3D printing of modified-release dosage forms loaded with aminosalicylates (4-ASA and 5-ASA)

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Abstract

The aim of this study was to explore the potential of fused-deposition 3-dimensional printing (FDM 3DP) to produce modified-release drug loaded tablets. Two isomers used in the treatment of inflammatory bowel disease (IBD), 5-aminosalicylic acid (5-ASA, mesalazine) and 4-aminosalicylic acid (4-ASA), were selected as model drugs. Commercially-produced polyvinyl alcohol (PVA) filaments were loaded with the drugs in an ethanolic drug solution. A final drug-loading of 0.06% w/w and 0.25% w/w was achieved for the 5-ASA and 4-ASA strands, respectively. 10.5 mm diameter tablets of both PVA/4-ASA and PVA/5-ASA were subsequently printed using an FDM 3D printer, and varying the weight and densities of the printed tablets was achieved by selecting the infill percentage in the printer software. The tablets were mechanically strong, and the FDM 3D printing was shown to be an effective process for the manufacture of the drug, 5-ASA. Significant thermal degradation of the active 4-ASA (50%) occurred during printing, however, indicating that the method may not be appropriate for drugs when printing at high temperatures exceeding those of the degradation point. The results of the dissolution tests conducted in modified Hank's buffer showed that release profiles for both drugs were dependent on both the drug itself and on the infill percentage of the tablet. Our work here demonstrates the potential role of FDM 3DP as an efficient and low-cost alternative method of manufacturing individually-tailored oral drug dosage, and also for production of modified-release formulations.

Key words

3D printing; controlled-release; fused deposition modeling; PVA; 4-ASA; 5-ASA; mesalamine; mesalazine; bicarbonate buffer

Introduction

Personalized, or individualized, medicinal products offer a number of advantages to patients worldwide. Not only do they reduce the incidence of adverse effects by tailored avoidance of over- or under-dosing individual patients as well as potentially increasing the ease of delivery, but also in improving adherence to therapy by providing a greater focus on one-to-one clinical management. Underpinned by recent technological advancements, there is a growing emphasis on realizing the value of developing such dosage forms by the pharmaceutical industry. Indeed, such value is not merely limited to tailoring individual doses *per se*, but in expanding the field to involve use of novel manufacturing techniques producing limited numbers of dosage forms either at the point of dispensing, or even at the point of use by the patient. To this end, one example of a novel manufacturing technique is that of 3-dimensional printing (3DP), which has so far demonstrated use in applications printing solid oral dosage forms suitable for human consumption, and is widely regarded as revolutionary in the field of pharmaceutical technology [1-3]. 3DP could be seen as a natural evolution from the related and currently-investigated methods of ink-jet printing, though whose potential as a manufacturing method is more limited to the printing of drug solutions onto flat substrates [4, 5], such as oral wafers [6], or the obtaining of aqueous droplets [7, 8].

By contrast, 3DP allows for the fabrication of a three-dimensional solid object of virtually any shape from a digital model by building up repetitively layer-by-layer, the intended object to create the final solid form. In the context of manufacturing pharmaceutical dosage forms, different type of systems have so far been used in the manufacture of zero-order release tablets [9], implants [10-14], bilayer tablets [15] or fast-dissolving devices comprising powder contained in a polymeric shell [16, 17].

A more recent development in 3DP technology that is both cost-effective and allows for the fabrication of hollow objects and pharmaceutical-grade polymers is that which involves the application of fused-deposition modelling (FDM), whereby a polymer is heated and extruded through a small tip of between 50-100 μm, and thereafter solidifies on a build plate. This allows for more precise control of droplet size, drug release and reproducibility, and therefore potentially for the personalization of drug therapy. However, this concept has yet to be formally evaluated as a means of manufacturing drug-loaded unit dosage forms.

The application of the FDM technology to simplify the manufacturing process and improve on the inherent properties and delivery of dosage forms may show clinically relevant significance for specific diseases, whereas some issues as the influence of

the printing temperature and the selection of the polymers on the stability of the drugs to be printed must be firstly evaluated.

