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3D printing of tablets using inkjet with UV photoinitiation

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ABSTRACT

Additive manufacturing (AM) offers significant potential benefits in the field of drug delivery and pharmaceutical/medical device manufacture. Of AM processes, 3D inkjet printing enables precise deposition of a formulation, whilst offering the potential for significant scale up or scale out as a manufacturing platform. This work hypothesizes that suitable solvent based ink formulations can be developed that allow the production of solid dosage forms that meet the standards required for pharmaceutical tablets, whilst offering a platform for flexible and personalized manufacture. We demonstrate this using piezo-activated inkjetting to 3D print ropinirole hydrochloride. The tablets produced consist of a cross-linked poly(ethylene glycol diacrylate) (PEGDA) hydrogel matrix containing the drug, photoinitiated in a low oxygen environment using an aqueous solution of Irgacure 2959. At a Ropinirole HCl loading of 0.41 mg, drug release from the tablet is shown to be Fickian. Raman and IR spectroscopy indicate a high degree of cross-linking and formation of an amorphous solid dispersion. This is the first publication of a UV inkjet 3D printed tablet. Consequently, this work opens the possibility for the translation of scalable, high precision and bespoke ink-jet based additive manufacturing to the pharmaceutical sector.

1. Introduction

With the Federal Drug Administration's (FDA) approval (FDA, 2015) of Spritam (the first commercially produced 3D printed medication, Aprecia Pharmaceuticals) there has been a further increase in interest in additive manufacturing (AM) based platforms to produce both personalized medicines and novel function (Alomari et al., 2015). Inkjet printing has been highlighted as a promising additive method due to its precision, accuracy, low cost, ability to deposit multiple materials contemporaneously, and simple scale up/out, with material throughput being dependant on the size of the printer and number of jets (Alomari et al., 2015; de Gans et al., 2004; Daly et al., 2015). It is a well-established tool for commercial and consumer image production, and has been incorporated into 3D printing methods for prototyping (O'Neil, 2012) and manufacture (FDA, 2015). For example, the manufacture of Spritam uses a binder jetting method whereby an aqueous binder solution is jetted onto a powder-bed (O'Neil, 2012; Rowe et al., 2000) in order to build high dose, porous 3D tablet structures which can rapidly disintegrate (FDA, 2015). Recent reports of inkjet printed medicines have been focused mainly on polymer melts and solutions, which are solidified by drying or cooling and require carrier substrates. Hence, the potential to rapidly produce free standing solid dosage forms using UV curable materials has yet to be explored in inkjet printing.

Drop on demand (DoD) printing is a non-contact print method which employs either piezoelectric or thermal mechanisms to eject a droplet from the printhead nozzle. In either method, a series of droplets are precisely deposited onto a substrate in order to produce two-dimensional images. Three-dimensional (3D) objects can be generated by sequentially printing/depositing successive two-dimensional (2D) images over multiple layers. However, materials availability for inkjet printing are limited, and efforts to broaden the materials range for biotechnology applications is an active area of AM research (Begines et al., 2016; He et al., 2016; Hart et al., 2016; Saunders and Derby, 2014; Gudapati et al., 2016).

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In addition to inkjet 3D printing, other 3D printing technologies have shown significant progress (Alhnan et al., 2016; Goyanes et al., 2015; Khaled et al., 2015a,b; Okwuosa et al., 2016; Sadia et al., 2016). Paste based extrusion printing (Khaled et al., 2015a,b) and fused deposition modelling (Goyanes et al., 2015; Okwuosa et al., 2016; Sadia et al., 2016) have demonstrated the potential of fabricating immediate and extended release dosage forms, as well as printing "polypills" which contain multiple actives (Goyanes et al., 2015; Khaled et al., 2015a,b), starting from approved pharmaceutical grade excipients.

Recent research in inkjet printed pharmaceuticals has focused on solutions (Alomari et al., 2015; Genina et al., 2013; Scoutaris et al., 2011; Sandler et al., 2011; Raijada et al., 2013; Lee et al., 2012; Acosta-Vélez et al., 2017), nanosuspensions (Pardeike et al., 2011), and melts (Içten et al., 2015; Zhu et al., 2013), each of which is primarily 2D. Reel to reel type flexographic (Raijada et al., 2013; Palo et al., 2015) printing, as well as inkjet printing in combination with electrospinning (Palo et al., 2017) have also been utilized. Sandler et al. investigated the release profiles and crystallization behaviour of inkjet-printed solutions of paracetamol, theophylline, and caffeine on edible films and porous paper (Sandler et al., 2011). Varan et al. has investigated the prolonged release behaviour of inkjet printed paxitaxel in a cyclodextrin inclusion complex and cidofovir encapsulated in polycaprolactone nanoparticles dispensed onto bioadhesive films (Varan et al., 2017). Low melting temperature PEG/naproxen mixtures (Içten et al., 2015; Zhu et al., 2013; Hsu et al., 2015) have been reported for melt based inkjet applications in which crystalline domains of the drug could be affected by PEG coatings (Hsu et al., 2015), or controlled melt cooling (Içten et al., 2015). Lee et al. successfully produced paxlitaxel loaded poly(lactic-*co*-glycolic acid) microparticles with various geometries (honeycombs, grids, rings and circles) and observed that the drug release rate was dependant on the surface area of the microparticles (Lee et al., 2012). However, these printing methods are limited in that the doses produced are films, often with an edible substrate incorporated into the dosage form. Evaporation of solvent, or cooling of the melt is also necessary in order to solidify the dose. A recent development is that of Acosta-Vélez et al. who reported a biocompatible and photocurable ropinirole HCl loaded ink which can be piezo printed, but requires a multistep process involving the manufacture of preformed 'tablets' into which the ink is deposited (Acosta-Vélez et al., 2017).

