Stereolithographic (SLA) 3D Printing of Oral Modified-Release Dosage Forms

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Abstract

The aim of this work was to evaluate the suitability of stereolithography (SLA) to fabricate drug-loaded tablets with modified-release characteristics. The SLA printer creates solid objects by using a laser beam to photopolymerise monomers. In this work polyethylene glycol diacrylate (PEGDA) was used as a monomer and diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide was used as a photo-initiator. 4-aminosalicylic acid (4-ASA) and paracetamol (acetaminophen) were selected as model drugs. Tablets were successfully printed and formulations with different properties were fabricated by adding polyethylene glycol 300 (PEG 300) to the printing solution. The loading of paracetamol and 4-ASA in the printed tablets was 5.69% and 5.40% respectively. In a realistic dynamic dissolution simulation of the gastrointestinal tract, drug release from the tablets was dependent on the composition of the formulations, but independent of dissolution pH. In conclusion SLA 3DP technology allows the manufacture of drug loaded tablets with specific extended-release profiles. In the future this technology could become a manufacturing technology for the elaboration of oral dosage forms, for industrial production or even for personalised dose.

Keywords: Three dimensional (3D) printing; modified release; controlled release; stereolithographic printing; 4-ASA; paracetamol; stereolithography

1. Introduction

3-dimensional printing (3DP) is becoming an increasingly popular technology, which provides the ability to fabricate structures of precise geometries. The first technology used for printing 3D structures in pharmaceutics was achieved by inkjet printing a liquid binder solution onto a powder bed (Rowe et al., 2000; Wu et al., 1996). The process begins by spreading a layer of powder onto a piston plate, followed by addition of liquid binder solution to bind the powder particles together. The process is repeated until the desired geometry is created (Katstra et al., 2000). This is the method used to manufacture Spritam®, the first 3D printed medicine to be approved by the FDA. However, powder-bed printing limits the geometries of the shapes that can be printed (in particular, cavities are difficult to incorporate).

Fused-deposition modeling (FDM) is another type of 3DP technology. Here, extruded polymer filaments are melted into a semi-liquid state when passed through a heated nozzle. The softened filaments are then deposited onto a build platform in a layer by layer process to harden (Goyanes et al., 2014). One of the advantages of this technology is higher resolution compared with powder-bed printing, which allow creation of more complex scaffolds and to achieve better dosing accuracy (Goyanes et al., 2015b). FDM also offers advantages of good mechanical strength (Chia and Wu, 2015), and the printed dosage forms can be designed to achieve different releases profile by modifying the infill percentage, 3D model design or surface area of the formulation (Goyanes et al., 2014; Goyanes et al., 2015e; Goyanes et al., 2015f). A challenge for FDM is the limited choice of thermoplastic materials with good melt viscosity properties for extrusion. Another disadvantage for FDM is the inability to load temperature sensitive substances during extrusion due to the high processing temperature. In a previous study, approximately 50% of the model drug 4-aminosalicylic acid (4-ASA) was degraded during 3D printing (Goyanes et al., 2015a).

Stereolithography (SLA) is a further type of 3DP technology, widely used in the field of tissue engineering (Arcaute et al., 2010; Arcaute et al., 2006). In this case, production of the object is based on the solidification of a liquid resin by photopolymerization. A laser is focused on to a specific depth in a vat of resin, causing localized polymerization (and so solidification).

Solidification is repeated in a layer by layer manner until a solid, 3D object is produced (Melchels et al., 2010). In SLA printing, the energy imparted by the laser is important and is influenced by the power of the light source, the scanning speed, the exposure time and the amount of polymer and photoinitiator (Chia and Wu, 2015). The major advantage of SLA printing is its versatility, as drugs can be mixed with the photopolymer prior to printing, and become trapped in the solidified matrices. SLA is also superior to other 3DP techniques in terms of resolution (20 μm in comparison with 50-200 μm for other fabrication technology), (Melchels et al., 2010), which is limited only by the width of the focused laser. An additional benefit is that localized heating is minimized during printing, which may mean the technique is more suited to fabrication of dosage forms encapsulating thermally labile drugs. The main drawbacks of SLA technology are the limited number of photocrosslinkable polymers that are available, and the fact these materials are currently not on the generally recognized as safe (GRAS) list. Over the past few years a number of photocrosslinkable polymers have been developed, such as Poly(ethylene glycol) diacrylate (PEGDA) (Chan et al., 2010; Vehse et al., 2014), poly(2-hydroxyethyl methacrylate) (pHEMA) (Hanson Shepherd et al., 2011), poly(ethylene glycol) dimethacrylate (PEGDMA) (Arcaute et al., 2006; Dhariwala et al., 2004) and poly(propylene fumarate)/diethyl fumarate (PPF/DEF) (Fisher et al., 2002).