For the purpose of this study we have selected two aminosalicylates as model drugs. Aminosalicylates are first-line therapies of the many drugs used in the treatment of inflammatory bowel disease (IBD). 5-aminosalicylic acid (5-ASA) - the most commonly used- is considered to be the most efficacious of the aminosalicylates, and is consequently widely prescribed. A second aminosalicylate drug – 4-aminosalicylic acid (4-ASA) which is more commonly employed as an anti-tuberculosis agent rather than one included in treatment strategies for IBD – was also investigated. The chemical structure of 4-ASA is only distinguished from 5-ASA by the position of its NH2 group (Figure 1), though this small variation is sufficient to affect all of the biological activity of the isomers, their melting points, and their respective solubilities, though their molecular weights are otherwise identical (153.13g/mol).

The specific aims of this work were to evaluate the feasibility of printing tablets loaded with the drugs 4-ASA and 5-ASA using an FDM 3DP, and to explore whether varying the print settings allows for control over the dissolution kinetics of the final tablet, thereby offering a new method of manufacturing controlled-release dosage forms. The drug stability during the 3D printing process and the drug release performance in the biorrelevant media modified Hank's buffer (bicarbonate buffer) were also evaluated.

Materials and Methods

Materials

Filament:

Polyvinyl alcohol (PVA, a water-soluble synthetic polymer represented by the formula $(C_2H_4O)_n$) was purchased as an extruded filament (1.75mm diameter, print temperature 190-220°C, batch No: 2013-10-18, Makerbot Inc., USA).

Drugs:

5-aminosalicylic acid (5-ASA) was obtained from PharmaZell GmbH, Raubling, Germany, water-solubility 840 mg/mL [18] and 4-aminosalicylic acid (4-ASA) was purchased from VWR International Ltd., Poole, UK, water solubility 1690 mg/L [19]

Absolute ethanol of analytical grade and salts for preparing buffer dissolution media were acquired from VWR International Ltd., Poole, UK.

Methods

Preparation of PVA filament loaded with drug: 15g of the commercially available filament of PVA (~5 m) were immersed in a 100mL beaker containing 50 mL of ethanol where 500mg of the drug (5-ASA or 4-ASA) were dispersed. The saturated ethanolic dispersions of the drug with the filaments were covered with parafilm to avoid the evaporation of the ethanol and kept under magnetic stirring for 24h. The drug-loaded filaments were then place on a tray, dried in an oven at 60°C to constant weight (approximately for 1.5h) and finally stored in a vacuum desiccator. The drug-loading of the filaments was determined by HPLC analysis (below).

Printing of 5-ASA and 4-ASA tablets: Tablets were fabricated with the previously drug-loaded filaments using a commercial fused-deposition modelling 3D printer, MakerBot Replicator 2 Desktop 3D printer (MakerBot Inc, USA). The templates used to print the tablets were designed with MakerWare Software (v. 2.2.2). The selected size for the tablet was X=10.54mm, Y=10.45mm and Z=3.79mm, as the size of an average table. The printer settings that were found to produce the best tablets for both drugs were: standard resolution with the raft option activated and an extrusion temperature of 210 °C, speed while extruding (90mm/s), speed while traveling (150mm/s), number of shells (2) and layer height (0.20mm). The infill percentage was varied (10%, 50% or 90%) in order to produce tablets of different characteristics (Table 1 and Figure 2).

Thermal characterization of the model drugs, filament and the drug-loaded filaments:

Differential scanning calorimetry (DSC)

Measurements were performed on Q2000 DSC (TA instruments, Waters, LLC, USA) with 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 50ml/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 were reported as extrapolated onset unless otherwise stated. TA aluminum pans and lids (Tzero) were used with an average sample size of 8-10mg.

Thermogravimetrical analysis (TGA)

Samples were heated at 10°C/min in open aluminium pans using TA Instruments 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.

Characterization of the tablets:

Determination of tablet morphology

Dimensions of the tablets (diameter and thickness) were measured using a digital calliper. Pictures of the tablets were taken with a Nikon CoolpixS6150 with the macro option of the menu.

Determination of tablet hardness

The hardness (Crushing strength) of ten tablets 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 tablet fractures. The units of force employed to quantify breaking force were Newtons.

Determination of tablet friability

Approximately 6.5 g of tablets were weighed and placed into the drum of a Friability Tester Erweka type TAR 10 (Erweka GmbH, Heusenstamm, Germany). The drum was then rotated at 25 rpm for 4 min and the sample re-weighed. The friability of the sample is given in terms of weight loss, expressed as a percentage of the original sample weight.

