Fabricating 3D printed orally disintegrating printlets using selective laser sintering

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Abstract

Selective laser sintering (SLS) is a three-dimensional printing (3DP) technology often employed in the manufacturing of plastic, metallic or ceramic structures. The aim of this study is to demonstrate the feasibility of SLS to manufacture novel solid dosage forms with accelerated drug release properties, and with the a view to fabricate orally disintegrating formulations. Two polymers (hydroxypropyl methylcellulose E5 (HPMC E5) and vinylpyrrolidone-vinyl acetate copolymer (Kollidon® VA 64)) were prepared with 5% paracetamol (used as a model drug) and 3% Candurin® gold sheen colorant. Modulating the SLS printing process resulted to accelerated dissolution profiles for both polymer-based formulations. Complete drug release occurred at approximately 4 h, 3 h and 2 h for three investigated HPMC formulations. The same trend was observed for Kollidon® based formulations. Kollidon® printlets printed at a laser scanning speed of 300 mm/s were able to completely disintegrate in a small volume of water in less than four seconds, exhibiting orally disintegrating release characteristics. Printlet breaking force values showed appropriate mechanical properties suitable for handling by end users. X-ray micro-CT showed that following the modulation of SLS printing parameters, the printlets exhibited a reduction in density and therefore, an increase in open porosity. The work reported here is the first to demonstrate the feasibility of SLS 3DP to fabricate printlets with accelerated drug release and orally disintegrating properties. This investigation has confirmed that SLS is amenable to the pharmaceutical research of modern medicine manufacture.

1. Introduction

For the majority of therapeutic agents used to induce systemic effects, the oral route is still considered to be the most preferred method of administration, owing to its high patient compliance when compared to other available routes (Bhagat 2017, Rathbone 2015). However, oral administration in the form of tablets, capsules and liquid dosage forms is a disadvantage for specific patient groups. Dysphagia represents a significant challenge, specifically for geriatric and paediatric populations, and patients who are uncooperative. This, therefore, can affect medication adherence and result in increased morbidity and mortality rates (Carnaby-Mann and Crary 2005). The shift in developments of patient-centric dosage forms, however, have led to the emergence of novel technologies such as orally disintegrating tablets (ODTs). Rapid drug intervention and increased bioavailability and absorption can be achieved following the contact of an ODT with saliva, or a small volume of water in the oral cavity (Parkash et al. 2011, Draskovic et al. 2017). According to the European Pharmacopoeia, ODTs are dosage forms that disintegrate in less than 3 minutes (Pharmacopoeia 2005). The Food and Drug Administration (FDA), however, characterise ODTs as dosage forms that completely dissolve within 30 seconds (CDER 2008). ODTs, therefore, are not limited to those experiencing dysphagia, but rather, are an alternative method for those seeking a quick and easy method of administration, capable of being taken without a glass of water.

ODTs are normally characterised as low density, low crushing strength and high porosity formulations. Separate strategies are further required in the manufacturing process to produce mechanically resistant ODTs without compromising the disintegration times (Al-khattawi and Mohammed 2013). There are a number of conventional methods of manufacturing ODT formulations such as direct compression, spray drying, freeze drying and tablet moulding. Some of these methods, however, show some disadvantages with respect to manufacturing costs, complexity and limitations in low drug loadings (Nagar 2011, Aslani and Beigi 2016). In addition, in order to prepare an ODT product, a meticulous choice of excipients in drug development is critical in the determination of product characteristics, namely mechanical strength, stability, taste and mouth feel and disintegration time (Al-Khattawi et al. 2014).

Despite the significant technological advancements in the 21st century, innovation in pharmaceutical manufacturing techniques has fundamentally remained unchanged for around 200 years. Three-dimensional printing (3DP) is an additive manufacturing technology and is a revolutionary technique for the fabrication of personalised dosing and dimension-specific dosage forms (Goyanes et al. 2017b, Goyanes et al. 2017a). Thus, 3DP has the potential to cause a revolutionary shift in medicine manufacture.

Spritam® is the first and only FDA-approved medicine manufactured by a ZipDose technology®, based on 3D powder-bed (PB) printing techniques (Zieverink 2016). With this method, the final product is fabricated by a printer head that selectively deposits a liquid binder across a powder mixture of commonly used ODT excipients and the active pharmaceutical ingredient (API) in a layer-by-layer approach. Spritam®, is in fact, an ODT formulation of levetiracetam that rapidly disintegrates in the oral cavity from 2 to 27 seconds following administration with a sip of water (ApreciaPharmaceuticals 2016).

A promising 3DP technology that is explored for its feasibility in the printing of solid dosage forms with accelerated release characteristics is selective laser sintering (SLS). SLS is an industrial additive manufacturing technique that uses a powder bed to fabricate a 3D structure. However, instead of a liquid binder, SLS uses a laser to sinter powder particles together and completes a 3D object layer-by-layer. SLS technology presents multiple advantages when compared with PB due to its solvent-free process and high turnover rate (Fina et al. 2017). The starting materials often employed by SLS are powdered forms of plastics, ceramics and metal alloys that require high temperatures for the sintering process to be successful. It is known that these harsh printing conditions have deterred the introduction of SLS to the pharmaceutical field as the high-energy lasers may impair drug characteristics (Alhnan et al. 2016, Yu et al. 2008). However, we have identified that SLS is, indeed, capable of fabricating 3D printed tablets (known as Printlets™). Our previous study has demonstrated that, following the use of thermoplastic pharmaceutical grade polymers, three different drug loadings of paracetamol (up to 35%) were successfully printed (Fina et al. 2017).

The aim of this study was to prove that SLS 3D printing can be used to accelerate the drug release of printed formulations and ultimately to create orally disintegrating printlets. The

versatility of the printer was evaluated using two different polymers that have not been explored by SLS 3DP to this date and different printing parameters (laser speed). Paracetamol was selected as model drug.