To the best of our knowledge, there has been no attempt to explore the potential of SLA printing to fabrication of unit-dose, oral modified-release dosage forms. Thus, the specific aim of this study was to evaluate the suitability of printing drug loaded tablets by SLA printing. 4-ASA and paracetamol were chosen as model drugs, the former because it is known to be thermally labile (and to degrade significantly when printed by FDM machines) (Goyanes et al., 2015a) and the latter because it is thermally stable and has previously been printed using FDM printing (Goyanes et al., 2015e). The effect of polymer composition on drug release kinetics was also evaluated.

2. Materials and methods

Poly(ethylene glycol) diacrylate (PEGDA, average MW 700), Poly(ethylene glycol) (PEG 300, average MW 300) and diphenyl(2,4,6-trimethylbenzoyl) phosphine oxide (DPPO) and

paracetamol (MW 151.16) were purchased from Sigma-Aldrich, UK. 4-Aminosalicylic acid (4-ASA, MW 153.14) was purchased from Acros Organics, UK. The salts for preparing the buffer dissolution media were purchased from VWR International Ltd., UK.

2.1 Preparation of photopolymer solution

PEGDA and PEG 300 were the primary materials used to prepare the photoreactive solutions. PEGDA and PEG 300 were mixed in ratios of 9:1, 6.5:3.5 or 3.5:6.5 (v/v) to a total volume of 20 mL. DPPO was then added to the mixture at a concentration of 1% (w/v). The solution was thoroughly mixed for at least 8 hours until the photoinitiator was dissolved completely. Paracetamol or 4-ASA was then added to the solution to a concentration of 5.9% (w/w) (Table 1). The solution was mixed thoroughly to dissolve the drug completely, and the resulting photopolymer solution was loaded into the printer.

2.2 Printing dosage forms

A commercial Form 1+ SLA 3D printer (Formlabs Inc, USA) equipped with a 405nm laser was utilized for printing tablets. The printer allows fabrication of objects with a resolution of 300 microns and a layer thickness of 25, 50, 100 or 200 microns. The templates used to print the tablets were designed with Autodesk Meshmixer 2014® (Autodesk Inc., USA) and exported as a stereolithography file (.stl) into the 3D printer software (Preform Software v. 1.9.1, Formlabs, UK). The basic selected 3D geometry was a torus, 11mm diameter x 4mm height, with a central hole of 3mm diameter. The material was set up as flexible and the layer thickness was 0.1mm. Five tablets were printed at the same time for each formulation.

2.3 Environmental scanning electron microscopy (ESEM)

The Surface and cross-section images of the printed tablets were captured with a FEI Quanta 200F Scanning Electron Microscope (FEI, UK) to evaluate the microstructure of the devices. The voltage and working distance were set at 5 V and 50 mm, respectively. The samples were not coated and pictures were taken under environmental-pressure conditions. Pictures of the devices were taken with a Nikon CoolpixS6150 with the macro option of the menu.

2.4 X-ray powder diffraction (XRPD)

The 3D printed discs (23mm diameter x 1mm height) with and without drugs were analysed, together with samples of pure 4-ASA and paracetamol. 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.

2.5 Determination of drug concentration in the photopolymer solution and 3DP tablets

Photopolymer solution (0.2 g) was diluted with acetonitrile (20 mL). After thoroughly mixing, an aliquot of solution (100 μL) was further diluted with water (900 μL) and the drug concentration was determined with HPLC (Hewlett Packard 1050 Series HPLC system, Agilent Technologies, UK).

For determination of drug loading in 3DP tablets, the tablet was crushed and placed in a volumetric flask with acetonitrile (250 mL) under magnetic stirring overnight (n=2). Samples of the solutions were then filtered through 0.45 μm filters (Millipore Ltd, Ireland) and the concentration of drug determined with HPLC.

The mobile phase for paracetamol analysis consisted of a gradient system of (A) water (adjusted to pH 2 with orthophosphoric acid) and (B) acetonitrile. The mobile phase was pumped at a flow rate of 1 mL/min under the following gradient program: 0-15 min, 5-20% B; 15-16 min, 20-5% B, through a Luna 5 μm C18 column, 150 x 4.6 mm (Phenomenex, UK), maintained at 40 °C. The eluent was screened at a wavelength of 247 nm and the retention time was 7.0 min.

Concentrations of 4-ASA in the samples were measured with a mobile phase consisting of acetonitrile (24%), water (76%) and orthophosphoric acid (900 μL/L) pumped through a Discovery HSF5 column (4.6 x150 mm) maintained at 40ºC. The mobile phase was pumped at a flow rate of 1 mL/min and the eluent was screened at a wavelength of 303 nm. The injection volume was 20 μL and the retention time was 3.3 minutes. All measurements were

161 performed in duplicate.