Determination of drug loading

A tablet or a section of drug-loaded strand before printing (approx. 0.3g) were placed in a 1L volumetric flask containing deionized (DI) water under magnetic stirring until complete dissolution. Samples for analysis were then filtered through 0.45 µm filters (Millipore Ltd, Ireland) and concentration of drug was determined by HPLC (n=2).

Concentrations of 4-ASA in the samples were measured by HPLC-UV (Hewlett Packard 1050 Series HPLC system, Agilent Technologies, UK). The validated high performance liquid chromatographic assay entailed pumping a mobile phase, consisting of acetonitrile (24%), water (76%) and orthophosphoric acid (900 µL/L),

through a Discovery HSF5 column (4.6 x 150 mm) 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 303 nm. Samples for analysis were injected (20 μL) onto a reverse phase (5 μm particle size) column (Supelco, Pennsylvania, USA).

Concentrations of 5-ASA were determined by injecting 20 μL sample onto a HPLC-UV (Hewlett Packard 1050 Series HPLC system, Agilent Technologies, UK). The validated high performance liquid chromatographic assay entailed pumping a mobile phase, consisting of methanol (5%), water (95%) and trifluoroacetic acid (500 μL/L), through a reverse phase column: 5 μm particle size, 4.6 x 150 mm, Discovery HSF5 (Supelco, Pennsylvania, USA). The mobile phase was pumped at 40 °C at a flow rate of 1 mL/min and the eluent was screened at a wavelength of 228 nm.

Dissolution testing

Drug release profiles from the 3DP tablets were obtained using a USP-II apparatus (Model PTWS, Pharmatest, Germany). In each assay, the tablets were placed at the bottom of the vessel and were stirred (50 rpm) in dissolution medium (900 mL) at 37°C. Tests were conducted in triplicate under sink conditions. During the dissolution test, samples of 4-ASA were automatically removed and filtered through 0.1mm filters and drug concentration was determined using an in-line UV spectrophotometer (Cecil 2020, Cecil Instruments Ltd., Cambridge, UK) operated at 302 nm. Data were processed using Icalis software (Icalis Data Systems Ltd, Berkshire, UK). In the case of 5-ASA, drug concentration was determined using the HPLC method described previously due to the low absorbance of the drug and interference with the polymer.

Tablets were tested in a modified bicarbonate buffer (pH 6.8) controlled by an Auto pH System™ [20]. Bicarbonate buffer was chosen because of its better resemblance to the physiological characteristics of gastrointestinal fluid (pH, ionic composition and buffer capacity) [21]. The medium, adapted from Hank's buffer, is primarily a bicarbonate buffer, in which bicarbonate (HCO_3^-) and carbonic acid (H_2CO_3) co-exist in equilibrium, along with dissolved CO_2. Adjusting the concentration of carbonic acid (H_2CO_3) and bicarbonate (HCO_3^-) allows control of the buffer pH. Purging the solution with carbon dioxide, which promotes the formation of carbonic acid, decreases the pH. Similarly, purging with an inert gas (such as Helium) which removes dissolved CO_2 from the solution reduces the carbonic acid to bicarbonate ratio, increases the pH. The purging of gases is regulated by an Auto pH System™, automatically triggered by a pH feedback from the solution. Controlling the pH of the medium to pH

6.8 simulates the pH conditions of the small intestine. Additionally, other components are added to simulate the ionic strength and composition of gastrointestinal fluid (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 $NaHCO_3$, CO_2 quantity sufficient to maintain the pH at 6.8).

Results and discussion

The manufacture of solid dosage forms incorporating 4-ASA or 5-ASA by FDM 3DP fabrication was performed by use of a commercially-extruded PVA polymer.

The PVA filaments are the only water-soluble commercially-available filaments used in 3D printing to date. They are generally used to print sections of plastic devices that can be lately removed by placing the object in water. Here the PVA filaments used were loaded from an ethanolic rather than aqueous solution, the latter of which was shown to result in undesirable and rapid dissolution of the PVA filament during trial attempts. The drug (4-ASA or 5-ASA) loaded into the pre-extruded PVA polymer followed a method identical to the loading of hydrogels: In this way, the polymer filament was placed in the drug solution before being removed and dried. Based on the assumption that no chemical interaction occurs between the drug and polymer, the drug passively diffuses into the polymer matrix and is trapped following the drying phase. This ensures that the diameter of the polymer filament remains constant, and is therefore easily extruded by the printer. The method is also cheap, versatile and requires little development other than selection of a suitable solvent.

