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Fabrication of Extended-Release Patient-Tailored Prednisolone Tablets via Fused Deposition Modelling (FDM) 3D Printing

Justyna Skowrya^{1,2}, Katarzyna Pietrzak^{1,3}, Mohamed A Alhnan^{1*}

¹ School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, Lancashire, UK

² Faculty of Pharmacy with the Laboratory Medicine Division, Medical University of Warsaw, Warsaw, Poland

³ Faculty of Pharmacy, Medical University of Lodz, Lodz, Poland

*Corresponding author: MAIbedAlhnan@uclan.ac.uk

1. Introduction

Personalized medications focussed on efficient diagnostic genetics as well as flexible drug delivery and targeting (Holmes et al., 2009). A patient-tailored formulation additionally includes flexible dose manufacturing techniques that allow accurate and dynamic change of dose in response to patient needs. Such an approach may become of significance when a wide range of dose or active pharmaceutical ingredient (API) with narrow therapeutic window is included in the patient's therapeutic plan. In addition, financial pressure on healthcare systems has encouraged trends of reducing the number of inpatients through providing efficient outpatient services such as Telehealthcare (McKinstry et al., 2009; McLean et al., 2013). It is therefore of great interest to provide an efficient and safe patient-tailored, dose-controlling system for outpatients which can be remotely and digitally controlled by a healthcare provider.

As oral tablets remain the most popular dosage form for patients, there is an increasing demand for a versatile and highly adjustable production method of tablets. Traditional methods of tablet manufacture typically require the use of large batches, multiple production steps, designated and expensive facilities and experienced operators. The high cost of this approach combined with its rigid nature rendered it less suitable a means for preparing personalised medicine (Khaled et al., 2014). Ideally, for a production method to address the new challenges of personalised medicine, it should be i) highly adjustable, ii) affordable, iii) of minimal space requirements, iv) controllable by network and v) safe.

Several computer-controlled 3D printing approaches have been developed to produce oral tablets as an alternative to conventional tableting. The design was based on a laying powder bed followed by the deposition of a binder solution from the print-head in a multilayer three dimensional fashion (Katstra et al., 2000; Yu et al., 2009; Yu et al., 2007). The proposed technology provided rapid dissolving (Yu et al., 2007), extended release (Yu et al., 2009) and multi-phase delayed release patterns (Rowe et al., 2000). However, the process required a high level of powder flow control, moisture content control, and was limited by the choice of binder. Marked improvement could be achieved when considering the accuracy of dosing, aesthetic quality of the tablet and the thickness of layer deposition (Sandler et al., 2014a). More recently, a bench top 3D printer was utilized to fabricate a bilayer tablet with immediate

and extended release pattern (Khaled et al., 2014). However, the slow solidification and shrinking of the gel model affected the shape of the finished tablets.

Fused deposition modelling (FDM) is a widely implemented method for 3D printing of solid objects (Lim, 2010). The expiration of patents of this technology is likely to lead to wide utilization of the 3D printing by a large number of consumers at a relatively low cost. The process uses pre-prepared thermoplastic polymeric filament (typically with a diameter of 1.75 mm) as an 'ink' and passes it through a high temperature nozzle where it is heated to a semi-liquid state. The software-controlled nozzle deposits the heated material in layer-by-layer pattern to form a 3D structure with a typical thickness of 100-300 μ m. In a rare example, Masood (2007) investigated the influence of compactness of a 3D printed model tablets and the inter-filament space on dye penetration through the printed tablets. More recently, Sandler et al. (2014b) demonstrated the fabrication of an anti-biofilm medical device using a 3D printer and antibacterial loaded PVA filaments. Goyanes et al. (2014) investigated the influence of changing the degree of infill percentage on fluorescein release from cylindrical matrix. However, limited research is available on the use of FDM in the fabrication of dosage forms as well as the accuracy of weight and dosage of this manufacturing technique.

The aim of this work is to investigate the feasibility of producing extended-release prednisolone tablets as well as controlling the dose via digital manipulation of the printed volume. Poly(vinyl alcohol) (PVA) is biodegradable and widely used in the pharmaceutical field as an extended release matrix for oral delivery (Carstensen et al., 1981), transdermal patches (Wan and Lim, 1992) as well as mucoadhesive and viscosity enhancer for ocular preparations (Davies et al., 1991; Wilson et al., 1983). The availability of PVA as a filament for 3D printer enabled its use as a model polymer in this study.