2. Materials and Methods

Paracetamol USP grade (Sigma-Aldrich, UK) was used as a model drug (MW 151.16, solubility at 37ºC: 21.80 g/L. HPMC (hydroxypropyl methylcellulose) Vivapharm E5 was acquired from JRS PHARMA, Germany. HPMC is a grade E type 2910, meaning that its average content of methoxyl group is 29% and its average content of hydroxypropyl group is 10% with a viscosity of 5mPa·s. Kollidon® VA 64 is a vinylpyrrolidone-vinyl acetate copolymer, kindly donated from BASF, UK. Candurin® Gold Sheen was purchased from Azelis, UK. The salts for preparing the buffer dissolution media were purchased from VWR International Ltd., UK.

2.1. Printing Process

For all the formulations, 100 g of a mixture of drug and excipients were blended using a mortar and pestle (Table 1). 3% of Candurin® Gold Sheen was added to the formulations to enhance energy absorption from the laser and aid printability. Powder mixtures were then transferred to a Desktop SLS printer (Sintratec Kit, AG, Brugg, Switzerland) to fabricate the oral dosage formulations. AutoCAD 2014 (Autodesk Inc., USA) was used to design the templates of the cylindrical printlets (10 mm diameter x 3.6 mm height). 3D models were exported as a stereolithography (.stl) file into 3D printer Sintratec central software Version 1.1.13.

Powder in the platform reservoir (150 x 150 x 150 mm) of the printer was moved by a sled to a building platform (150 x 150 x 150 mm) creating a flat and homogeneously distributed layer of powder. The surface printing temperatures for HMPC and Kollidon® formulations were 135°C and 100°C, respectively. The 2.3 W blue diode laser (445 nm) was activated to sinter the powder on to the building platform in a certain pattern based on the .STL file. At this point, the reservoir platform moved up, the building platform moved down, and the sled distributed a thin layer of powder on top of the previous layer. This process was repeated

layer-by-layer until the object was completed. Printlets were then removed from the powder bed and the excess powder was brushed off. Ten printlets of each formulation were printed at the same time.

Table 1. Printlet polymer content and printing parameters

Formulation[a]	HPMC (% content)	Kollidon® (% content)	Chamber temperature (°C)	Surface temperature (°C)	Laser scanning speed (mm/s)
H100	92	–	115	135	100
H200	92	–	115	135	200
H300	92	–	115	135	300
K100	–	92	80	100	100
K200	–	92	80	100	200
K300	–	92	80	100	300

[a]All formulations contain 3% w/w Candurin® Gold Sheen and 5% paracetamol.

2.2. Thermal Analysis

Differential scanning calorimetry (DSC) was used to characterise the powders and the drug loaded printlets. DSC measurements were performed with a Q2000 DSC (TA instruments, Waters, LLC, USA) at a heating rate of 10°C/min. Calibration for cell constant and enthalpy was performed with indium (Tm = 156.6°C, ΔHf =28.71 J/g) according to the manufacturer instructions. Nitrogen was used as a purge gas with a flow rate of 50 mL/min for all the experiments. Data were collected with TA Advantage software for Q series (version 2.8.394), and analysed using TA Instruments Universal Analysis 2000. All melting temperatures are reported as extrapolated onset unless otherwise stated. TA aluminium pans and lids (Tzero) were used with an average sample mass of 8 – 10 mg.

2.3. X-ray Powder Diffraction (XRPD)

Discs of 23 mm diameter x 1 mm height made from the mixtures of drug and excipients were 3D printed and analysed. Samples of pure paracetamol and the mixtures were also analysed. The X-ray powder diffraction patterns were obtained in a Rigaku MiniFlex 600 (Rigaku, USA) using a Cu Kα X-ray source (λ = 1.5418Å). The intensity and voltage applied were 15

mA and 40 kV. The angular range of data acquisition was 3 – 60° 2θ, with a stepwise size of 0.02° at a speed of 5°/min.

2.4. Characterisation of the printlets

2.4.1. Determination of printlet morphology

The diameter and thickness of the printlets were measured using a digital calliper. Images were taken with a Sony α6300 digital camera.

2.4.2. Determination of the mechanical properties of the printlets

The printlet breaking force of 6 printlets of each type was measured using a traditional tablet hardness tester TBH 200 (Erweka GmbH, Heusenstamm, Germany), whereby an increasing force is applied perpendicular to the tablet axis to opposite sides of a tablet until the printlet fractures.

2.4.3. Scanning Electron Microscopy (SEM)

Surface and cross-section images of the printlets were taken with a scanning electron microscope (SEM, JSM-840A Scanning Microscope, JEOL GmbH, Germany). All samples for SEM testing were coated with carbon (~30 – 40 nm).

2.4.4. X-ray Micro Computed Tomography (Micro-CT)

A high-resolution X-ray micro computed tomography scanner (SkyScan1172, Bruker-microCT, Belgium) was used to 3D visualize the internal structure, density and porosity of the printlets. All oral formulations were scanned with a resolution of 2000 x 1048 pixels. 3D imaging was performed by rotating the object through 180° with steps of 0.4° and 4 images were recorded for each of those. Image reconstruction was performed using NRecon software (version 1.7.0.4, Bruker-microCT). 3D model rendering and viewing were performed using the associate program CT-Volume (CTVol version 2.3.2.0) software. The collected data was analysed using the software CT Analyzer (CTan version 1.16.4.1). Different colours were used to indicate the density of the printlets. Closed and open porosity values were calculated using the 3D analysis in the morphometry preview (200 layers were selected at the central part of the printlets as area of interest and analysed).