Final drug-loading in the strands were relatively low, however, at 0.24% w/w for 4-ASA and four-fold lower at 0.06 w/w for 5-ASA.The more reduced drug-loading for 5-ASA is likely due to the near-insolubility in ethanol as compared to the ethanol-soluble 4-ASA [22]. This fact reveals the importance of the selection of the solvent of the drug solution and could open paths to optimize drug loading into the strands.

Analysis of the 4-ASA content of 3D printed tablets showed a reduction in drug content to 0.12% w/w, indicating that around half the drug was thermally degraded as it passed through the heated extruder of the printer (210 ºC). This is likely due to the fact that 4-ASA melts and decomposes at temperatures between 130-145ºC as shown by TGA and DSC data obtained for 4-ASA (Fig. 3).

Indeed, selection of this drug enabled us to determine that there is a significant drug degradation when printing at temperatures higher than that of the decomposition

temperature of the drug, even though the residence time in the print head might be small (on the order of seconds). By comparison, printed tablets of the more thermally stable 5-ASA did not show any reduction in drug content during the printing process, attributable to the fact that the printing temperature (210 ºC) is lower than that of the degradation point of 5-ASA. Analysis of TGA and DSC (Fig. 3) confirm that 5-ASA is stable up to 230°C as 1.5% weight loss is shown and it starts to melt/degrade around 278-279°C.

In this case, we have probed that the use of FDM 3D printer is suitable for fabricating tablets of those drugs with melting points distinct (higher and lower) from the temperature required for the 3D printing process. The results, however, suggest that the method may not be appropriate for fabrication of solid dosage forms with drugs when printing at temperatures higher than that of the degradation temperature of the drug.

The thermal analysis of the PVA indicates that the filament melts around 180°C (Fig. 4) and the weight loss of around 4%w/w shown in the TGA curve before its melting point is most likely because of water evaporation. A separate experiment in the TGA where PVA was held isothermally at 100°C resulted in a weight loss of about 4% water. The degradation of PVA appears to occur just after melting starts and up to 260°C only ~3.5% is degraded. The DSC thermograms of drug-loaded filaments indicate both drugs interacting with PVA upon heating as reflected by the change in shape of the melting endotherm of PVA. As 5-ASA has a higher melting point than that of filament, it is most likely to dissolve in the molten PVA. 4-ASA has a much lower melting point and possibly its degradation while the PVA is melting is affecting the latter's melting process.

Some technological approaches could enable overcoming the inconveniences of printing at temperatures higher than the degradation temperature of the drug, for instances in the future the use of other polymer filaments with melting temperatures below the melting point of the drug.

The tablet template *per se* was imported into the Makerware software prior to printing as a stereolithography (.stl) file, which only encodes the surface data of the object to be printed and requires the thickness of the surface to be defined in order to print the desired object(s). The effect of varying the infill percentage on the physical characteristics of the tablets (size and weight) and on the drug release were also investigated to determine the impact on these parameters, and hence to allow for manufacture optimization. The infill percentage which controls both the density and mechanical strength of the object can be set during the printing process or adjusted

