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Fabrication of drug-loaded hydrogels with stereolithographic 3D printing

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ABSTRACT

3D printing (3DP) technologies have been attracting much recent interest as new methods of fabricating medicines and medical devices. Of the many types of 3DP available, stereolithographic (SLA) printing offers the unique advantage of being able to fabricate objects by cross-linking resins to form networked polymer matrices. Because water can be entrapped in these matrices, it is possible in principle to fabricate pre-wetted, drug-loaded hydrogels and devices. Here, SLA printing was used to prepare ibuprofen-loaded hydrogels of cross-linked polyethylene glycol diacrylate. Hydrogels containing up to 30% w/w water, and 10% w/w ibuprofen, were successfully printed. Dissolution profiles showed that drug release rates were dependent on water content, with higher water content hydrogels releasing drug faster. The conclusion is that SLA 3DP offers a new manufacturing route to pharmaceutical hydrogels.

1. Introduction

Tablets (first patented in 1843) and two-piece capsules (first patented in 1846) have dominated formulation strategy for oral delivery since their invention; in part this is because both these dosage forms lend themselves to large-scale mass production. This reduces unit cost but at the expense of dose flexibility and so most products are available in a limited number of dose strengths. However, the advent of newer, more potent actives with narrow therapeutic indices and the increasing drive towards personalisation of medicines (in terms of dose strength and/or drug combinations) (Alomari et al., 2015) are changing the landscape of pharmaceutical manufacturing and forcing the pharmaceutical industry to consider new methods of pharmaceutical production.

The recent development of 3D printing (3DP) technologies has resulted in a new era of additive manufacturing approaches in which material is deposited layer-by-layer to fabricate solid objects (Dimitrov et al., 2006). 3DP offers many qualities ideally suited to meet the challenges facing the pharmaceutical sector; small production runs, broad versatility in dose and/or drug combinations and the possibility to use a wide range of excipients to solubilise, target or control drug release (Goyanes et al., 2017a; Khaled et al., 2015; Rowe et al., 2000; Sadia et al., 2016).

The first 3DP technology for pharmaceuticals used an ink-jet printer to jet a liquid binder onto a powder bed, adhering particles together to form an agglomerated mass (Rowe et al., 2000; Wu et al., 1996). In this technology, objects are fabricated by stacking agglomerated layers on top of each other and tablets are comprised primarily of powders, so are compositionally similar to powder compacts, but have the advantage that they can be fast disintegrating (this is the approach used to make Spritam®, the first 3D printed tablet approved by the FDA). More recently another powder bed technology using a laser to sinter and agglomerate the powder has been reported, selective laser sintering (SLS) (Fina et al., 2017). An alternative technology, the use of fused-deposition modelling (FDM) for printing tablets has been demonstrated (Goyanes et al., 2014, 2015a, 2015b, 2015e) and acceptability of the medicines evaluated (Goyanes et al., 2017b). FDM 3DP is particularly suited to the use of polymeric excipients, as it uses extruded filaments as a primary feedstock, and so offers a manufacturing route to controlled-release 3D printed tablets (Printlets™). Being comprised of extruded filaments, FDM printlets have good porosity and high surface area and their drug release profiles are easily controlled by varying factors such as geometry, polymer selection and degree of infill during printing. One challenge for FDM 3DP currently is the limited choice of commercially available thermoplastic materials with good extrusion properties for printing; while it is possible to formulate polymer blends with good printable properties oneself, this adds complexity and an extra development step. Another is the significant risk of degrading thermally labile drugs during printing (Goyanes et al., 2016); in a previous study, approximately 50% of 4-ASA was degraded during 3D printing process (Goyanes et al., 2015a).

A third type of 3DP technology is stereolithography (SLA). In this approach, the 'printhead' is a laser beam, focused into a tank of liquid resin. The laser causes photopolymerisation of the resin, forming a

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cross-linked polymeric matrix and so production of a solid mass. Again, objects are fabricated by solidifying them in a layer-by-layer process. SLA 3DP has been widely used in the field of tissue engineering (Arcaute et al., 2010, 2006), tissue scaffolding (Kim et al., 2017; Lee et al., 2017) and more recently to make microparticles (Raman et al., 2016; Yang et al., 2015), but its use in fabricating unit doses for oral delivery is less common. Partly, this is because of the limited number of photo-crosslinkable monomers that are available, although over the last few years more systems have been developed, such as polyethylene glycol diacrylate (PEGDA) (Chan et al., 2010; Vehse et al., 2014), poly-2-hydroxyethyl methacrylate (pHEMA) (Hanson Shepherd et al., 2011), polyethylene glycol dimethacrylate (PEGDMA) (Arcaute et al., 2006; Dhariwala et al., 2004) and polypropylene fumarate-diethyl fumarate (PPF-DEF) (Fisher et al., 2002). One of the big advantages of SLA printing is that the active ingredient and/or any excipients can be incorporated into the resin as long as they are miscible. It does not matter whether the drug or excipients have photopolymerisable functional groups; upon cross-linking of the resin, any extra components simply become trapped in the polymeric matrix. This is a highly convenient method of drug loading/functionalization suggested more than 20 years ago by West and Hubbell (1995) and more recently demonstrated by Vehse et al. (2014), who incorporated aspirin in cross-linked PEGDA matrices, and Wang et al. (Wang et al., 2016) who printed modified-release printlets containing paracetamol or 4-ASA.