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163 *2.6 Dissolution test conditions*

164 Drug dissolution profiles for the 3D printed tablets were obtained with a USP-II apparatus
165 (Model PTWS, Pharmatest, Germany). 1) the formulations were placed in 750 mL of 0.1 M
166 HCl for 2 h to simulate gastric residence time, and then 2) transferred into 950 mL of modified
167 Hanks (mHanks) bicarbonate physiological medium for 35 min (pH 5.6 to 7); 3) and then in
168 modified Krebs buffer (1000ml) (pH 7 to 7.4 and then to 6.5). The modified Hanks buffer
169 based dissolution medium (Liu et al., 2011) (136.9 mM NaCl, 5.37 mM KCl, 0.812 mM
170 $MgSO_4.7H_2O$, 1.26 mM $CaCl_2$, 0.337 mM $Na_2HPO_4.2H_2O$, 0.441 mM KH_2PO_4, 4.17 mM
171 $NaHCO_3$) forms an in-situ modified Kreb's buffer (Fadda et al., 2009) by addition of 50 mL of
172 pre-Krebs solution (400.7 mM $NaHCO_3$ and 6.9 mM KH_2PO_4) to each dissolution vessel.

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174 The formulations were tested in the small intestinal environment for 3.5 h (pH 5.6 to 7.4); this
175 was followed by pH 6.5, which represents the colonic environment. These parameters were
176 selected to simulate typical conditions for intestinal transit of pharmaceutical formulations and
177 pH values in different segments of the GI tract in fasted individuals. The buffer capacity and
178 ionic composition of the physiological bicarbonate buffers also closely match the buffer
179 capacities of the intestinal fluids collected from different parts of the gut in humans (Fadda et
180 al., 2009; Goyanes et al., 2015c; Goyanes et al., 2015d; Liu et al., 2011; Varum et al., 2013).

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182 The medium is primarily a bicarbonate buffer in which bicarbonate (HCO_3^-) and carbonic acid
183 (H_2CO_3) co-exist in an equilibrium, along with CO_2 (aq) resulting from dissociation of the
184 carbonic acid. The pH of the buffer system can be decreased by purging CO_2 (g) in the
185 solution, which promotes the formation of carbonic acid. Similarly, an inert gas (such as
186 helium), which removes the dissolved CO_2 from the solution, increases the pH of the medium.
187 The purging of gases is controlled by an Auto pH System™ (Merchant et al., 2014), which
188 consists of a pH probe connected to a source of carbon dioxide gas (pH-reducing gas), as
189 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 drug released from the formulations was determined using an in-line UV spectrophotometer (Cecil 2020, Cecil Instruments Ltd., Cambridge, UK) at the wavelength of 244nm for paracetamol or 302 nm for 4-ASA. Data were processed using Icalis software (Icalis Data Systems Ltd, Berkshire, UK).

3. Results and Discussion

Paracetamol and 4-ASA were readily dissolved in the photopolymer solution. The colour of the paracetamol solution was clear while the 4-ASA solution was light brown. A torus shape was selected for 3D printing due to its complexity compared with conventional discs, and because of its difficulty in manufacture by conventional production techniques, such as powder compaction. In addition, this design offers not only increased surface area over a conventional disc, but also a relatively constant surface area during dissolution (Hansson et al., 1988; Kim, 1995). The layer thickness was chosen as 0.1mm although this SLA printer could achieve the resolution of 0.025mm. The increased layer thickness could significantly decrease the printing time.

Drug loaded tablets were successfully fabricated for the first time with the SLA printer (Figures 1). 3D printed tablets showed the same colour of the initial photopolymer solution and uniformity in size (11.02 ± 0.02 mm diameter x 4.01 ± 0.01 mm height, with a central hole, 2.98 ± 0.04 mm diameter).

The theoretical drug loading of the formulations was selected as 5.9% (w/w) to avoid solubility issues of the drugs into the PEG/PEGDA systems. The loading of paracetamol and 4-ASA in 3DP tablets is similar to that in the photopolymer solution (Table 1). The minor decrease of drug recovery in the printed tablets compared to that in photopolymer solution could be because of the incomplete drug extraction from drug-polymer matrix. The drug loading in 3DP

tablets is similar to the theoretical drug loading, indicating no drug was degraded during the 3D printing process. This fact is especially relevant for 4-ASA since the degradation of 4-ASA using FDM 3D printing has been previously reported (Goyanes et al., 2015a). In that study approximately half the drug was degraded during extrusion through the heated nozzle of the printer. The results from the SLA printing suggest that fabrication of thermally labile drugs can be achieved. Drug loading could be easily calculated by determining the drug concentration of photopolymer solution because no drug loss occurs during the printing process. In contrast, when preparing the filaments for FDM printer, drug loading was sometimes lower than expected due to the adherence of powered drug to the walls of the containers during extrusion or irregular extrusion of components (Goyanes et al., 2015b). Another advantage over FDM 3DP is that the printing is a one-step method, without need of previous processes, just dissolution of the drug in the printing solution.