2. Materials and Methods

2.1. Materials

Prednisolone was purchased from Severn Biotech Ltd (Kidderminster, UK). Polyvinyl alcohol (PVA) filaments (melting point 160-170 $^{\circ}$ C, specific heat 0.4 Cal/g $^{\circ}$ C, Density 1.25–1.35 g/cm 3) were purchased from Reprapcentral (UK). Glycerol, acetonitrile and methanol were supplied

by British Drug Houses (BDH, London, UK). Scotch blue painter's tape 50 mm was supplied by 3M (Bracknell, UK).

2.2. Preparation of prednisolone loaded PVA filament

PVA filaments were loaded with prednisolone via incubation in a saturated solution of prednisolone in methanol at 30 °C for 24 hours. After which, the filaments were dried in over at 40°C and weighed every 1 hour until a stable weight obtained. To assess loading efficiency, three representative samples of PVA (100mg) were incubated in 100 ml of 1:1 methanol: water mixture under sonication for 2 hours and were assessed using HPLC as detailed in section 2.5. The loading percentage of the filament was calculated as shown in equation 1.

$$\text{Loading Percentage (S)} = 100 \times \frac{\text{Mass of prednisolone}}{\text{Total mass of filament}} \quad \text{Equation 1}$$

2.3. Tablet design and printing process

Blank and drug loaded PVA tablets were designed in an ellipse shape using Autodesk® 3ds Max® Design 2012 software version 14.0 (Autodesk, Inc., USA) and saved in STL format (Figs.1a and 1b). The design was imported to the 3D printer's software, MakerWare Version 2.4.0.17 (Makerbot Industries, LLC., USA) (Fig.1). A series of tablets with increasing volumes were printed by modifying the dimensions of the design: length x width x heights (L, H, W) without altering the ratios between these dimensions ($W = H = 0.4 L$). The volume of the design (V) was calculated as:

$$V = \pi \frac{L}{2} \frac{W}{2} H = 0.04 \pi L^3 \quad \text{Equation 2}$$

In order to make a correlation between the volume of the design and the mass of the printed tablet (M), a series of tablets of increased volume was printed and accurately weighed. A linear equation describing this relationship was established:

$$M = 1.0322 V + 24.898 \quad \text{Equation 3}$$

since the target dose D (mg) is calculated as:

$$D = M.S/100 \quad \text{Equation 4}$$

where M is the mass of the tablet and S is the percentage of loading filament. Therefore, the required dimension (L) to achieve a target dose (D) from filament with loading percentage (S) can be calculated as:

$$L = \sqrt[3]{25 \frac{\left(\frac{100 D}{S}\right) - 24.898}{1.0322 \pi}} \quad \text{Equation 5}$$

A series of tablets were printed according to equation 5 to achieve a target dose of 2, 3, 4, 5, 7.5 or 10 mg. Table 1 illustrated the details of dimensions, expected and measured mass of these tablets.

2.4. Modification of 3D printer

A MakerBot Replicator® 2X Experimental 3D Printer (MakerBot Industries, New York, USA) was utilized to print blank PVA tablets. Blank tablets (PVA only) were printed using default settings of the software for PLA filament as follows: type of printer: Replicator 2X; type of filament: PLA; resolution: standard; temperature of nozzle: 230°C; temperature of building plate: 20 °C; speed of extruder 90 mm/s while extruding and 150 mm/s while traveling; infill: 100%; height of the layer: 200 µm. No supports or rafts were utilized in the printed model.

In order to be able to print prednisolone loaded PVA tablets, the following modifications were implemented:

- i) Kapton tape layer (default) provided poor adhesion of the designs to the built plate. Blue Scotch painter's tape was applied to the surface of the printing board to improve adhesion to the surface layer.
- ii) The filament passed through a plasticizer station containing glycerol before entering the heating nozzle.
- iii) Increasing extruder temperature during printing from 230 °C to 250 °C was essential to maintain constant flow of prednisolone loaded PVA filament.

2.5. Determination of drug content

In order to assess prednisolone content in drug loaded filaments and the printed tablets, each tablet (or 100 mg of filament) was accurately weighed and transferred to a 500 ml volumetric flask. Tablets were incubated for 1 hour in 150 ml of distilled water under sonication followed by completing the volume with methanol to 500 ml, and subsequent sonication for an additional 4 hours at 50 °C. After cooling to room temperature, samples were filtered through a 0.22 µm Millex-GP syringe filter (Merck Millipore, USA) and prepared for HPLC analysis.