2.4.5. Determination of Drug Content

Three individual printlets of each formulation were placed in separate volumetric flasks with deionized water (250 ml). Samples of solution were then filtered through 0.4 µm filters (Millipore Ltd., Ireland) and the concentration of drug determined with high-performance liquid chromatography (HPLC) (Hewlett Packard 1050 Series HPLC system, Agilent Technologies, UK). The validated HPLC assay entailed injecting 20 µL samples for analysis using a mobile phase, consisting of methanol (15%) and water (85%), through an Ultra C8 5 µm column, 250 x 4.6 mm (Restek, USA) maintained at 40°C. The mobile phase was pumped at a flow rate of 1 mL/min and the eluent was screened at a wavelength of 247 nm.

2.4.6. Dynamic dissolution testing conditions

Drug dissolution profiles for the formulations were obtained with a USP-II apparatus (Model PTWS, Pharmatest, Germany): 1) the formulations were placed in 750 mL of 0.1M HCl for 2 h to simulate gastric residence time, and then 2) transferred into 950 mL of modified Hanks (mHanks) bicarbonate physiological medium for 35 min (pH 5.6 to 7); 3) and then in modified Krebs buffer (1000 ml) (pH 7 to 7.4 and then to 6.5). The modified Hanks buffer based dissolution medium (Liu et al. 2011) (136.9 mM NaCl, 5.37 mM KCl, 0.812 mM $MgSO_4.7H_2O$, 1.26 mM $CaCl_2$, 0.337 mM $Na_2HPO_4.2H_2O$, 0.441 mM KH_2PO_4, 4.17 mM $NaHCO_3$) forms an in-situ modified Kreb's buffer (Fadda et al. 2009) by addition of 50 mL of pre-Krebs solution (400.7 mM $NaHCO_3$ and 6.9 mM KH_2PO_4) to each dissolution vessel.

The formulations were tested in the small intestinal environment for 3.5 h (pH 5.6 to 7.4), (Goyanes, Hatton and Basit 2015a, Goyanes et al. 2015b, Fadda et al. 2009, Liu et al. 2011). The medium is primarily a bicarbonate buffer in which bicarbonate (HCO_3^-) and carbonic acid (H_2CO_3) co-exist in an equilibrium, along with CO_2 (aq) resulting from dissociation of the carbonic acid. The pH of the buffer is controlled by an Auto pH System™ (Merchant, Frost and Basit 2012, Merchant et al. 2014), which consists of a pH probe connected to a source of carbon dioxide gas (pH-reducing gas), as well as to a supply of helium (pH-increasing gas), controlled by a control unit. The control unit is able to provide a dynamically adjustable pH during testing (dynamic conditions) and to maintain a uniform pH value over the otherwise unstable bicarbonate buffer pH. The paddle speed of the USP-II was fixed at 50 rpm and the tests were conducted at 37 ± 0.5 °C (n = 3). The percentage of drug released

from the printlets was determined using an in-line UV spectrophotometer (Cecil 2020, Cecil Instruments Ltd., Cambridge, UK) at 247 nm. Data were processed using Icalis software (Icalis Data Systems Ltd, Berkshire, UK).

2.4.7. Disintegration testing conditions

Disintegration tests of the printlets were conducted in a petri-dish containing 20 mL of water with a starting temperature of 37 ± 0.5°C. A printlet was gently placed on the water surface and time was recorded until a complete disintegration was observed. Six printlets were evaluated for each formulation.

3. Results and Discussion

Two pharmaceutical excipients that have not been explored previously with SLS 3DP (HPMC and Kollidon®) were initially tested to assess their printability, alone and in combination with 5% paracetamol. The polymers were evaluated with the aim of producing accelerated release formulations by modulating the SLS laser scanning speed, with ultimately, the view of fabricating printlets with ODT characteristics.

The fabrication of solid dosage forms was successfully achieved at different laser scanning speeds (Table 2) to obtain three different types of formulations for each polymer. All formulations contained 3% w/w colorant Candurin® gold sheen and 5% paracetamol. Candurin® gold sheen is a pharmaceutically accepted excipient commonly used in film coating of tablets and was added to the formulation to accentuate the printing process. Printing without Candurin® gold sheen has been attempted in a previous study (Fina et al. 2017), however, the sintering process was not successful as the powder did not absorb the laser at this wavelength. 3% w/w Candurin® gold sheen was found to provide an excellent degree of sintering suitable to manufacture oral formulations; therefore, the same amount has been added in the present study.

The printlets represented a conventional cylindrical tablet shape and were yellow in colour due to the colorant (Figure 1).

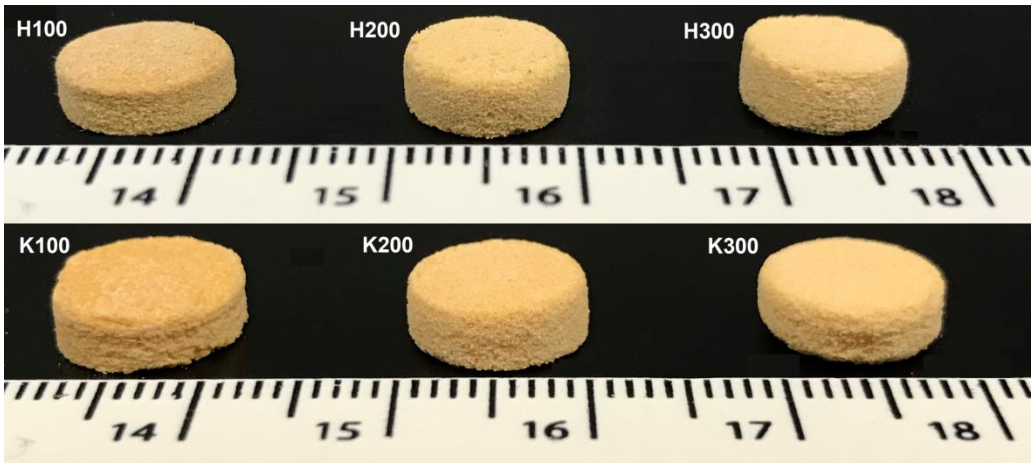

Figure 1. Images of the HPMC and Kollidon® printlets (units are in cm).

