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Fabricating 3D printed orally disintegrating printlets using selective laser sintering

Fabrizio Fina[a], Christine M. Madla[a], Alvaro Goyanes[b,*], Jiaxin Zhang[a], Simon Gaisford[a,b], Abdul W. Basit[a,b,*]

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

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ABSTRACT

Selective laser sintering (SLS) is a three-dimensional printing (3DP) technology employed to manufacture plastic, metallic or ceramic objects. The aim of this study was to demonstrate the feasibility of using SLS to fabricate novel solid dosage forms with accelerated drug release properties, and with a view to create orally disintegrating formulations. Two polymers (hydroxypropyl methylcellulose (HPMC E5) and vinylpyrrolidone-vinyl acetate copolymer (Kollidon® VA 64)) were separately mixed with 5% paracetamol (used as a model drug) and 3% Candurin® Gold Sheen colorant; the powder mixes were subjected to SLS printing, resulting in the manufacture of printlets (3DP tablets). Modulating the SLS printing parameters altered the release characteristics of the printlets, with faster laser scanning speeds accelerating drug release from the HPMC formulations. The same trend was observed for the Kollidon® based printlets. At a laser scanning speed of 300 mm/s, the Kollidon® printlets exhibited orally disintegrating characteristics by completely dispersing in < 4 s in a small volume of water. X-ray micro-CT analysis of these printlets indicated a reduction in their density and an increase in open porosity, therefore, confirming the unique disintegration behaviour of these formulations. The work reported here is the first to demonstrate the feasibility of SLS 3DP to fabricate printlets with accelerated drug release and orally disintegrating properties. This investigation has confirmed that SLS is amenable to the pharmaceutical research of modern medicine manufacture.

1. Introduction

For the majority of therapeutic agents used to induce systemic effects, the oral route is still considered to be the most preferred method of administration, owing to its high patient compliance when compared to other available routes (Bhagat et al., 2017; Rathbone et al., 2015). However, oral administration in the form of tablets, capsules and liquid dosage forms is a disadvantage for specific patient groups. Dysphagia represents a significant challenge, specifically for geriatric and paediatric populations, and patients who are uncooperative. This, therefore, can affect medication adherence and result in increased morbidity and mortality rates (Carnaby-Mann and Crary, 2005). The shift towards the development of patient-centric dosage forms, however, has led to the emergence of novel technologies such as orally disintegrating tablets (ODTs). Rapid drug intervention and increased bioavailability and absorption can be achieved following the contact of an ODT with saliva, or a small volume of water in the oral cavity (Draskovic et al., 2017; Parkash et al., 2011). According to the European Pharmacopoeia, ODTs are dosage forms that disintegrate in < 3 min (Pharmacopoeia, 2005). The Food and Drug Administration (FDA), however, characterise ODTs as dosage forms that completely dissolve within 30 s (CDER, 2008). ODTs, therefore, are not limited to those experiencing dysphagia, but rather, are an alternative method for those seeking a quick and easy method of administration, capable of being taken without a glass of water.

ODT formulations are normally characterised by their low density, low crushing strength and high porosity. Separate strategies are further required in the manufacturing process to produce mechanically resistant ODTs without compromising the disintegration times (Al-khattawi and Mohammed, 2013). Conventional methods of manufacturing ODT formulations include direct compression, spray drying, freeze drying and tablet moulding. Some of these methods, however, show some disadvantages with respect to manufacturing costs, complexity and limitations in low drug loadings (Aslani and Beigi, 2016; Nagar et al., 2011). In addition, in order to prepare an ODT product, a meticulous choice of excipients in drug development is critical in the

* Corresponding authors at: Department of Pharmaceutics, UCL School of Pharmacy, University College London, 29-39 Brunswick Square, London WC1N 1AX, UK (A.W. Basit).
E-mail addresses: a.goyanes@FabRx.co.uk (A. Goyanes), a.basit@ucl.ac.uk (A.W. Basit).

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determination of product characteristics, namely mechanical strength, stability, taste and mouth feel and disintegration time (Al-Khattawi et al., 2014).

Despite the significant technological advancements in the 21st century, innovation in pharmaceutical manufacturing techniques has fundamentally remained unchanged for around 200 years. Three-dimensional printing (3DP) is an additive manufacturing technology and is a revolutionary technique for the fabrication of personalised dosing and dimension-specific dosage forms (Goyanes et al., 2017a; Goyanes et al., 2017b; Trenfield et al., 2018). Thus, 3DP has the potential to cause a revolutionary shift in medicine manufacture.

Spritam® is the first and only FDA-approved medicine manufactured by 3D powder-bed (PB) printing (Zieverink, 2016). With this method, the final product is fabricated by a printer head that selectively deposits a liquid binder across a powder mixture of commonly used ODT excipients and the active pharmaceutical ingredient (API) in a layer-by-layer approach. Spritam®, is in fact, an ODT formulation of levetiracetam that rapidly disintegrates in the oral cavity between 2 and 27 s following administration with a sip of water (ApreciaPharmaceuticals, 2016).

