Development of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing

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Abstract

The aim of this study was to manufacture 3D printed tablets (printlets) from enteric polymers by single filament fused deposition modeling (FDM) 3D printing (3DP). Hot melt extrusion was used to generate paracetamol-loaded filaments from three different grades of the pharmaceutical excipient hypromellose acetate succinate (HPMCAS), grades LG, MG and HG. One-step 3DP was used to process these filaments into enteric printlets incorporating up to 50% drug loading with two different infill percentages (20 and 100%). X-ray Micro Computed Tomography (Micro-CT) analysis revealed that printlets with 20% infill had cavities in the core compared to 100% infill, and that the density of the 50% drug loading printlets was higher than the equivalent formulations loaded with 5% drug. In biorelevant bicarbonate dissolution media, drug release from the printlets was dependent on the polymer composition, drug loading and the internal structure of the formulations. All HPMCAS-based printlets showed delayed drug release properties, and in the intestinal conditions, drug release was faster from the printlets prepared with polymers with a lower pH-threshold: HPMCAS LG > AS MG > AS HG. These results confirm that FDM 3D printing makes it possible not only to manufacture delayed release printlets without the need for an outer enteric coating, but it is also feasible to adapt the release profile in response to the personal characteristics of the patient, realizing the full potential of additive manufacturing in the development of personalised dose medicines.

Introduction

Three-dimensional printing (3DP) is an additive manufacturing technique that creates solid objects layer by layer (Alomari et al., 2015; Sanderson, 2015). 3D printing is an umbrella term that encompasses a range of different printing technologies. For instance, powder bed - inkjet printing, which was developed in the late 90s, is based on spreading layers of powder onto a piston plate, followed by addition of liquid binder solution to bind the powder particles together. This technology is used in the manufacture of the first 3D printed formulation approved by the FDA, Spritam® (Aprecia_Pharmaceuticals, 2015; Katstra et al., 2000; Rowe et al., 2000; Yu et al., 2009). An alternative printing process that is becoming more affordable is stereolithography (SLA). In this technology, the production is based on the solidification of a liquid resin by photopolymerization using a source of light that causes localized polymerization (solidification) of photocrosslinkable polymers. SLA has also recently been proposed as a means to manufacture oral dosage forms (Wang et al., 2016) as well as personalized facial masks for topical drug delivery (Goyanes et al., 2016a). A further 3DP technology is gel extrusion, which works on using a syringe based system that extrudes a paste on to the build plate layer by layer which solidifies by evaporation of the solvent or by cooling (Khaled et al., 2014; Khaled et al., 2015).

Of all of the 3DP technologies, fused-deposition modeling (FDM), offers possibly the most immediate potential for small-scale unit dose fabrication (Goyanes et al., 2014). The principle underpinning FDM technology is the deposition of thin strands of melted polymer from a filament on a build plate creating one layer of the object to be printed. The build plate then moves down and another layer is deposited. Repeating these steps in a layer-by-layer manner the final object is obtained (Goyanes et al., 2014; Goyanes et al., 2015a). FDM is simple and cost-effective and has been shown to be extremely versatile in the development of drug delivery systems (Goyanes et al., 2015f), especially personalised oral medicines (Goyanes et al., 2014; Goyanes et al., 2015a; Skowyra et al., 2015), medical devices (Genina et al., 2015) and wound dressings (Hassan et al.).

FDM 3DP offers the possibility of fabricating solid oral dosage forms, including complex modified release products. Modified-release (MR) dosage forms are formulations in which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms. Examples of MR drug products include delayed release formulations (e.g. enteric coated) where the drug is released

with a delay after its administration. Oral enteric dosage forms (gastro-resistant formulations) are used clinically to prevent drug release in the stomach and allow release in lower regions of the gastrointestinal (GI) tract. The enteric polymers in use include synthetic or semi-synthetic pH sensitive material containing ionisable carboxylic acid groups that remain unionized in the low pH conditions of the stomach but become ionised at the higher pH environment of the small or large intestine, therefore enabling the coating to dissolve and the drug to be released (Liu et al., 2009).