The printlets of the same formulations showed very similar weights (Table 2). The printlets fabricated at different laser speeds of the same polymer blend, however, were different in mass. Printlets made with slower laser scanning speeds are heavier than those prepared at higher laser speed as the powder particles are subjected to a higher energy input from the laser, and thus, become increasingly molten. This leads to a higher number of necks forming between each layer. As the empty spaces are reduced, there is more room for powder particles to be sintered which creates a denser and heavier printlet.

Table 2. Printlet composition

Formulation	Weight (mg ± SD)	Printlet breaking force (N ± SD)	Closed porosity (% ± SD)	Open porosity (% ± SD)	Drug remaining (% ± SD)
H100	219.2 ± 0.2	144.3 ± 6.0	1.2 ± 0.1	15.3 ± 2.5	101.5 ± 1.8
H200	144.9 ± 0.6	52.7 ± 4.5	0.1 ± 0.0	31.0 ± 4.0	100.4 ± 0.9
H300	124.5 ± 0.5	15.7 ± 3.1	0.1 ± 0.0	34.5 ± 1.7	100.2 ± 0.5
K100	230.4 ± 0.8	171.2 ± 7.5	3.6 ± 0.4	16.4 ± 3.1	100.1 ± 1.0
K200	184.7 ± 0.7	27.3 ± 9.3	2.7 ± 0.2	27.8 ± 2.3	100.7 ± 0.9
K300	137.8 ± 0.7	13.7 ± 1.5	0.3 ± 0.0	40.0 ± 4.1	100.4 ± 0.5

All the formulations show appropriate properties for handling and do not break easily whilst manipulating. The printlet breaking force data show values between 14 N for printlets prepared at higher laser scanning speeds and up to 171 N for those fabricated at lower laser speeds (Table 2). For each polymer, there is a clear relationship between the laser speed and the strength of the formulations. Prinlets printed at higher laser speeds exhibit lower crushing strengths due to the reduced sintering impact and the lower number of necks formed between the powder particles. Since there is no minimum requirement for the breaking force of ODT formulations, if these fast dissolving printlets are individually packed in blisters (like most ODT formulations), they would be perfectly accepted by end users.

X-ray micro-CT was used to visualise the internal structure and density of the printlets (Figure 2) and to calculate their closed and open porosity (Table 2). Closed porosity can be identified as the pores of the printlet that do not extend to the external environment. Following the immersion of the printlet in the dissolution media, the media cannot penetrate

into the closed pores unless it dissolves through the external walls of the pores. Open porosity, however, relates to the presence of empty spaces inside the printlet that are connected between them and with the external environment. When surrounded by dissolution media, an open pored structure would dissolve faster than that of a structure with closed pores. Total porosity, therefore, can be defined as the sum of closed and open pores. In both HPMC and Kollidon® formulations, the same porosity trend can be identified; printlets prepared at a higher laser scanning speed show a higher porosity value which is in agreement with the lower mass (Table 2).

The formulations printed with a laser scanning speed of 100 mm/s showed that the external shell was higher in density (lighter in colour) when compared to the inner core (more intense in colour) (Figure 2). This is inherently due to the sintering process and laser scanning process where dense wall formations can occur (Cheah 2002). Formulations printed at 200 mm/s are more red in colour, indicating lowered densities when compared with the printlets formed at 100 mm/s as the powder surface is less exposed to transmitted heat energy from an accelerated laser beam. The printlets fabricated at 300 mm/s are distinctively red in colour, further highlighting the decrease in density. Therefore, it can be suggested that increasing the SLS scanning speed can produce less dense structures due to a reduced sintering effect of the powdered materials.

