature [39] and thus is also conceivable for this

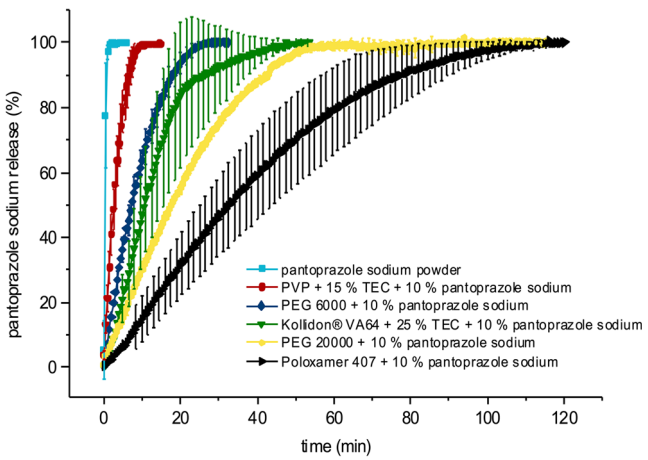

Fig. 8 *In vitro* drug release from printed tablets with different polymers (100% infill) using the paddle apparatus with phosphate buffered solution pH 6.8, 37°C, 100 rpm, mean values of $n = 3 \pm SD$.

dissolution setup. With a complete drug release within 60 min tablets of PEG 20,000 and the vinylpyrrolidone-vinyl acetate copolymer Kollidon® VA64 also did not release the drug as fast as the desired 15 min. In literature reports, extrusion temperatures are higher and dissolution rates are lower (finished API release within 90 or 300 min for indomethacin or famotidine, respectively) for extruded Kollidon® VA64 dosage forms due to the absence of the high amounts of plasticizer [40, 41]. Printing tablets with the polymeric matrix PEG 6000 led to a considerably faster drug release with a dissolution time of 29 min, in line with the 90% drug release in 30 min measured for PEG 4000 extrudates with carbamazepine [27]. PEG 6000 tablets with 5% sodium polyacrylate und 5% pantoprazole did not show accelerated drug release compared to PEG 6000 tablets without swelling agent as both demonstrated nearly congruent release profiles (data not shown). PVP K12 tablets exhibited an even faster drug release than PEG tablets that was completed in approximately 10 min and thus comply with the target time of 15 min for complete dissolution. Apart from the freely soluble API in this study, both - PEG and PVP - are also often reported to form solid dispersions by HME and improve solubility of poorly soluble drugs [33, 34, 42, 43].

Tablets with Different Infill Rates

To further accelerate dissolution, PEG 6000 and PVP K12 tablets were also printed with a lower infill rate and thus a higher porosity. The concept of printing lower fill densities of tablets was already successfully shown e.g. for intragastric floating tablets (hollow tablet shell, infill rate 0%) with a sustained release of domperidone [44]. Beyond that, a faster drug release by decreasing the infill density has been demonstrated for printed PVA tablets, but dissolution times are still very long with 1 h, 4 h or 6 h for curcumin (0% infill, [45]), 4-aminosalicylic acid (10% infill, [14]) or fluorescein (10% infill, [15]), respectively. Drug release profiles of PEG 6000 and PVP K12 tablets with infill rates of 50%, 90% and 100% printed in this study are shown in Fig. 9. Taking the standard deviations into account an acceleration of the drug release for PEG tablets was not detected, except for a slight trend towards faster release for the 50% infill rate tablets. This lack of faster release inspite of lower infill rate might be explained by the confluence of extruded polymer strands due to the low viscosity of the PEG 6000 melt resulting in a less pronounced grid structure especially in horizontal direction, as already described above. For printed PVP tablets the acceleration of the drug release is detectable, whereby the difference between the 100% and 90% is not as clear as for the 50% infill tablets. With the decrease of the infill rate to 50% the time for complete drug release was decreased to 3 min, approximately 7 min faster than the 100% infilled PVP tablets, owing to an increased surface area for dissolution. This successfully proved that printing geometries that could not be produced by classical manufacturing techniques as powder compression e.g. due to inner cavities might be able to improve the drug release compared to solid monolithic tablets. This also appears highly promising for the immediate release of poorly soluble drugs e.g. from amorphous solid dispersions. Moreover, the fast and ultra-fast releasing polymers PEG 6000 and PVP K12 are also very well suited for thermo-sensitive APIs as extrusion and printing temperatures do not exceed 100°C for all tested compositions with pantoprazole sodium.

CONCLUSION

This work provides new insights into FDM of immediate release tablets with special attention to low processing temperatures. Five different polymers (PVP K12, PEG 6000, Kollidon® VA64, PEG 20,000, poloxamer 407) could be successfully extruded and printed to tablets containing the thermo-sensitive drug pantoprazole sodium at temperatures below 100°C. The application of an enteric coating that would be necessary for this acid-labile model substance was not addressed in this work, but will be part of following investigations. A fast drug release from printed tablets that was completed within 10 min or 29 min was observed for PVP

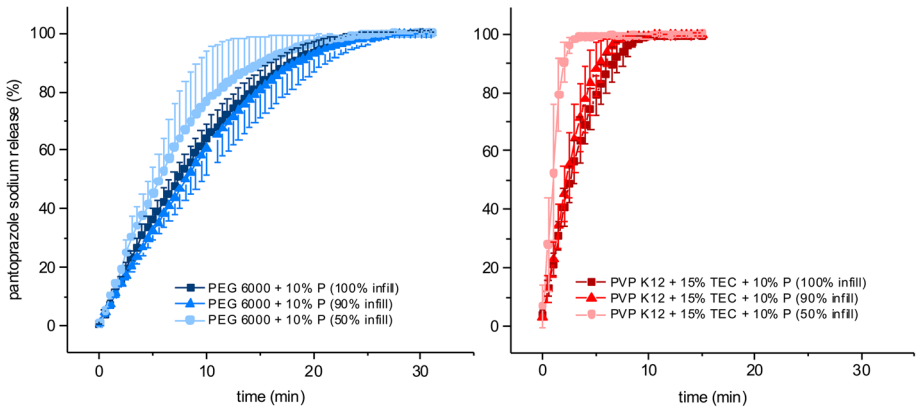

Fig. 9 *In vitro* pantoprazole sodium (P) release from printed tablets (polyethylene glycol (PEG) 6000 left, polyvinylpyrrolidone K12 (PVP K12) right) with different infill rates using the paddle apparatus with phosphate buffered solution pH 6.8, 37°C, 100 rpm, mean values of n = 3 + / - / ± SD.

K12 and PEG 6000 tablets, respectively. For PVP it was even possible to decrease the time for total drug release from 10 min to ultra-rapid 3 min by reducing the infill rate to 50% and thus increasing the tablet porosity. To our knowledge this is the fastest drug release from FDM printed tablets described in literature so far. These results give a good impression of the possibilities FDM and a shape design can provide and may serve as a basis for future applications in the field of immediate release tablets with challenging drugs e.g. thermally unstable drugs.

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