Prednisolone concentration was determined through HPLC analysis method using an Agilent HPLC 1260 series (Agilent Technologies, Inc., Germany) equipped with Kinetex C18 column (100 x 2.1 mm, particle size 2.6 µm) (Phenomenex, Torrance, USA). The mobile phase (water: acetonitrile) was used in gradient concentrations: (60:40 at time 0, 40:60 at time 8-12 min and 60:40 at time 12.01-14 min) at a flow rate of 0.5 ml/min. The injection volume was set at 40 µl and the UV detector employed an absorbance wavelength of 250 nm. Temperature of the column was maintained at 45 °C and stop time for each sample was 14 min.

2.6. Scanning Electron Microscopy

The surface morphology of the PVA filament, extruded filament from the nozzle of the 3D printer as well as the printed tablet was assessed using a Quanta-200 SEM microscope at 20 kV. Samples were placed on metallic stubs and gold coated under vacuum for 2 min using JFC-1200 Fine Coater (Jeol, Tokyo, Japan), prior to imaging.

2.7. X-Ray Powder Diffraction

A powder X-ray diffractometer, D2 Phaser with Lynxeye (Bruker, Germany) was used to assess the crystallinity of prednisolone in the drug loaded tablets. Samples were scanned from 2 Theta = 5° to 50° using a scan type coupled with a two theta/theta scintillation counter over 30 min.

2.8. Differential Scanning Microscopy

A Mettler Toledo DSC823e DSC (Mettler, Switzerland) was utilized to perform thermal analysis. Samples of approximately 5 mg were accurately weighed and placed in a 40 µL

standard aluminium pan DSC analysis. Analysis was carried on under a nitrogen environment (50 mL/min). In order to exclude the effect of humidity, samples were heated to 100 °C for 5 min then cooled to -20 °C at a rate of 10 °C/min. This was followed by a heat scan from -20 °C to 300 °C at a rate of 10 °C/min. All measurements were carried out in triplicates.

2.9. *In Vitro* drug release study via flow-through dissolution

A flow-through cell (Sotax, Switzerland) dissolution apparatus with an open loop system was utilized to assess drug release pattern from the 3D printed tablets. The dissolution apparatus was connected to piston pumps and a fraction collector (Sotax, Switzerland). Cells of 12 mm diameter containing 5 mm glass beads were utilized during the study. Filtration was conducted using 25 mm glass microfiber filter discs (FG/B) (Whatman, US) which were placed above the cells. The prednisolone loaded tablets were analysed using dissolution media of a pH 1.2 (HCl 0.1M) for 2 hours followed by phosphate buffer (pH 6.8) for additional 22 hours at 37± 0.5°C. The flow rate was 8ml/min and samples were collected to Sotax fraction collector at time intervals 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 15, 18, 21 and 24 hours. Samples were further filtered through 0.22 µm Millex-GP syringe filter (Merck Millipore, USA) and analysed by HPLC (section 2.5). Three tablets of each strength were assessed.

3. Results and discussion

Ellipse shaped tablets were printed using an FDM 3D printer loaded with original PVA (drug free) filament. When a series of PVA tablet with increasing dimensions were printed, a high level of correlation was identified between the theoretical volume of the tablet design and the mass of the printed tablets ($R^2 = 0.9996$). This indicated the ability of FDM 3D printing method to achieve a sufficient control of the mass of the printed tablets. Such ability is a key advantage for developing a mini-manufacturing unit that can tailor tablet mass by manipulating the volume of the design through an input on software.

In order to investigate the ability of the printed tablet to contain a given dose of API and control its release, a model drug needed to be incorporated into PVA filament before loading it in the nozzle of the 3D printer. Prednisolone was chosen as a model drug due to its high thermal stability and neutral nature. A simple loading process based on incubation in methanolic solution was developed. The yielded prednisolone loaded filament showed a drug loading of approximately 1.9% w/w. The choice of methanol as a loading solution was based on its ability to dissolve the drug and swell PVA without dissolving or damaging the physical integrity of the original filament. Other solvents such as ethanol and acetone were found to have a degrading effect on the PVA filament or a poor loading efficiency respectively and were deemed unsuitable for the loading process.