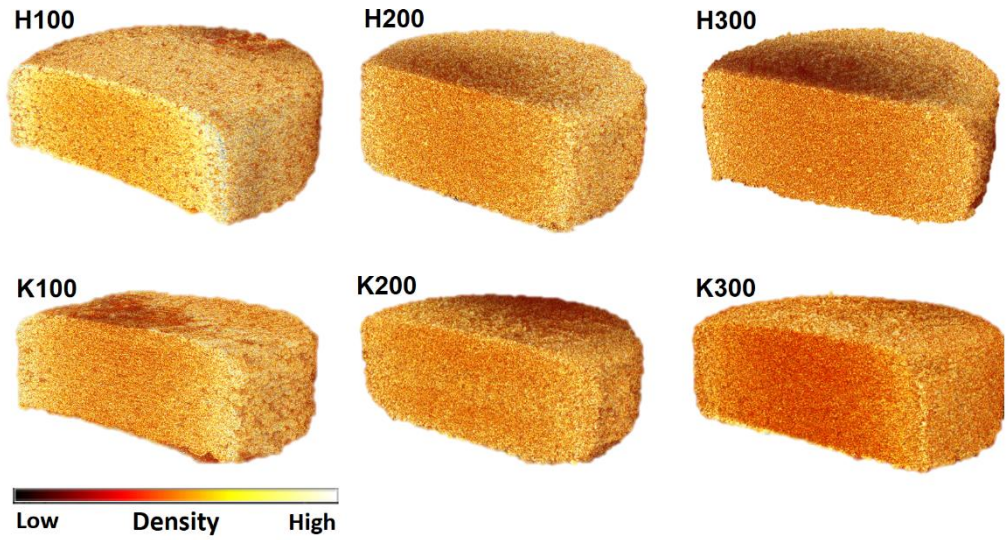

Figure 2. X-ray micro-CT images of a half section of the printlets

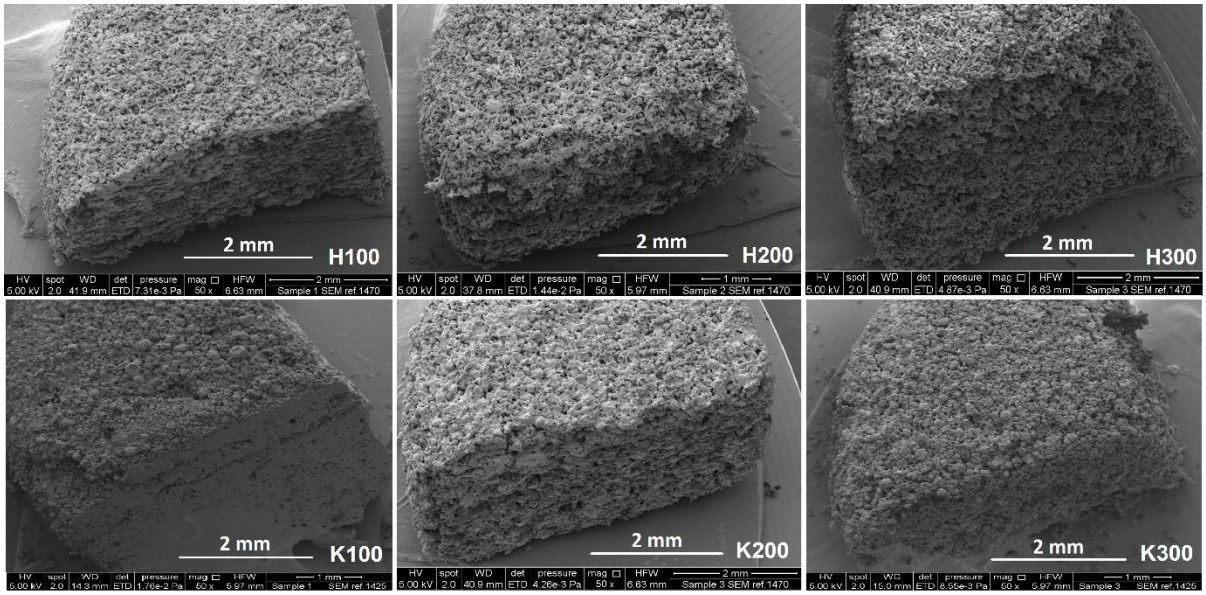

Figure 3. SEM images of the vertical sections of the printlets

SEM images provided a visual confirmation of the porosity of the printlets (Figure 3). The printlets fabricated at 100 mm/s show the partial fusion of the powder particles whilst the formulations created at 200 mm/s, and more notably in both HPMC and Kollidon® 300-formulations, single powder particles can be easily identified. This suggests that increasing the laser scanning speed reduces the sintering of powder particles together, which, as a result, leaves more empty spaces in between each particle. This results to an increased overall porosity (Table 2), and potentially facilitate the dissolution of the printlets.

Drug loading of the formulations (outlined in Table 2) was evaluated by HPLC (Fina et al. 2017) which confirmed that degradation of paracetamol did not occur by SLS printing as the results were found to be very similar to the theoretical drug loading value. DSC and X-ray analyses of the drug, HPMC and Kollidon® polymers and mixed materials prior to printing and of the printlets were performed to identify the drug phase state and to what degree the drug is incorporated into the polymers (Figures 4 and 5). Before printing, DSC data showed that the paracetamol raw ingredient exhibited a melting endotherm at approximately 172°C, indicative of form I which melts at 168°C (Sibik et al. 2014). The DSC data of the printlets exhibited a broad melting endotherm before 100°C, which is a result of water evaporation. The DSC data of the printlets, however, showed no evidence of a melting endotherm at approximately 168°C. This demonstrated that the drug is either molecularly dispersed within the polymer matrix as a solid dispersion or that the drug dissolved in the polymer as the

temperature increased during the DSC analysis. It is possible to observe a melting endotherm associated to the melting of paracetamol in the physical mixture for HPMC powder mixtures. This, therefore, suggests that the drug is in its crystalline form. This was not visible in the Kollidon® formulations as 5% drug loading may not be sufficient for identification in a thermograph.