The manufacture of budesonide 3D printed tablets (printlets) with enteric properties comparable to two commercial formulations was previously reported by coating 3D printed cores with an enteric polymer (Eudragit® L100) in a fluid bed coater (Goyanes et al., 2015b). More recently, Eudragit L100-55 filaments were produced and used to print the coating of 3D printed cores to provide enteric properties, avoiding the use of fluid bed coating (Okwuosa et al., 2017). This approach allows the fabrication of single dosage forms eliminating the need of batches for the coating process, although it is necessary to use two filaments, one for the core with the drug and one for the external layers.

A method for rapidly producing delayed release tablets without the need for a separate coating or multiple printing nozzles in which the dose can be tailored to individual patients with appropriate drug release properties would be of great value for the production of medicines at the point of dispensing. The aim was to couple hot melt extrusion and 3DP to achieve this goal.

Hot melt extrusion (HME) is used to manufacture drug-loaded filaments used in FDM printing. HME is a widely used technique in the pharmaceutical industry, in which the raw materials are forced to mix in a rotating screw at elevated temperatures before being extruded through a die to produce a strand of uniform characteristics. In this regard, a variety of polymers have been extruded and 3D printed in recent years (Goyanes et al., 2014; Melocchi et al., 2016; Sadia et al., 2016). Hypromellose acetate succinate (HPMCAS) is an enteric polymer, which is mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose. HPMCAS is marketed in three different grades depending on the ratio between acetyl and succinoyl groups - L, M and H - with pH thresholds of 5.5, 6.0 and 6.5 respectively (Rowe et al., 2009; Shin-Etsu_AQOAT, 2015).

The aim of this work is to manufacture with a single filament enteric matrix printlets (printlets: 3D printed tablets) containing paracetamol using three different grades of HPMCAS (LG, MG, HG),

different drug loadings (5% and 50%) and different internal structure (20% - 100% infill). X-ray Micro Computed Tomography (Micro-CT) was employed as an advanced tool to visualize the inner structure of the printlets with different infills as well as the different densities and porosity degrees. Drug dissolution behaviour in biorelevant media was also evaluated.

2. Materials and methods

Materials

Paracetamol USP grade (Sigma-Aldrich, UK) was used as a model drug (BCS Class I, high solubility and high permeability, MW 151.16, solubility at 37ºC: 21.80 g/L (Yalkowsky and He, 2003)). Three different types of granular hydroxypropylmethylcellulose acetate succinate – HPMCAS LG, HPMCAS MG and HPMCAS HG – (Aqoat®, from Shin-Etsu Chemical, Japan) were evaluated. Methylparaben NF grade (Amresco, USA) was used as a plasticizer and magnesium stearate (Sigma–Aldrich Co. Ltd., UK) as a lubricant. The salts for preparing the buffer dissolution media were purchased from VWR International Ltd., UK.

Methods

Preparation of drug-loaded filaments by hot melt extrusion (HME)

For each batch, 40g of a blend of drug and excipients was prepared. The excipients were mixed in a mortar and pestle with the drug (paracetamol), until no agglomerated particles of drug or polymers were observed. The compositions of the formulations evaluated in this study are listed in Table 1. The theoretical drug contents of the mixtures were 5 or 50% w/w. The mixture of drug and excipients was then extruded using a single-screw filament extruder (Noztec Pro hot melt extruder, Noztec, UK) in order to obtain the drug loaded filament (extrusion temperature 80-110°C, Table 1, nozzle diameter 1.75 mm, screw speed 15 rpm). The extruded filaments obtained were protected from light and kept in a vacuum desiccator until printing. The drug-loading of the filaments was determined by HPLC analysis.