A promising 3DP technology that is explored here for its feasibility in the printing of solid dosage forms with accelerated release characteristics is selective laser sintering (SLS). SLS is an industrial additive manufacturing technique that uses a powder bed to fabricate a 3D structure. However, instead of a liquid binder, SLS uses a laser to sinter powder particles together and completes a 3D object layer-by-layer. SLS offers multiple advantages over PB due to its solvent-free process and high turnover rate (Fina et al., 2017). The starting materials usually employed in SLS are powdered forms of plastics, ceramics and metal alloys that require high temperatures for the sintering process to be successful. It is known that these harsh printing conditions have deterred the introduction of SLS to the pharmaceutical field as the high-energy lasers may impair drug characteristics (Alhnan et al., 2016; Yu et al., 2008). However, we have identified that SLS is, indeed, capable of fabricating 3D printed tablets (known as Printlets™). Our previous study has demonstrated that, following the use of thermoplastic pharmaceutical grade polymers, three different drug loadings of paracetamol (up to 35%) were successfully printed (Fina et al., 2017).

The aim of this study was to investigate if SLS 3D printing can be used to fabricate solid printlets with accelerated drug release characteristics and orally disintegrating properties.

2. Materials and methods

Paracetamol USP grade (Sigma-Aldrich, UK) was used as a model drug (MW 151.16, solubility at 37 °C: 21.80 g/L. HPMC (hydroxypropyl methylcellulose) Vivapharm E5 was acquired from JRS PHARMA, Germany. Kollidon® VA 64 is a vinylpyrrolidone-vinyl acetate copolymer, kindly donated by BASF, UK. Candurin® Gold Sheen was purchased from Azelis, UK. The salts for preparing the buffer dissolution media were purchased from VWR International Ltd., UK.

2.1. Printing process

For all the formulations, 100 g of a mixture of drug and excipients were blended using a mortar and pestle (Table 1). 3% of Candurin® Gold Sheen was added to the formulations to enhance energy absorption from the laser and aid printability. Powder mixtures were then transferred to a Desktop SLS printer (Sintratec Kit, AG, Brugg, Switzerland) to fabricate the oral dosage formulations. AutoCAD 2014 (Autodesk Inc., USA) was used to design the templates of the cylindrical printlets (10 mm diameter × 3.6 mm height). 3D models were exported as a stereolithography (.stl) file into 3D printer Sintratec central software Version 1.1.13.

Powder in the platform reservoir (150 × 150 × 150 mm) of the printer was moved by a sled to a building platform (150 × 150 × 150 mm) creating a flat and homogeneously distributed layer of powder. The surface printing temperatures for HMPC and Kollidon® formulations were 135 °C and 100 °C, respectively. The 2.3 W blue diode laser (445 nm) was activated to sinter the powder on to the building platform in a certain pattern based on the .STL file. At this point, the reservoir platform moved up, the building platform moved down, and the sled distributed a thin layer of powder on top of the previous layer. This process was repeated layer-by-layer until the object was completed. Printlets were then removed from the powder bed and the excess powder was brushed off. Ten printlets of each formulation were printed at the same time.

Table 1
Printlet polymer content and printing parameters.

Formulation[a]	HPMC (% content)	Kollidon® (% content)	Chamber temperature (°C)	Surface temperature (°C)	Laser scanning speed (mm/s)
H100	92	–	115	135	100
H200	92	–	115	135	200
H300	92	–	115	135	300
K100	–	92	80	100	100
K200	–	92	80	100	200
K300	–	92	80	100	300

[a] All formulations contain 3% w/w Candurin® Gold Sheen and 5% paracetamol.

2.2. Thermal analysis

Differential scanning calorimetry (DSC) was used to characterise the powders and the drug loaded printlets. DSC measurements were performed with a Q2000 DSC (TA instruments, Waters, LLC, USA) at a 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 50 mL/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 are reported as extrapolated onset unless otherwise stated. TA aluminium pans and lids (Tzero) were used with an average sample mass of 8–10 mg.

2.3. X-ray powder diffraction (XRPD)

Discs of 23 mm diameter × 1 mm height made from the mixtures of drug and excipients were 3D printed and analysed. Samples of pure paracetamol and the mixtures were also analysed. The X-ray powder diffraction patterns were obtained in a Rigaku MiniFlex 600 (Rigaku, USA) using a Cu Kα X-ray source (λ = 1.5418 Å). The intensity and voltage applied were 15 mA and 40 kV. The angular range of data acquisition was 3–60° 2θ, with a stepwise size of 0.02° at a speed of 5°/min.

2.4. Characterisation of the printlets

2.4.1. Determination of printlet morphology

The diameter and thickness of the printlets were measured using a digital calliper. Images were taken with a Sony α6300 digital camera.

2.4.2. Determination of the mechanical properties of the printlets

The printlet breaking force of 6 printlets 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 printlet fractures.