European Journal of Pharmaceutical Sciences 68 (2015) 11–17

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing

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ARTICLE INFO

Article history:
Received 11 October 2014
Received in revised form 17 November 2014
Accepted 18 November 2014
Available online 25 November 2014

Keywords:
Rapid prototyping
Fused filament fabrication
FFF
Personalized
Patient-specific
3D printer

ABSTRACT

Rapid and reliable tailoring of the dose of controlled release tablets to suit an individual patient is a major challenge for personalized medicine. The aim of this work was to investigate the feasibility of using a fused deposition modelling (FDM) based 3D printer to fabricate extended release tablet using prednisolone loaded poly(vinyl alcohol) (PVA) filaments and to control its dose. Prednisolone was loaded into a PVA-based (1.75 mm) filament at approximately 1.9% w/w via incubation in a saturated methanolic solution of prednisolone. The physical form of the drug was assessed using differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD). Dose accuracy and *in vitro* drug release patterns were assessed using HPLC and pH change flow-through dissolution test.

Prednisolone loaded PVA filament demonstrated an ability to be fabricated into regular ellipse-shaped solid tablets using the FDM-based 3D printer. It was possible to control the mass of printed tablet through manipulating the volume of the design (R^2 = 0.9983). On printing tablets with target drug contents of 2, 3, 4, 5, 7.5 and 10 mg, a good correlation between target and achieved dose was obtained (R^2 = 0.9904) with a dose accuracy range of 88.7–107%. Thermal analysis and XRPD indicated that the majority of prednisolone existed in amorphous form within the tablets. *In vitro* drug release from 3D printed tablets was extended up to 24 h.

FDM based 3D printing is a promising method to produce and control the dose of extended release tablets, providing a highly adjustable, affordable, minimally sized, digitally controlled platform for producing patient-tailored medicines.

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 personalized medicine (Khaled et al., 2014). Ideally, for a production method to address the new challenges of personalized 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

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http://dx.doi.org/10.1016/j.ejps.2014.11.009
0928-0987/

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 μm. 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 availably 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 °C, specific heat 0.4 Cal/g °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 3 M (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 h. After which, the filaments were dried in over at 40 °C and weighed every 1 h until a stable weight obtained. To assess loading efficiency, three representative samples of PVA (100 mg) were incubated in 100 ml of 1:1 methanol: water mixture under sonication for 2 h and were assessed using HPLC as detailed in Section 2.5. The loading percentage of the filament was calculated as shown in Eq. (1).

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

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 (Fig. 1a and b). 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 × width × 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:

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

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:

$$M = 1.0322\,V + 24.898 \quad (3)$$

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

$$D = M.S/100 \quad (4)$$

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:

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

A series of tablets were printed according to Eq. (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. Scotch Blue 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.