When a similar series of tablets were printed with prednisolone loaded PVA filament (Table 1), the correlation between theoretical volume and the mass of the printed tablet was maintained ($R^2 = 0.9983$, Equation 2). This signified the potential of FDM 3D printer to manufacture a solid tablet with accurate dose, responding to an individual patient's need when minute increment of dosing is required. The finishing quality of prednisolone loaded tablets was observed to be similar to blank tablets (made with PVA filaments as received) indicating the possibility of adapting a different print setting to suit particular filament composition (Fig. 1c).

The morphology of the PVA filament before and after undergoing fused depositing modelling was investigated via SEM imaging. Images of prednisolone loaded PVA filaments (1.75mm) showed a smooth surface of the filament (Fig. 2). However, upon extrusion through the 3D printer nozzle at an elevated temperature, the surface of extruded filaments (200µm)

appeared to be generally rough with irregular pores and voids between layers, this may be due to the rapid evaporation of water content and evaporable additives upon exposure to high temperature.

SEM images of surface of prednisolone loaded PVA indicated an irregular and rough surface with partially fused filament (Fig. 2). The side of the tablet showed overlaid layers of filament with an approximate height of 200 μm . When the inner surface of a 50% printed tablet was assessed, the directions of the fused filament were distinct between the peripheral and central domains (Fig.3). This might be related to a widely used filling pattern of fused filaments dictated by a software (commonly referred to as slicing engine), where a shell structure is built to outline the outer surface of the design whilst the central space can be either a consistent filling or with one or more empty compartments.

To establish the ability of such 3D printing method to control dosage, theoretical doses based on tablet mass and measured dose of prednisolone in the tablet were compared (Fig. 4). The range of dose accuracy was between $88.70\% \pm 0.79$ for 10 mg tablet and $107.71\% \pm 9.96$ for 3 mg tablet (Table 2). The coefficient of determination between target and achieved dose ($R^2 = 0.9905$) showed that it is possible to fabricate tablets with desired dose of prednisolone through volume modification. The technology holds the potential of digitally controlling a patient's dose via simple software input. It can also be assumed that degradation of prednisolone in the nozzle under elevated temperature was minor due to the thermal stability of prednisolone at 250 $^{\circ}\text{C}$ (Palanisamy and Khanam, 2011) and the relative short exposure time of filament in the nozzle (extrusion speed of 90 mm/s).

The physical form of prednisolone within the 3D printed tablets was investigated using thermal and diffractometry methods. Thermal analysis (DSC) showed prednisolone crystals to have a peak at 203 $^{\circ}\text{C}$ corresponding to the melting point of prednisolone (Fig. 5). The prednisolone loaded tablet showed a glass transition temperature (T_g) of 45 $^{\circ}\text{C}$ whereas PVA filament appeared to have a T_g of 35 $^{\circ}\text{C}$. It was expected that the T_g of prednisolone loaded tablet to be lower than PVA filament due to the plasticizing effect of prednisolone. Such an increase in the T_g could be attributed to loss of plasticizer(s) in the PVA during incubation in methanol for drug loading. The absence of such an endothermic peak of prednisolone in drug

loaded tablets suggested that the majority of prednisolone is in amorphous form within the PVA matrix.

On the other hand, XRPD indicated typical peaks of prednisolone at $2\theta = 8.7, 14.7$ and 18.6 (Fig. 6) (Nishiwaki et al., 2009). The absence of such peaks in prednisolone loaded tablets suggested that the majority of prednisolone exists in amorphous form. Both blank PVA filament and drug loaded PVA tablets showed peaks at $2\theta = 9.3^\circ, 18.7^\circ$ and 28.5° . Such peaks may be related to the semi-crystalline structure of PVA (Gupta et al., 2011). As the exact PVA filament composition was not disclosed by the manufacturer, it was not possible to attribute these peaks.

