International Journal of Pharmaceutics 527 (2017) 21–30

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

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

Alvaro Goyanes[a], Fabrizio Fina[b], Annalisa Martorana[b], Daniel Sedough[b], Simon Gaisford[a,b], Abdul W. Basit[a,b,*]

[a] FabRx Ltd., 3 Romney Road, Ashford, Kent, TN24 0RW, UK
[b] UCL School of Pharmacy, University College London,29-39 Brunswick Square, London, WC1N 1AX, UK

ARTICLE INFO

Article history:
Received 28 March 2017
Received in revised form 7 May 2017
Accepted 9 May 2017
Available online 11 May 2017

Keywords:
Three dimensional printing
Controlled-release
Fused deposition modeling
Paracetamol
Acetaminophen
Additive manufacturing
Personalized medicines
Additive manufacture
Rapid prototyping

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 > HPMCAS MG > HPMCAS 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.

1. 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, 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, 2015a).

* Corresponding author at: UCL School of Pharmacy, University College London,29-39 Brunswick Square, London, WC1N 1AX, UK
E-mail address: a.basit@ucl.ac.uk (A.W. Basit).

http://dx.doi.org/10.1016/j.ijpharm.2017.05.021
0378-5173/

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, 2015a; Skowyra et al., 2015), medical devices (Genina et al., 2015) and wound dressings (Hassan et al., 2017).

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

2.1. 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 37 °C: 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.

2.2. Methods

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

For each batch, 40 g 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.

2.2.2. 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

Table 1
Composition of the filaments.

Filament	Filament composition				Hot Melt Extrusion temperature (°C)
	Drug	Polymer	Plasticizer	Lubricant	
HPMCAS LG 5	5% Paracetamol	75% HPMCAS LG	15% Methylparaben	5% magnesium stearate	80
HPMCAS MG 5	5% Paracetamol	75% HPMCAS MG	15% Methylparaben	5% magnesium stearate	80
HPMCAS HG 5	5% Paracetamol	75% HPMCAS HG	15% Methylparaben	5% magnesium stearate	80
HPMCAS LG 50	50% Paracetamol	40% HPMCAS LG	5% Methylparaben	5% magnesium stearate	110
HPMCAS MG 50	50% Paracetamol	40% HPMCAS MG	5% Methylparaben	5% magnesium stearate	100
HPMCAS HG 50	50% Paracetamol	40% HPMCAS HG	5% Methylparaben	5% magnesium stearate	110