FDM 3D printing

Oral drug delivery formulations were manufactured from the drug-loaded filaments using a commercial fused-deposition modeling 3D printer (MakerBot Replicator 2X, MakerBot Inc, USA). AutoCAD 2014 (Autodesk Inc., USA) was used to design the templates of the printlets, exported as a stereolithography (.stl) file into 3D printer software (MakerWare v. 3.7.0, MakerBot Inc., USA). The .stl format contains only the object surface data, and all the other

parameters need to be defined from the MakerBot software in order to print the desired object. The printer settings were selected as follows to obtain printlets with the best resolution: High resolution without raft and an extrusion temperature of 180-190°C (Table 2), speed while extruding (90 mm/s), speed while travelling (150 mm/s), number of shells (2) and layer height (0.10 mm). Two infill percentages were selected (20 and 100%) in order to produce printlets of low and high density. The selected 3D geometry was a cylindrical printlet (10mm diameter x 3.6mm height).

Thermal analysis

DSC measurements were performed with a Q2000 DSC (TA instruments, Waters, LLC, USA) at a heating rate of 10°C/min, after preheating cycle to 120°C to remove water of the samples. Calibration for cell constant and enthalpy was performed with indium (T_m = 156.6°C, ΔH_f =28.71 J/g) according to the manufacturer's 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 pin-holed hermetic lids (T_{zero}) were used with an average sample mass of 8-10 mg.

For TGA analysis, samples (average weight: 3-5 mg) were heated at 10°C/min in open aluminium pans with a Discovery TGA (TA instruments, Waters, LLC, USA). Nitrogen was used as a purge gas with a flow rate of 25 mL/min. Data collection and analysis were performed using TA Instruments Trios software and % mass loss and/or onset temperature were calculated.

X-ray powder diffraction (XRPD)

Discs (23mm diameter x 1mm height, 100% infill) made from drug-loaded polymers filaments were 3D printed and analysed. Sample of pure paracetamol and pure HPMCAS polymers 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.

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.

Printlets were scanned using no filter with a resolution of 2000x1048 pixels. Image reconstruction was performed using NRecon software (version 1.7.0.4, Bruker-microCT). Beam hardening, ring artefacts and post alignments were adjusted to obtain the best possible images. 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 and porosity properties of the extruded filaments and printlets.

Scanning Electron Microscopy (SEM)

Morphology of the extruded feedstock and printlets were evaluated by scanning electron microscopy (SEM) using a Philips XL30 FEG SEM, operating at 20kV. Samples were placed on double-sided carbon tape, mounted on stubs and sputter coated using a Polaron E5000 machine with Au/Pd. Samples were coated for 1 minute prior to imaging.

Printlet morphology characterisation

The physical dimensions of the devices were measured using a digital calliper. Pictures of the devices were taken with a Nikon CoolpixS6150 with the macro option of the menu.

Determination of drug loading

A caplet or a section of drug-loaded filament (approx. 0.3g) was placed in a volumetric flask (1L deionized water to which 2 drops of 5M NaOH were added to increase the pH in order to dissolve the polymers) under magnetic stirring until complete dissolution (n=2). Samples of solutions were then filtered through 0.45 μm filters (Millipore Ltd., Ireland) and the concentration of drug determined with HPLC (Hewlett Packard 1050 Series HPLC system, Agilent Technologies, UK). The validated high performance liquid chromatographic assay entailed injecting 20 μL samples for analysis using a mobile phase, consisting of 85% of water and 15% of methanol, through a Luna 5 mm C8 column, 25 x 4.6 cm (Phenomenex, UK) 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. All measurements were made in duplicate.

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 0.1 M 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 (1000ml) (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), followed by pH 6.5 representing the colonic environment.(Fadda et al., 2009; Goyanes et al., 2015c; Goyanes et al., 2015d; 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 et al., 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). Sample of the dissolution media (1mL) was withdrawn every hour and the drug concentrations were determined by HPLC to calculate the percentage of drug released from the formulations.