In vitro release pattern of prednisolone from 3D printed PVA tablets was studied via a pH-change flow-through cell dissolution system. Fig. 7 indicated that prednisolone tablets with different weights exhibited a similar *in vitro* release profile. The majority of drug release (>80%) took place after 12 hours for 2 and 3 mg tablets and over 18 hours for tablets with doses of 4, 5, 7.5 and 10 mg. Approximately 100% of prednisolone release was attained within 16 hours for tablets with 2 and 3 mg drug loading. The faster release of prednisolone from the smaller size tablets is likely to be related to their larger surface area/mass ratio which promotes both drug diffusion and the erosion of PVA matrix. By the end of the dissolution test (24 hours), it was visually evident that the tablet had completely eroded within the flow-through cell. Several studies reported PVA to form a hydrogel system where drug release is governed by an erosion mechanism (Vaddiraju et al., 2012; Westedt et al., 2006).

In summary we have reported a significant adaptation of a bench top FDM 3D printer for pharmaceutical applications. The resultant tablets were solid structures with a regular ellipse shape and adjustable weight/dose through software control of the design's volume. This fabrication method is applicable to other solid and semisolid dosage forms such as implants and dermal patches.

4. Conclusion

FDM based 3D printing was adapted to engineer and control the dose of extended release tablets. Prednisolone loaded PVA filament demonstrated the ability to be printed into ellipse shaped tablets using 3D printer. The mass of a printed tablet was digitally controlled by manipulating the design's volume through computer software. The precision of dose control ranged between 88.7%-107%. Thermal analysis and XRPD suggested that the majority of prednisolone exists in amorphous form within the PVA matrix while prednisolone release from a 3D printed tablet was extended over 24 hours. In principle, FDM 3D printers can be exploited as a platform to construct flexible dose tablets from purpose-built drug-containing filaments.

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List of tables

Table 1 The target dose, dimensions, theoretical volume, theoretical and measured mass of prednisolone loaded PVA tablets

Table 2 The target dose, filament drug loading, theoretical and measured dose, and dose accuracy of prednisolone loaded PVA tablets

List of figures

Fig. 1 a) Design of 3D printed tablets b) rendered image of tablet as viewed in MakerWare, c) Blank (top) and prednisolone loaded (bottom) PVA based tablets

Fig. 2 SEM images of a) surface view and b) cross section of PVA filament, and PVA after extrusion from nozzle of fused deposition modelling based 3D printer: c) 1000 μm magnification d) 50 μm magnification

Fig. 3 SEM images of a) side surface, b) top surface and c) inner side of 50% accomplished prednisolone loaded PVA tablet.

Fig. 4 Relationship between target and achieved dose of prednisolone loaded tablets.

Fig. 5 DSC thermograph of prednisolone, PVA filament and prednisolone loaded PVA tablet

Fig. 6 XRPD spectra of prednisolone, PVA filament and prednisolone loaded PVA tablet

Fig. 7 *In vitro* release pattern of prednisolone from 3D printed PVA tablets using pH-change flow-through dissolution system

Table 1: The target dose, dimensions, theoretical volume, theoretical and measured mass of prednisolone loaded PVA tablets

Tablet target dose (mg)	Dimensions (L x W x H) (mm)	Tablet theoretical volume (mm³)	Tablet theoretical mass (mg)	Tablet measured mass (mg)± SD
2	8.39x3.36x3.36	74.23	101.52	102± 1.73
3	10.11x4.04x4.04	129.66	158.73	168.30±1.43
4	11.29x4.52x4.52	180.92	211.64	216.18±1.01
5	12.34x4.94x4.94	236.31	268.82	283.44±5.03
7.5	14.00x5.60x5.60	344.71	380.71	396.67±4.93
10	15.50x6.20x6.20	467.66	507.61	498.67±5.69

Table 2: The target dose, filament drug loading, theoretical and measured dose, and dose accuracy of prednisolone loaded PVA tablets

Tablet target dose (mg)	Filament drug loading (%)	Theoretical dose (mg) ±SD	Measured dose (mg) ±SD	Dose accuracy (%) ±SD	CV (%)
2	1.97	2.01±0.03	1.98±0.10	98.67±3.43	3.48
3	1.89	3.18±0.03	3.43±0.34	107.71 ± 9.96	9.25
4	1.89	4.09±0.02	4.37±0.11	107.06±2.98	2.79
5	1.86	5.27±0.09	5.27±0.22	99.95±2.51	2.51
7.5	1.97	7.81±0.10	6.99±0.22	89.49±2.37	2.65
10	1.97	9.82±0.11	8.71±0.17	88.70±0.79	0.89

— Prednisolone — PVA filament — Prednisolone loaded PVA tablet