311 in order to modulate physical properties of the resulting object; if no infill is printed,
312 the resulting object will be hollow. Through such modulation, and by varying these
313 parameters, the dissolution profile of the tablets printed can also be altered: Herein,
314 tablets were printed with three different infill percentages (10, 50 and 90%). It can be
315 seen from Table 1 and the photographs in Figure 2 that the tablet weights expectedly
316 increased with an increasing infill percentage. The size of the tablets remains almost
317 constant (the tablet thickness increases slightly while increasing the infill), with
318 resulting tablets demonstrating high reproducibility in physical dimensions, along with
319 high mechanical strength resistant to damage on handling.
320 The characteristics of these 3D tablets make that some parameters usually
321 measured in tablets manufactured with tableting machines reveals unnecessary. For
322 example the friability of all the formulations was 0%, showing that the 3D tablets are
323 more than suitable for technological process as coating, handling or packaging.
324 The hardness data show values between 330 and 390N for the tablets of 10 % infill
325 and close to 485 N for those with higher % infill. The obtained values of harness of
326 the tablets do not actually represent crushing strength, since the tablet does not
327 break. The values obtained from the 10% infill tablets correspond with the value of
328 deformation of the tablet; for tablets with higher % infill, the values represent approx.
329 the maximum value measured by the tablet hardness tester.
330
331 Dissolution testing of both 4–ASA and 5-ASA printed tablets was subsequently
332 conducted in Hank's bicarbonate buffer (pH 6.8), given that bicarbonate buffers are
333 considered to be more closely representative of human small intestinal fluid than
334 phosphate or other compendial buffer systems [23, 24]. Patterns of drug release
335 were shown to differ according to the drug formulated and the infill percentage
336 (Figure 5): For 5-ASA, the dissolution profiles were identical during the first hour of
337 testing, with 50% drug release and the total drug release reached in less than 4
338 hours for all formulations. However, faster drug release was observed from those
339 formulations tested featuring a lower infill percentage.
340 The dissolution profiles of 4-ASA tablets by contrast were more dependent on the
341 infill percentage of the tablets. Here, 10% infill tablets showed complete release after
342 4 hours dissolution, but both the 50 and 90% infill tablets showed burst release
343 followed by slow release, indicating that a greater infill percentage was responsible
344 for slowing the rate of drug release. The dissolutions data thus confirm that it is
345 indeed possible to modulate the dissolution profile of 3DP tablets by careful selection
346 of the printing parameters, given that a faster drug release can be obtained lowering
347 the infill percentage. Gupta et al [25] showed that the swelling ratio of PVA hydrogels

was dependent on polymer concentration, with higher concentrations resulting in reduced swelling ratios. As such, it is this effect which may be controlling the release profiles of both 4-ASA and 5-ASA from the printed tablets. A reduction of the size of the formulations during the dissolutions tests is observed, suggesting that erosion processes may be involved in the mechanisms responsible for drug release from this 3D printed formulations, though on the other hand our results here show also the significance of the model drug's role on the drug release profile.

Conclusion

Here, we have formulated and produced tablets containing the drugs 4-ASA and 5-ASA via a 3D printing method with varying infill percentages, demonstrating the feasibility of using FDM 3DP to fabricate drug-loaded tablets.

The FDM 3D printing can be considered as an effective process for the production of tablets incorporating drugs such 5-ASA. On the other hand, the substantial degradation of the drug 4-ASA (50%) during the 3D printing process suggests that the method may not be appropriate, however, for the manufacture of drugs when printing at temperatures higher than that of the drug degradation temperature. The high extrusion temperature (210 ºC) needed to print with PVA strands is a potential drawback, whereas the use of other polymer filaments may enable to print at temperatures below the decomposition temperature of the drug to avoid the degradation.

Moreover, we have also demonstrated considerable differences of dissolution profiles in the biorrelevant media modified Hank's buffer (bicarbonate buffer) for the two isomers (4-ASA and 5-ASA) manufactured by this approach, highlighting the importance of drug selection on the release profile. Furthermore, we have shown that the release profiles obtained can be also modified by selection of the printing parameters. The infill percentage modulates the dissolution profile and a faster drug release can be obtained lowering the infill percentage of the tablets.

This initial study, indeed, demonstrates the feasibility of fabricating personalized medicines and modified-release dosage forms by FDM 3DP, despite of the low doses of both 4-ASA and 5-ASA.Further developments and refinements in the field will enable this promising approach to become a bona fide method of producing personalized medicines.

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Figure Caption

Figure 1. Chemical structure of 5-ASA (left) and 4-ASA (right)

Figure 2: Images of the 3DP fabricated tablets as a function of infill percentage

Figure 3. TGA and DSC plots for A) 4-ASA and B) 5-ASA.

Figure 4. TGA and DSC plots for A) PVA filament B) 4-ASA-loaded filament and C) 5-ASA-loaded filament.

Figure 5: Dissolution profiles of 3DP tablets with varying infill percentages in modified Hank's buffer (pH 6.8)