3. Results and discussion

HME technology was successfully employed to extrude mixtures of paracetamol and the different grades of HPMCAS into filaments of appropriate physical characteristics and diameter for FDM 3D printing. All the mixtures were prepared incorporating 5 or 50% paracetamol, plasticizer and lubricant (Table 1). The use of HPMCAS of particle size similar to that of the drug and blending with the mortar and pestle enabled the formation of a homogeneous mixture to be produced. Methylparaben was included in all the formulations as a plasticizer. Different mixtures of polymers and plasticizers were screened initially; however, most of these formulations provided filaments unsuitable for printing due to the lack of appropriate flexibility and resistance. 15% and 5% w/w methylparaben were found to provide appropriate physical characteristics for all the HPMCAS grades tested. Methylparaben was selected as a main plasticizer due to its superior plasticization efficiency and delayed drug release profile compared with other

plasticizers (triethyl citrate, polyethylene glycol 8000, citric acid monohydrate and acetyltributyl citrate) as reported in a study with polymethacrylate matrix pellets obtained by HME (Schilling et al., 2010).

All the filaments were prepared with 5% w/w magnesium stearate, which was found to be extremely useful in facilitating the extrusion process due to its lubricant properties. The extrusion process for all the formulations was smooth and the extrusion temperature for the filaments incorporating 5% drug (80°C) was particularly low compared with a previous study conducted by Mehuys et al. (2005), where a mixture of HPMCAS LG and 25% of plasticizer (triacetin) was prepared; even though the amount of plasticizer was almost double compared with the current study (15% methylparaben) a higher extrusion temperature (110-120°C) was needed. This finding may highlight the important role of magnesium stearate in reducing the extrusion temperature. Filaments incorporating 50% paracetamol required higher extrusion temperatures. All the extruded filaments obtained in the present study showed the appropriate characteristics for 3D printing in terms of diameter and elasticity-brittleness, with final drug loadings in the filaments similar to the theoretical drug loadings (4.9-5.1% and 46.0-49.0%)

TGA data of drug loaded filaments predicted no degradation of the excipients or the drug at the printing temperature (≤190°C) (Figure 1). TGA data of the three pure HPMCAS polymers showed a weight loss ranging from 1.9 to 3.1% w/w mainly due to the water evaporation (Figure 1). The noticeable mass loss for the active compound alone could be related to the first stage of decomposition, whereas previous studies already confirmed the stability of paracetamol in FDM 3DP at temperatures as high as 190°C (Goyanes et al., 2015e; Goyanes et al., 2015f). TGA data for magnesium stearate showed an excellent stability at the printing temperature and the weight loss observed before 100°C can be attributed to a loss of absorbed water. On the other hand, methylparaben which has a relatively low boiling point, showed an evaporation process starting at about 100°C and which was completed at above 200°C.

The weight loss up to 190 °C ranged from 2 to 5.5% w/w for all the filaments. The weight loss of the formulations incorporating 5% of paracetamol is slightly higher due to evaporation of methylparaben that is in higher percentage than in formulations incorporating 50% drug. The need for lower amounts of methylparaben when incorporating 50% paracetamol is attributed to the plasticizing effect of the drug.

DSC and X-ray analyses of the pure substances, mixed materials before HME and 3D printed discs were performed to explore the degree to which the drug is incorporated into the polymers

(Figure 2 and 3). DSC data shows that paracetamol raw material melts at around 168°C indicative of form I (Goyanes et al., 2015e). The DSC data of the 5% paracetamol formulations shows no evidence of melting at around 168°C, indicating that the drug is either molecularly dispersed within the polymer matrix as a solid dispersion or the percentage is too low to be detected. X-ray powder diffraction data corroborates this extent. Diffractograms of the formulations do not show any paracetamol peak and the patterns of the pure polymers and the filaments show the same characteristics (Figure 3). This confirms that the drug is present in an amorphous phase within the polymer matrix.

On the other hand, DSC data from formulations incorporating 50% drug show a large endotherm attributed to the melting of paracetamol. This indicates that part of the drug is in crystalline form, probably due to the high percentage of drug that saturates the solubilising capacity of the polymers. In accordance with the DSC, X-ray diffractograms show semi-crystalline patterns with the presence of the characteristic paracetamol peaks.

A further confirmation stems from the SEM images of the filaments (Figure 4) and printlets (Figure 5). Filaments and printlets loaded with 5% of paracetamol lacked the presence of crystals on the surface. On the contrary, filaments and printlets with 50% of paracetamol had a much higher presence of crystals on the surface.