Table 1. Drug concentration in photopolymer solution and 3DP tablets

4-ASA formulations	4-ASA concentration in photopolymer solution (%, w/w)	4-ASA loading in 3DP tablets (%, w/w)	% Drug remaining after printing
90%PEGDA/10%PEG300	5.75 ± 0.03	5.28 ± 0.04	91.8
65%PEGDA/35%PEG300	5.76 ± 0.13	5.44 ± 0.04	94.4
35%PEGDA/65%PEG300	5.72 ± 0.19	5.48 ± 0.00	95.9
Mean	5.75 ± 0.12	5.40 ± 0.09	94.1
Paracetamol formulations	**Paracetamol concentration in photopolymer solution (%, w/w)**	**Paracetamol loading in 3DP tablets (%, w/w)**	**% Drug remaining after printing**
90%PEGDA/10%PEG300	6.17 ± 0.07	5.97 ± 0.02	96.6
65%PEGDA/35%PEG300	5.75 ± 0.14	5.56 ± 0.01	96.7
35%PEGDA/65%PEG300	5.83 ± 0.38	5.55 ± 0.11	95.1
Mean	5.92 ± 0.27	5.69 ± 0.22	96.1

XRPD data shows that both 4-ASA and paracetamol are in an amorphous state within the tablets, as no peaks appeared in the patterns of the formulations (Figure 2). The drug is completely dissolved in the photopolymer solution and according to these results there is no

crystallization of the drug during the photopolymerization process. The ESEM pictures of the cross section of the tablets confirm this extent and no crystals of drugs are observed (Figure 3). On the surface of the torus it is possible to observe the different layers formed to create the final object.

The 3D printed tablets were tested in the dynamic *in vitro* model, which simulates gastric and intestinal conditions of the GI tract (Goyanes et al., 2015d). The dissolution profiles of 4-ASA and paracetamol loaded tablets show that drug release commences in the gastric phase and continues during the intestinal phase for all formulations (Figures 4). The drug release is not affected by the pH of the media, indicating that the formulations are pH independent. These results differ from those reported by (Vehse et al., 2014) where drug release from matrix scaffolds 3D printed using the same technology was considerably faster. These different profiles could be explained on the composition of the 3D printed object and on the 3D design of the formulation.

Changes in the ratios of PEGDA/PEG 300 did play an important role in drug release rates. For paracetamol loaded tablets, formulations with a low percentage of PEGDA generally showed faster release rates. Almost 100% of paracetamol was released after 10 hours from the formulations containing 35% PEGDA, while only 84% and 76% release after 10 hours was measured for formulations containing 65% and 90% PEGDA, respectively. Similar trends were observed for the 4-ASA formulations. 4-ASA tablets with 35% PEGDA showed fastest release, with complete release within 9 hours. Interestingly, the 4-ASA formulations with 65% PEGDA and 90% PEGDA showed more similar drug release profiles. The reduction in the concentration of PEGDA probably increases the drug release rate because of a lower degree of cross-linking in the tablet matrix. PEG 300 itself cannot crosslink, so increasing the proportion of this polymer means greater molecular mobility in the tablet core and a greater likelihood of dissolution during testing. Images of the tablets before and after the dissolution test (after dried), show a reduction of the size of the tablets when the concentration of PEG 300 is high (Figure 5), indicating that the PEG300 gets released together with the drugs.

The dissolution data therefore suggest that controlled release could be achieved by selecting suitable concentration of each polymer in photopolymer solution, as a faster drug release can be obtained by reducing the percentage of PEGDA. Therefore, SLA printer also has a potential to design an immediate release dosage form by choosing the suitable PEGDA/PEG300 ratio.

4. Conclusions

Tablets containing 4-ASA and paracetamol were successfully produced with an SLA printer. This technology offers a simple, fast method to fabricate drug-loaded tablets with high resolution. Compared with FDM 3D printing, SLA printing reduces drug degradation and so offers an alternative route to produce tablets incorporating thermo-sensitive drugs.

Varying the percentage of crosslinkable polymers in the tablets modulates the drug dissolution profiles. Higher ratios of PEGDA reduce the dissolution rate while higher concentration of PEG 300 promotes drug release.

SLA 3D printing may be considered as an appropriate method to manufacture modified-release oral dosage forms, for industrial production or even for personalised dose.

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