Where PEG-based resins are used, water may be incorporated prior to printing in the photopolymerisable solution, leading to the intriguing possibility of printing pre-wetted hydrogels (Wang et al., 2015). This approach has been used to make extracellular microenvironments for cancer research (Park and Gerecht, 2015) but has not to our knowledge been explored for fabricating drug-loaded dosage forms. Because the degree of cross-linking will be influenced by the ratio of diluent/water to resin and/or the concentration of cross-linking agents, drug-loaded hydrogels should in principle be capable of being manufactured with tunable drug-release profiles. However, one concern with the use of photo-polymerised systems is that a photo-initiator (PI) is required in the formulation. The PI, which converts to reactive radicals upon exposure to light to catalyse polymerization of the resin, may be present in relatively high concentrations and so there are concerns as to potential toxicity (Ng et al., 2006). In this work, we explore the use of SLA printing to fabricate controlled-release drug-loaded hydrogels using a pharmacologically non-toxic PI, riboflavin (vitamin B2). Riboflavin has been shown to be an effective PI in producing hydrogels of cross-linked dextran-methacrylate (Kim and Chu, 2009).

2. Materials & methods

Polyethylene glycol diacrylate (PEGDA, average MW 700), polyethylene glycol (PEG300, average MW 300), riboflavin, triethanolamine (TEA), diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (DPPO) and ibuprofen were purchased from Sigma Aldrich Ltd (UK). The salts for preparing the buffer dissolution media were purchased from VWR International Ltd., Poole, UK. All materials were used as received.

2.1. 3D printing

All printlets (3D printed tablets) were printed with a Formlabs 1 + SLA printer (Formlabs Inc, USA). The printer is equipped with a 405 nm laser and can fabricate objects with a resolution of 300 μm and a layer thickness of 25, 50, 100 or 200 μm. The template used to print the printlets (a cylinder, 10.5 mm diameter, 3.5 mm height) was designed with Autocad and exported as a stereolithographic file (.stl) into the 3D printer software (Preform Software v. 1.9.1, Formlabs, UK). PEGDA was used as the photopolymerisable monomer while PEG300 and water were used to alter the crosslinking density of the hydrogel. PEG300 was added to PEGDA in a ratio of 6:4 (v/v) and the water content of the formulations was varied. Two PI systems were used; DPPO (a commercially available PI which absorbs light between 380 and 425 nm (Arikawa et al., 2009) supplied by the manufacturer for cross-linking commercial printable resins), and riboflavin with triethanolamine (RT), riboflavin acting as the PI and triethanolamine as a coinitiator. Exact compositions of the formulations are given in Table 1. To print, a solution of PEGDA, PEG300 and water (where applicable) was mixed for 10 min, then ibuprofen (10% w/w) was added with constant stirring until complete dissolution. Riboflavin and triethanolamine or DPPO were added next, keeping the solution protected from light and with constant stirring until complete dissolution (approximately 25 min for riboflavin/triethanolanine and 8 h for DPPO). The mixture was then poured into the resin tray of the printer and printing initiated.

Table 1
Compositions (% w/w) of the initial resins used to print the hydrogels.

Name Comp.	DPPO	RT (no PEG)	RT	RT + 10% water	RT + 20% water	RT + 30% water
PEGDA	89.95	86.90	53.45	48.45	40.14	34.14
PEG300	0	0	33.45	28.45	20.76	22.76
Riboflavin	0	0.1	0.1	0.1	0.1	0.1
TEOHA	0	3	3	3	3	3
DPPO	0.05	0	0	0	0	0
Water	0	0	0	10	20	30
Ibuprofen	10	10	10	10	10	10

2.2. Physical properties

3D printed hydrogels were blotted with filter paper to remove any uncured liquid formulation on the surface right after fabrication, they were weighed and measured (width and height) using a digital calliper. The measurements were done in triplicate.

2.3. Determination of drug concentrations in the hydrogels

Printed hydrogels were crushed using a mortar and pestle with 50 mL of ethanol to enhance extraction of ibuprofen. The solution was diluted to 1 L with deionized water and kept with constant magnetic stirring for 24 h. Samples of the solutions were filtered through 0.45 μm filters (Millipore Ltd., Ireland) and the amount of drug in solution was determined using HPLC (Hewlett Packard 1050 Series HPLC system, Agilent Technologies, UK). The validated high performance liquid chromatographic assay consisted of a mobile phase of phosphate buffer, pH = 6.8 (65%) and acetonitrile (35%), pumped through an Eclipse 5 μm C18 column, 4.6 × 150 mm (Agilent) maintained at 30 °C at a flow rate of 0.7 mL/min. The eluent was screened at a wavelength of 222 nm. All measurements were made in duplicate.

2.4. Determination of swelling ratio (SR) and water content (WC)

3D-printed hydrogels were blotted with filter paper to remove any uncured liquid formulation on the surface immediately following fabrication, then they were weighed (W_i). The hydrogels were then placed into deionized water for 24 h, after which time the excess water was carefully wiped off and the hydrogels were weighed again (W_s). Hydrogels were also allowed to dry in an oven at 60 °C for 24 h to reach complete dryness (W_d). The SR and WC were calculated using the following equations:

$$SR = \frac{W_s}{W_i} \quad (1)$$

$$WC = \frac{W_i - W_d}{W_i} \times 100 \quad (2)$$