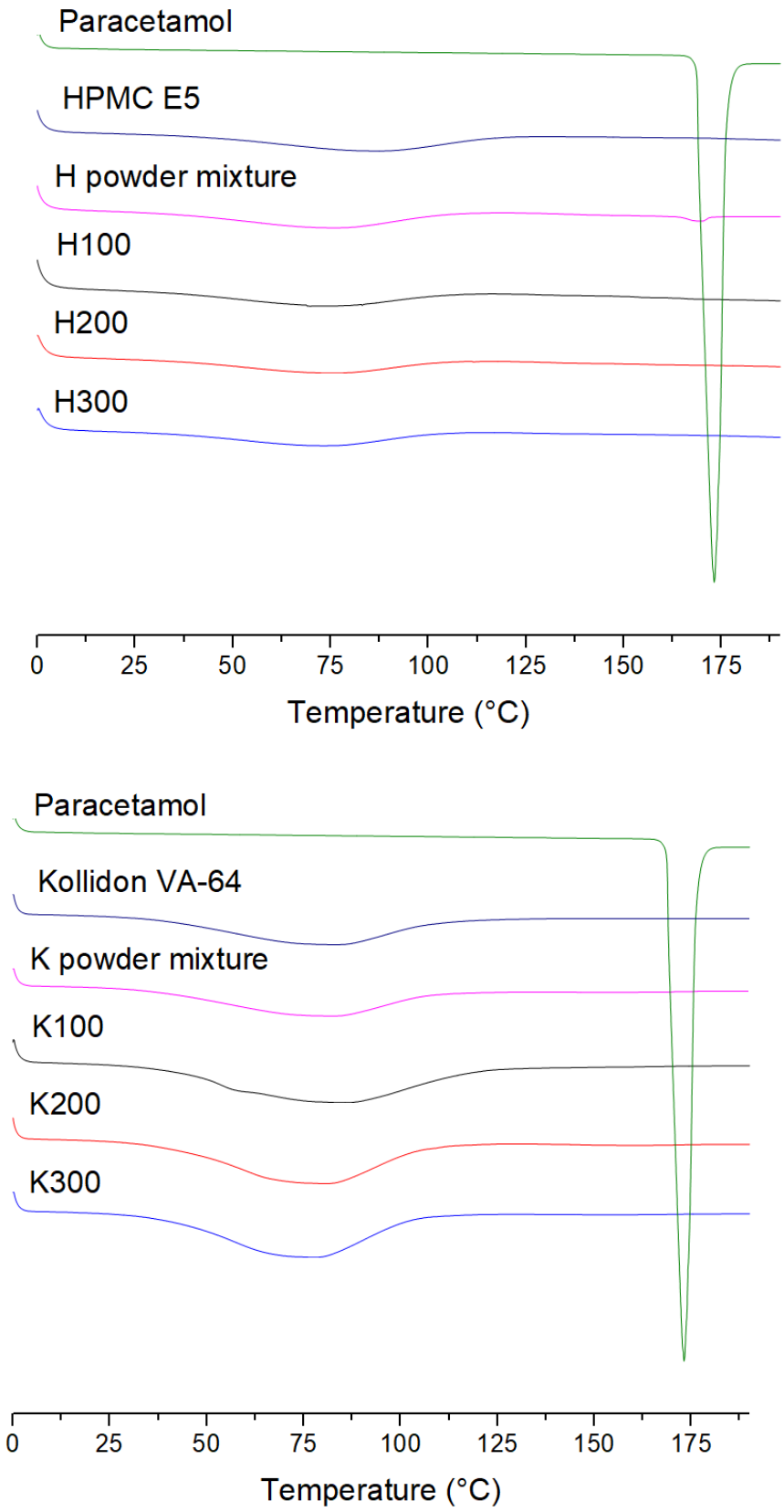

Figure 4. DSC thermograms of pure paracetamol, individual polymers, powder mixtures before printing and printlets printed at different laser scanning speeds.

Corroborating the results from the DSC, X-ray diffractograms demonstrated amorphous patterns in all the pure-polymers, physical mixtures and 3DP formulations for both HPMC and Kollidon® polymers (Figure 5). In addition, crystalline paracetamol peaks were not observed in the physical mixture as 5% may not be sufficient for identification in the diffractograms.