UV curing is widely used in the inkjet printing industry (Yeates et al., 2012) to rapidly solidify materials on demand. In this process the ink contains cross-linkable functional groups designed to be triggered by light, often with a photoinitiator promoting the process (Yeates et al., 2012). Similarly, photocross-linkable resins are used in stereolithography (SLA) printing, an AM process in which a vat of the resin is precisely cured by a laser in a layer by layer process to generate a 3D object. The suitability and mechanical properties of drug loaded UV curable inks have recently been evaluated for SLA based systems (Vehse et al., 2014; Wang et al., 2016) with major advantages being the capability to build scaffolds and complex (torus) tablet geometries with extended release profiles at ambient temperature (Wang et al., 2016). Despite the advantages, however, UV curable inkjet printable formulations have not been reported for the fabrication of solid dosage forms. Being able to combine 3D inkjet based printing with UV curing offers high resolution, rapid curing and the ability to alter geometry and material composition in a flexible, tuneable way. Furthermore, scale-up/out and speed-up of the process for commercial production has the potential to be achieved via increasing the number of jetting nozzles and/or printheads.

The scarcity of available photopolymerizable materials and high efficiency photoinitiators which are either generally regarded as safe (GRAS) or FDA approved makes UV ink formulation challenging. PEG is recognized by the FDA as an inactive tablet ingredient (Maximilien, 2009). PEG diacrylate is a network forming free radical addition type cross-linker that exhibits biocompatibility (Hoffman, 2002). However, residual unreacted monomer and macromer (Norman et al., 2017), as well as photoinitiator related decomposition products may be of concern in solid dosage forms depending on the concentrations released during dissolution (Williams et al., 2005; Xu et al., 2015). Ropinirole HCl (REQUIP ® GlaxoSmithKline Inc.), a dopamine agonist drug used in the treatment of Parkinson's and restless les syndrome, was chosen as an example drug in this study due to the range of oral doses commercially available. It is produced in immediate and extended release dosage forms ranging from 0.25 mg to 8.0 mg (GSK, 2015).

2. Materials and methods

2.1. Ink formulation

Inks were prepared with 0.50 wt% Irgacure 2959 photoinitator (BASF), 30 wt%, 2.00 wt% ropinirole HCl (Sequoia Research Products, >98%) and poly(ethylene glycol) diacrylate (PEGDA) (M = 700 g mol^{-1}, Sigma Aldrich), Irgacure 2959 was stirred into the PEGDA at elevated temperature (110 °C, 600 rpm) until dissolved. Water and the drug were then stirred into the solution (40 °C, 600 rpm) until dissolved. The ink was then degassed with nitrogen for 10 min and filtered the solution through a 0.45 mm pore size hydrophilic 13 mm diameter Millex PTFE filter (Sigma Aldrich) prior to cartridge loading. To block ambient light, which can prematurely cure the resin during ink formulation and printing, the ink vessel and cartridge were wrapped several times in silver duct tape. To minimize solvent loss during heating and degassing stages, the solution was sealed with a rubber septa cap. Base ink (i.e. API free) formulations, were prepared for control purposes and formulated with 2 wt% additional PEGDA in order to keep the water content constant. All materials were used as received.

2.2. Dynamic viscosity

In formulating the inks, the viscosity was measured and optimized using a Malvern Kinexus Rheometer (Worcester, UK) equipped with a cup and bob type sample geometry at (50 °C) at fixed shear rate (100 s^{-1}). All measurements were performed in triplicate.

2.3. Surface tension

The surface tension was determined with a Kruss DSA Drop shape analyser at 23 °C using the Pendant Drop Method. Ten drops were analysed for each ink.

2.4. Printing and processing parameters

The formulations were printed onto a poly(ethylene terephthalate) (PET) film substrate using a Dimatix Materials Printer (DMP-2830 Fujifilm, Lebanon, NH, USA). The printer was enclosed in a custom-built glove box and purged with nitrogen gas. O_2 levels were kept below 0.2% (2000 parts per million, ppm) throughout processing to reduce and control oxygen concentrations which can inhibit the curing transformations (i.e. initiation and propagation). The Dimatix Materials Cartridge (DMC-11610, Fujifilm Dimatix) contains 16 linearly aligned jets, spaced 254 μm apart with a ~10 pL drop volume. Curing of the material was carried out during printing with a LED UV lamp (365 nm, 600 mW cm^{-2}, Printed Electronics Limited, Tamworth, UK) bolted directly to the printhead mount and in-line with the print path at print cartridge