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Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing

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ABSTRACT

The aim of this work was to explore the feasibility of using fused deposition modelling (FDM) 3D printing (3DP) technology with hot melt extrusion (HME) and fluid bed coating to fabricate modified-release budesonide dosage forms. Budesonide was sucessfully loaded into polyvinyl alcohol filaments using HME. The filaments were engineered into capsule-shaped tablets (caplets) containing 9 mg budesonide using a FDM 3D printer; the caplets were then overcoated with a layer of enteric polymer. The final printed formulation was tested in a dynamic dissolution bicarbonate buffer system, and two commercial budesonide products, Cortiment® (Uceris®) and Entocort®, were also investigated for comparison. Budesonide release from the Entocort® formulation was rapid in conditions of the upper small intestine while release from the Cortiment® product was more delayed and very slow. In contrast, the new 3D printed caplet formulation started to release in the mid-small intestine but release then continued in a sustained manner throughout the distal intestine and colon. This work has demonstrated the potential of combining FDM 3DP with established pharmaceutical processes, including HME and film coating, to fabricate modified release oral dosage forms.

1. Introduction

3-dimensional printing (3DP) technology is being explored as a viable method of personalizing medicines at the point of use (Sanderson, 2015). Indeed, 3DP has the potential to circumvent formulation challenges associated with myriad drugs, including those with narrow therapeutic indices to those whose metabolism is influenced by genetic polymorphisms. In addition it facilitates the development of formulations incorporating more than one drug (Goyanes et al., 2015e). Such approaches could arguably revolutionize clinical management in practice, helping to improve medicine compliance and to achieve better therapeutic outcomes.

The first equipment used to prepare 3D printed medicines was based on powder bed—liquid 3D printing technology (Katstra et al., 2000; Rowe et al., 2000; Yu et al., 2009). This technology uses liquids to bind multiple layers of powder to create the desired geometry. The limited choice of binder solutions together with the need for high powder flow and moisture content control are some of the drawbacks that limit the use of these 3D printer types. However, in 2015, the first 3D printed formulation (Spritam®), based on powder bed—liquid 3D printing technology (ZipDose®), was approved by the FDA (Aprecia_Pharmaceuticals, 2015). Spritam® (levetiracetam) is a fast dissolving tablet formulation indicated for the treatment of epileptic seizures. This new product exemplifies the opportunities for the use of 3DP technologies to manufacture medicines at industrial scale, in addition to personalized therapy at the point of use.

Fused-deposition modeling (FDM) is a more recent 3DP approach, in which an extruded polymer filament is passed through a heated tip. The heat softens the polymer, which is then deposited onto a build plate to harden. Layers of the deposited and hardened polymer are then built up to create an object in three dimensions. This printing method can fabricate hollow objects as well as dosage forms with different drug release profiles; the latter is achieved by altering either the infill percentage (Goyanes et al., 2014) or surface area/volume ratio of the formulations (Goyanes et al., 2015d). FDM 3DP has higher resolution in comparison with previous printing methods, and can, therefore, achieve better dosing accuracy that is also easily adjusted by changing parameters in the computer software.

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The method of loading polyvinyl alcohol (PVA) polymer filaments with drug prior to printing has relied on the need for alcoholic solutions containing the active drug (Goyanes et al., 2014, 2015a; Skowyra et al., 2015), in which filaments are incubated overnight, but because of the passive nature of the process, it is only possible to achieve low drug loadings.

One means of overcoming this problem lies in the use of hot-melt extrusion (HME) to obtain drug-loaded PVA filaments (Goyanes et al., 2015d). In the pharmaceutical industry, HME is the process by which a rotating screw is used to pump drugs and/or excipients at elevated temperatures through a die to generate a product of uniform shape. HME is used to incorporate drugs within a matrix at a molecular level to form solid solutions/dispersions for drug delivery systems such as pellets and granules (Breitenbach, 2002; Mehuys et al., 2005; Schilling et al., 2010). Moreover, HME can reduce the number of processing steps in dosage form manufacturing, and can be automated as a continuous process to give better drug homogeneity.