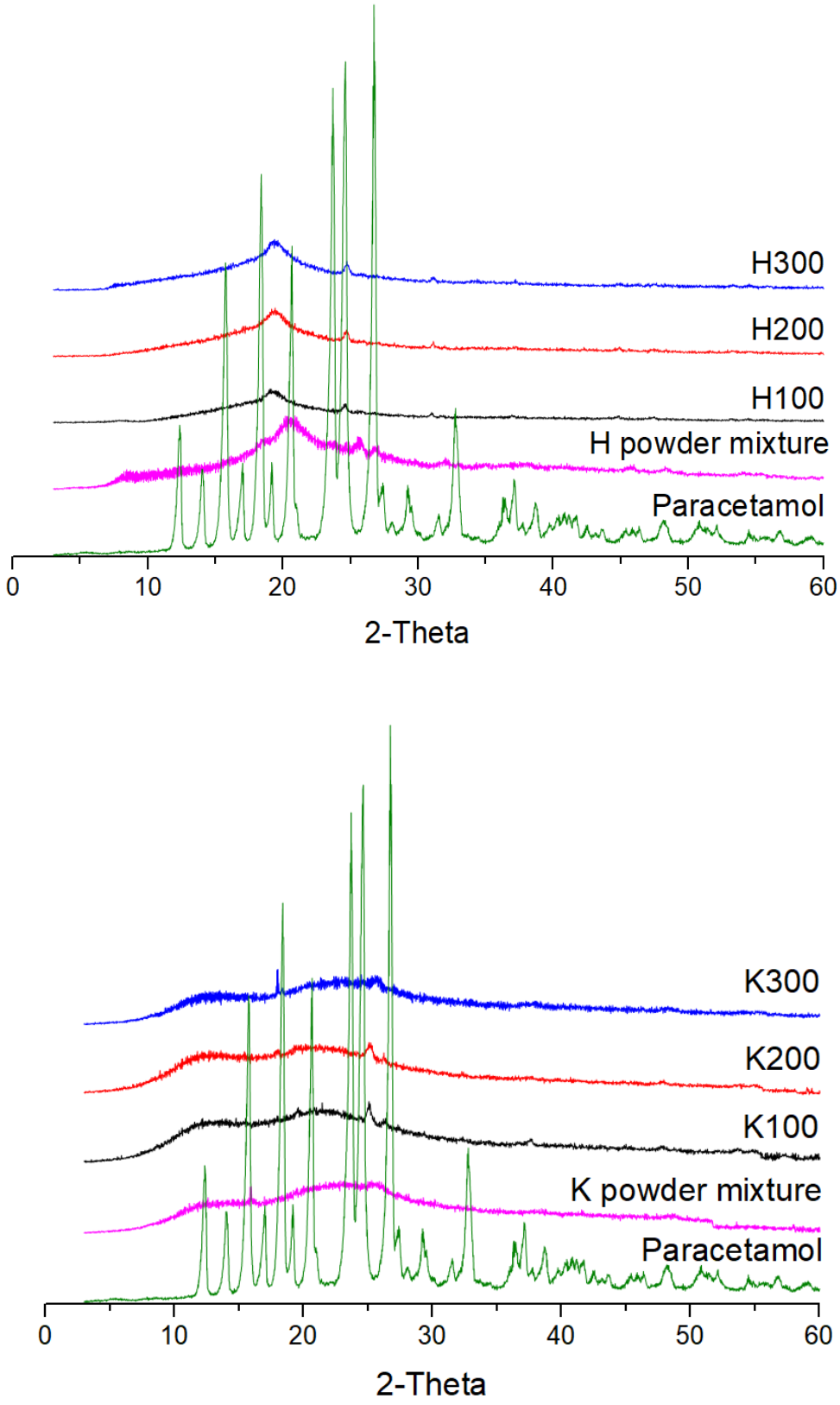

Figure 5. X-ray powder diffractograms of pure paracetamol, powder mixtures before printing and 3DP discs printed at different laser scanning speeds.

Figures 6 and 7 show the drug dissolution profiles of both HPMC and Kollidon® formulations. Printlets were tested in the dynamic *in vitro* model which stimulates gastric and intestinal conditions of the gastrointestinal tract (Goyanes et al. 2015b). Considering the dissolution profile for HPMC formulations, it is clear that increasing the speed from 100, 200 to 300 mm/s can modulate and ultimately increase drug release. For the H100 formulation, fabricated with a scanning speed of 100 mm/s, 100% paracetamol release occurred after approximately 4 h. As some HPMC printlets did not disintegrate after 2 hours in an acidic environment, a small portion of the printlets remained inside the sinker. These were then transferred into the dynamic dissolution bath. It was found that increasing the laser scanning speed from 100 mm/s to 200 mm/s was able to notably reduce the time taken for complete paracetamol release in the gastrointestinal environment to approximately 3 h. The H300 formulation which was fabricated at a laser scanning speed of 300 mm/s exhibited a shorter dissolution profile and achieved complete drug release at approximately 2 h.

All Kollidon® printlets disintegrated in the acid medium during the dissolution test and at a much faster rate than any of the HPMC formulations (Figures 6 and 7). The dissolution profile of Kollidon® printlets further demonstrate that increasing the laser scanning speed of SLS 3DP can modulate the drug release rate. More specifically, a higher laser scanning speed leads to a faster drug release due to the loose powder particles connections and porous structures fabricated through the layer-by-layer approach. With a laser scanning speed of 100 mm/s, complete drug release of the K100 formulation was achieved at 60 min, however, increasing the laser scanning speed to 200 mm/s and 300 mm/s altered the K200 and K300 formulations to release 95% paracetamol in under 5 min.

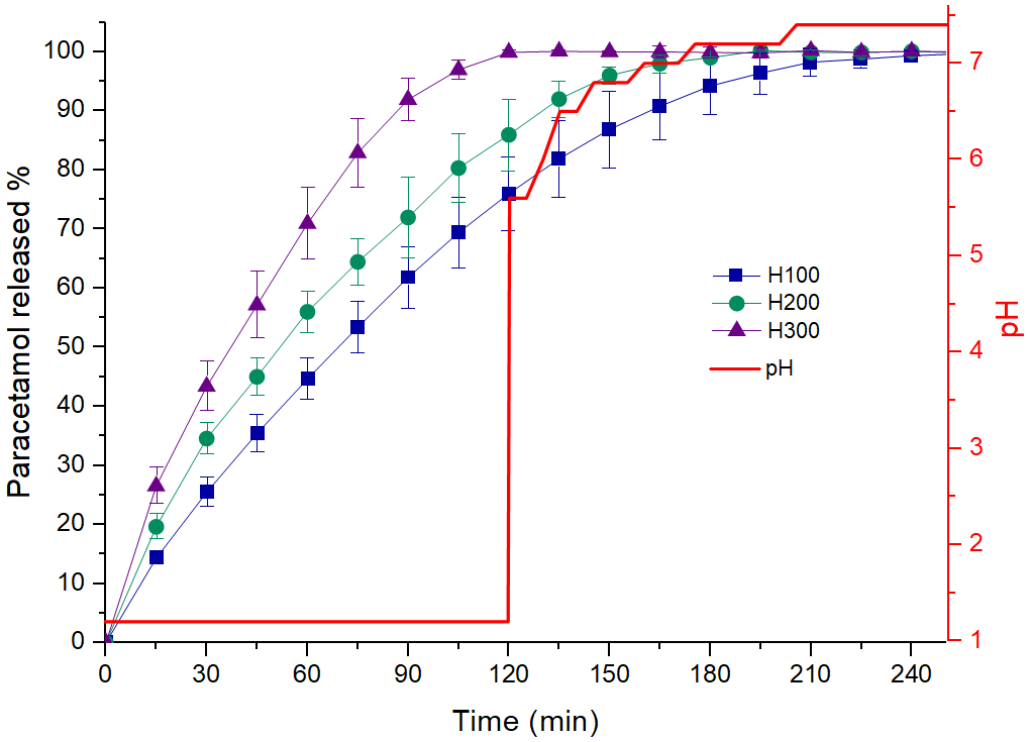

Figure 6. Dissolution profiles of HPMC based formulations (H100, H200 and H300). The red line shows the pH values of the media in an acidic environment for the first 2 hours, followed by exposure to basic pH in the dynamic dissolution test.