The printlets showed appropriate shape although the resolution of the printing was slightly affected by the higher percentage of paracetamol in the formulations (Figure 6). The attempt to incorporate higher drug loading percentages reduces, at some point, the quality of the filament making it not appropriate for 3D printing, although the use of other excipients as plasticizer could help to obtain considerably higher drug loading percentages than 50% w/w. The quality of the extruded filaments (e.g. constant diameter) influences the final results of the 3D printed formulation.

The mechanical properties of the printlets were satisfactory, not friable and easy to handle. Similarly to PVA printlets prepared in previous studies (Goyanes et al., 2014; Goyanes et al., 2015a), the printlets showed a plastic-like aspect with high strength which was not possible to quantify with a traditional tablet hardness tester and the friability of all the formulations was zero.

X-Ray micro-CT was employed to visualize the internal structure of the printlets. Different colours were given depending on the density level showing that the printlets containing higher percentage of paracetamol have higher density, which is in agreement with the higher weight of the printlets (Figure 7).

Dissolution tests of the formulations performed under biorelevant conditions show different release profiles for the different grades of HPMC-AS, confirming that the grade plays an important role in defining release kinetics (Figure 8). Drug release was faster from the printlets prepared with polymers with lower pH-threshold (HPMCAS LG > AS MG > AS HG). All the formulations independent of the percentage of drug loading released <10% drug in the acidic environment (first two hours), complying with the USP criteria for delayed release formulations (less than 10% drug release the first two hours in pH 1.2).
Printlets incorporating 50% paracetamol released the drug faster than the same formulations incorporating 5% paracetamol in the buffer stage. The effect of drug loading on the drug dissolution profiles of 3D printed formulations has been recently reported where the influence of porosity of 3D printed caplets containing either caffeine or paracetamol was studied (Goyanes et al., 2016b). It was concluded that higher the drug loading and drug solubility, the faster the release profile, while the microporous volume did not influence dissolution behaviour. The effect of drug loading is confirmed in the present study, where printlets loaded with 50% paracetamol released drug faster compared to the 5% formulations. However, all the formulations showed delayed release properties (less than 10% release in the gastric phase) even incorporating with 50% of paracetamol (BCS Class I drug), indicating that the system may be suitable for loading other equally highly soluble drug candidates.

All the formulations released drug faster once in the small intestine stage but even the fastest releasing formulation LG 50/100 took 8 hours to release the drug completely. Due to the slow dissolution of the polymer matrix, printlets with 20% infill were printed in an attempt to accelerate drug release. The infill percentage can be set by the user from the printing software. Each layer of a given object can be divided into two parts: shells and infill. The shells, or perimeters, are extruded outlines defining the shape of the layer. Infill is what happens in the space left over (if no infill is printed, the object will be hollow). More infill will make an object stronger and less will make it lighter and quicker to build. Since the infill percentage controls the filling of the hollow and the mechanical strength of the object, there is the potential to use this

parameter to modulate the physical properties of the printlet, and hence the dissolution profile (Goyanes et al., 2014; Goyanes et al., 2015a).
The 20% infill printlets showed appropriate shape and the quality was not affected by the hollow core. To visualize the internal structure of the printlets and assure that there were no holes in the shells of the formulations X-Ray micro-CT analysis was performed. As in the printlets with 100% infill the printlets with higher percentage of paracetamol have higher density (Figure 9). All the 20%infill printlets show hollow spaces in the inner part of their structure but these spaces are not connected with the outside, indicating that the shell is continuous.

All the formulations printed with 20% infill dissolved faster than the analogous printlets with 100% infill (Figure 10), The pH threshold of the polymers clearly determined the drug release rate profile of the printlets. Similarly to the 100% infill printlets, printlets with 20% infill showed faster drug release when prepared with HPMC-AS with lower pH threshold. All printlets prepared with HPMCAS LG and HPMCAS MG were completely dissolved after 12 hours, however, printlets prepared with HPMCAS HG did not completely dissolve after 24h.