In this study, the synthetic corticosteroid budesonide was selected as the model drug. Budesonide possesses strong affinity for corticosteroid receptors and features both potent topical anti-inflammatory effects (Gionchetti et al., 2014) and low systemic bioavailability. It is often used in the treatment of inflammatory bowel disease (IBD) (McConnell et al., 2009). Specifically in IBD, modifying budesonide release is a particularly desirable goal for the purposes of increasing its duration of action, achieving optimal therapeutic levels and reducing associated systemic side effects through targeting specific regions of disease activity in the gut. This is achieved mainly by the use of pH-dependent coatings applied to tablets or pellets, though there are significant differences in drug release and distribution between the commercial formulations (Goyanes et al., 2015b).

Here, we aimed to create a new budesonide dosage form, combining FDM 3DP with HME and fluid bed coating, to achieve appropriate dissolution kinetics. The suitability of the HME process to produce budesonide 3D-printable filaments was assessed, along with the potential of this method as a valid manufacturing process. The performance of the 3D printed formulation was evaluated and compared with two commercial pH dependent budesonide formulations (Cortiment® 9 mg and Entocort® CR 3 mg) in a dynamic physiological *in vitro* dissolution model of the human gastrointestinal tract.

2. Materials and methods

2.1. Materials

Polyvinyl alcohol (PVA), a water-soluble synthetic polymer with a molecular formula of $(C_2H_4O)_n$), was purchased as an extruded commercial filament from Makerbot Inc., USA (1.75 mm diameter, print temperature 190–220 °C).

Budesonide powder of micronized grade was obtained from Sigma–Aldrich, UK (molecular weight: 430.53 g/mol (Fig. 1); BCS class II, aqueous solubility 0.0215 mg/mL (Yalkowsky and He, 2003)).

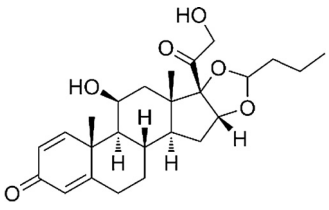

Fig. 1. Chemical structure of budesonide.

Eudragit® L100 (pH threshold of 6) was acquired from Evonik, Darmstadt, Germany, Triethyl citrate (TEC) and talc were purchased from Sigma–Aldrich, UK. Isopropanol supplied were of analytical grade. Salts for preparing buffer dissolution were purchased from VWR International Ltd., Poole, UK.

Commercial medicines tested in this study were as follows:

- Cortiment® 9 mg, prolonged release tablets (Ferring Pharmaceuticals, UK) (commercialized as Uceris® in the US) is tablet formulation with sustained release hydrophilic/lipophilic matrix core known as Multi Matrix System (MMX®) and an outer coating comprising methacrylic acid – methyl methacrylate copolymer (1:1) (Eudragit® L) and methacrylic acid – methyl methacrylate copolymer (1:2) (Eudragit® S) (eMC-Cortiment, 2015).
- Entocort® CR 3 mg capsules (AstraZeneca UK Limited, UK). Hard gelatine capsules for oral administration containing budesonide 3 mg as gastro-resistant prolonged-release granules. Granules coated with ethylcellulose and an outer layer of methacrylic acid-methyl methacrylate copolymer (1:1) (Eudragit® L); the enteric polymer has a dissolution pH threshold of 5.5 (Edsbacker and Andersson, 2004).

2.2. Methods

2.2.1. Preparation of PVA filament loaded with budesonide

The commercial PVA filament was cut into small cylindrical pellets (~2 mm) using a Pharma 11 Varicut Pelletizer (Thermo Fisher Scientific, UK). A commercial grinder (Wahl ZX789, Wahl store, UK) was used to produce a fine PVA powder with a small particle size which was then sifted through a sieve with a mesh size of 1000 μm. Budesonide (2 g, 5% drug w/w) was manually mixed in together with the PVA powder (38 g) using a mortar and pestle. The mixture was then extruded using a single-screw extruder (Noztek Pro filament extruder, NozteK, UK) at 170 °C through a nozzle with diameter 1.75 mm at screw speed of 15 rpm. The resulting filament was stored in a vacuum desiccator before printing. Budesonide loading in the filaments was determined by HPLC analysis.

2.2.2. 3D printing of budesonide dosage forms

Dosage forms were fabricated with the drug-loaded filament using a standard fused-deposition modelling 3D printer, MakerBot Replicator 2X Desktop (MakerBot Inc., USA). The template used to print the dosage form was designed with AutoCAD 2014® (Autodesk Inc., USA) and exported as a stereolithography (.stl) file into MakerWare v. 2.4.1 (MakerBot Inc., USA). The selected geometry of the dosage forms was a rounded hard capsule-shaped

Fig. 2. Caplet design.

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