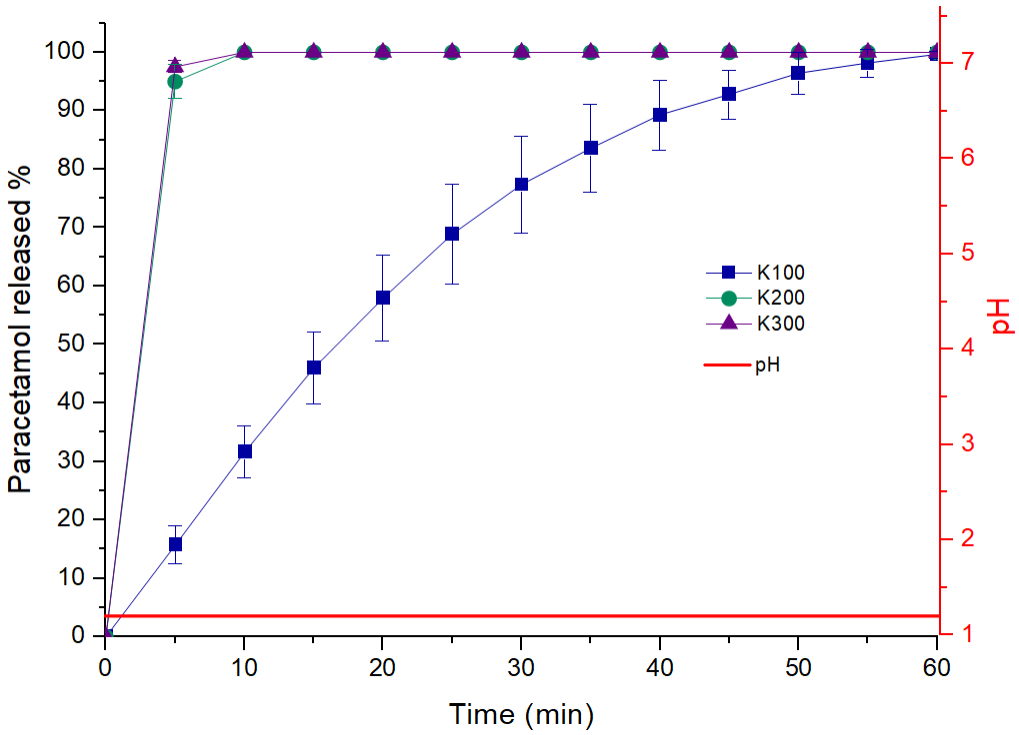

Figure 7. Dissolution profiles of Kollidon® based formulations (K100, K200 and K300) conducted in an acidic environment. The red line illustrates the pH values for the acidic environment.

As some of the formulations rapidly disintegrated, conventional dissolution tests were not representative to evaluate the respective disintegrating properties. Therefore, a new disintegrating test was employed to assess the printlets. The investigation was based on the Spritam® disintegration test (Aprecia Pharmaceutials 2016) whereby the printlets were placed in a petri dish containing approximately 20 ml of water. This disintegration method was applied to all formulations and outlined in Table 3. The H100, H200 and H300 formulations slowly dissolved and fully disintegrated over 600 s; these results are in agreement with the aforementioned dissolution profiles. The K100 formulation further demonstrated a disintegration time of over 600 s, however, modulating the laser scanning speed from 100 mm/s to 200 and 300 mm/s drastically decreased the disintegration time. The K200 formulation completely disintegrated at 320 s whilst K300 disintegrated at 4 s. The stark reduction in disintegrating time can be explained by the less energetic sintering process. This allowed the powder particles that formed the printlet to detach from each other as soon as they come in contact with the dissolution media. In addition, as shown by the higher porosity values, the media was able to easily enter the printlet structure and thus, accelerate the disintegration time. The European Pharmacopoeia considers formulations to be an ODT following complete disintegration in under 3 min although the FDA characterise ODT formulations to dissolve under 30 s. The disintegration time for K300 formulation, therefore, demonstrate ODT characteristics due to their rapid disintegrating time. Kollidon® is a polymer often employed in drug tabletting to act as a dry binder, granulating auxiliary and as a film-forming agent (Aktiengesellschaft 2000). To the author's knowledge, this particular polymer has not been incorporated to ODT formulations to induce fast dissolving characteristics. Therefore, the SLS technology is capable of modifying the properties of the excipients explored and their uses.

Table 3. Disintegration time of printlets

Formulation	Disintegration time (s)
H100	>600
H200	>600
H300	>600
K100	>600
K200	320 ± 38
K300	4 ± 3.2

Our results show that by modulating SLS printing parameters, this technology can be an alternative 3DP technique to PB fusion manufacturing processes already available in the market. Spritam® is fabricated using the ZipDose® technology to manufacture tablets for oral suspension. It is clear that SLS technology can modify the characteristics of polymers designed for other applications and transform them to be amenable for ODT formulations by fully disintegrating in a small volume of liquid in approximately 4 seconds. In addition, with SLS, there is no limitation due to moisture from the use of a liquid binder in PB fusion 3DP. Due to its solvent-free process, printlets manufactured by SLS can by readily dispensable and would not require an additional drying step following printing.

4. Conclusion

Printlets with different drug release properties can be manufactured by modulating the laser scanning speed of a SLS 3D printer. The versatility of SLS technology was demonstrated by drastically accelerating the drug dissolution profiles of printlets prepared with two pharmaceutical-grade polymers that have not been explored with SLS 3DP to date. Kollidon® based printlets were able to rapidly disintegrate within 4 seconds and were easily prepared by increasing the laser scanning speed to 300 mm/s, leading to a less energetic sintering process. The work first reported here exhibits the successful manufacture of medicines using an SLS 3D printer, thus, allowing the technology to be amenable for ODT formulations and transform polymer release characteristics. This investigation confirms the addition of SLS to the portfolio of 3DP technologies available for the commercial manufacture of medicines.

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