Even for the printlets with 20% infill, complete drug release in the buffer stage was not fully achieved within 3-4 hours (mean small intestinal transit time). Drug release from the printlets takes place along the small intestine and colon due to the slow dissolution of the polymer matrix. The release is slower than from formulations prepared by compression and over coating using enteric polymers, where drug release is generally faster once the coating ruptures or dissolves. On the other hand, since in these printlets the whole formulation is a matrix that shows pH sensitive properties, potential damage to the coating, which are per se brittle and prone to crack, will not mean the loss of the delayed drug release effects. For instance, the adopted general practice of splitting tablets that is recommended for some immediate release formulations (e.g. warfarin tablets) (Verrue et al., 2011) would not make the printlets lose their delayed release properties. It would be expected that the change in size/surface area by splitting could have an effect on dissolution (Goyanes et al., 2015e), but without changing completely the properties for what the formulations were designed (either to release the drug over a prolonged period of time or to release it at specific regions of the GI tract).
Drug release from 3D printed HPMCAS polymers is essentially governed by the relative contribution of two mechanisms, drug diffusion and polymer dissolution (surface erosion) (Reynolds et al., 2002). The contribution of each mechanism depends on different factors such nature of the excipients and drug loading. In previous works, drug release from polyvinyl alcohol

based 3D printed formulations was reported to be regulated through an erosion mediated process independent of the pH of the media (Goyanes et al., 2014; Goyanes et al., 2015e).

The dissolution data from the different printlets do show that it is possible to design devices with controlled and delayed drug release profiles by careful selection of the composition of the filaments using a single filament. Gastrointestinal physiology is dynamic and complex, and a multitude of known variables (e.g. gender, genetics, sex, disease state, food) can affect the overall bioavailability of drugs delivered via the oral route (Freire et al., 2011; McConnell et al., 2008; Varum et al., 2013). Since patients respond differently to drugs, the development of a patient centric system for individuals (e.g pediatric, elderly, gender) would improve efficacy and reduce side effects. FDM appears to be a versatile approach suitable for manufacturing delayed release formulations using different polymers, to prepare personalized delayed release printlets without using coating approaches, making it possible to adjust the dose to the requirements of the patient.

Conclusion

FDM 3D printing allowed rapid manufacture of delayed release matrix printlets with three different grades of the enteric polymer HPMC-AS (LG, MG and HG) using a single filament incorporating different drug loadings (up to 50% paracetamol) and different infill. Micro-CT analysis showed that printlets with 20% infill contain cavities in the core compared to 100% infill, and that the density of the 50% drug loading printlets was higher than the printlets loaded with 5%. In dissolution, less than 10% drug release took place in the gastric phase; in the intestinal phase, drug release profiles were dependent on the polymer composition of the printlets, the percentage of drug loading and the internal structures. It is therefore feasible to target different regions of the gastrointestinal tract using these printlets. These results may enable manufacture not only of personalized oral dosage forms with the required amount of drug but also to adapt the dissolution profile based on the personal characteristics of the patient, achieving the full potential of additive manufacturing in the development of personalized medicines.

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Figure captions

Figure 1. TGA results of A) the drug loaded filaments and B) drug and excipients.

Figure 2. DSC thermograms of pure paracetamol, mixture of the excipients and drug before HME and 3D printed formulations.

Figure 3. X-ray powder diffractograms of 3D printed discs, HPMCAS polymers and paracetamol.

Figure 4. SEM images of LG 5% paracetamol (A) and LG 50% paracetamol (B) filaments.

Figure 5. SEM images of printlets (A) LG 5/100 and (B) LG 50/100.

Figure 6. Printlets incorporating A) 5% paracetamol and B) 50% paracetamol. From the left: LG, MG and HG.

Figure 7. X-Ray micro-CT images of LG printlets showing different densities. **A** LG 5/100, **B** LG 50/100.

Figure 8. Drug dissolution profiles from printlets. Red line shows the pH values of the media.

Figure 9. X-Ray micro-CT images of LG printlets showing the hollow internal structure. **A** LG 5/20, **B** LG 50/20.

Figure 10. Drug dissolution profiles from printlets with 20%. Red line shows the pH values of the media.