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Personalisation of warfarin therapy using thermal ink-jet printing

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ABSTRACT

Warfarin is a widely used anticoagulant that is critical in reducing patient morbidity and mortality associated with thromboembolic disorders. However, its narrow therapeutic index and large inter-individual variability can lead to complex dosage regimes. Formulating warfarin as an orodispersible film (ODF) using thermal ink-jet (TIJ) printing could enable personalisation of therapy to simplify administration. Commercial TIJ printers are currently unsuitable for printing the milligram dosages, typically required for warfarin therapy. As such, this study aimed to modify a commercial TIJ printing system to formulate personalised warfarin ODFs containing therapeutic dosages. A TIJ printer was modified successfully with the printer functionality intact; the substrate (paper) rolling mechanism of the printer was replaced by printing onto a stationary stage. Free film substrates were composed of hydroxypropyl methylcellulose (20%*w*/w) and glycerol (3%w/w). The resulting ODFs were characterised for morphology, disintegration, solid-state properties and drug content. Printed film stability was assessed at 40 °C/75% relative humidity for 30 days. Therapeutic warfarin doses (1.25 and 2.5 mg) were successfully printed onto the film substrates. Excellent linearity was observed between the theoretical and measured dose by changing the warfarin feed concentration (R^2 = 0.9999) and length of the print objective, i.e. the Y-value, (R^2 = 0.9998). Rapid disintegration of the ODFs was achieved. As such, this study successfully formulated personalised warfarin ODFs using a modified TIJ printer, widening the range of applications for TIJ printing to formulate narrow therapeutic index drugs.

1. Introduction

Warfarin is the primary drug of choice for long-term anticoagulation in a variety of conditions, including venous thrombosis, pulmonary embolism and atrial fibrillation (Reynolds et al., 2007; BNF, 2017). However, its narrow therapeutic index and large inter-individual variability create a number of challenges (Kimmel, 2008). Warfarin dosages must be individualised for each patient to ensure that the anticoagulant effect is safe and effective, typically reflected in an International Normalised Ratio (INR) range of 2–3 (Crowther et al., 1999). Critically, inadequate control of INR can lead to severe adverse effects; under-anticoagulation can predispose patients to thrombosis, whereas over-anticoagulation can increase the risk of bleeding (Kimmel, 2008).

Despite the importance of maintaining warfarin within the therapeutic range, around 50% of patients fail to achieve their target INR (Matchar et al., 2002). Warfarin has also been listed in the top three most likely drugs to cause adverse reactions leading to hospital admissions (Pirmohamed et al., 2004). This could be partly explained by warfarin's inherently complex dosage regime and monitoring requirements. Therapeutic doses for different patients can vary widely, requiring anywhere between 4.5 and 77.25 mg per week (Wang and Hsaio, 2012; Wadelius et al., 2003). However, commercially available warfarin tablets are manufactured in only a few fixed strengths (0.5 mg, 1 mg, 3 mg and 5 mg) (BNF, 2017). As such, patients are often required to take a combination of strengths, split tablets or take different dosages on alternate days. This increases the risk of patient confusion, medication errors and non-adherence, potentially leading to severe adverse effects or therapeutic failure (Kimmel, 2008; Wong et al., 1999).

Personalised medicine has been suggested as a solution to ensure the safe and effective use of narrow therapeutic index drugs (Mini and Nobili, 2009; Alomari et al., 2015). In the case of warfarin, tailored dosing has been estimated to prevent 85,000 serious bleeding events and save $1.1 billion each year within the United States alone (McWilliam et al., 2006). As such, there is a major clinical need for the development of warfarin as a formulation that permits dose flexibility and personalisation.

Advances in personalised medicines demand precise, rapid and flexible manufacturing platforms capable of printing customised dosage

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forms directly at the point of care. Inkjet printing, a form of 2-Dimensional (2D) printing, has received increasing attention within pharmaceuticals. The general process involves dissolving or suspending an active pharmaceutical ingredient into a liquid carrier in order to create an "ink". The small 'ink' droplets (2–180 pL) are then ejected from a nozzle onto a solid substrate using either thermal (TIJ) or piezoelectric ink-jets. Both techniques have previously been used to deposit active pharmaceutical ingredients onto edible substrates (Uddin et al., 2015; Lee et al., 2012; Meléndez et al., 2008; Buanz et al., 2011; Vakili et al., 2017). A thermal inkjet printer was utilised for this work.

In brief, a TIJ system is comprised of a print head on a cartridge which serves as a reservoir for the 'ink'. A current is pulsed through a resistive element in the print head, causing an internal temperature rise and subsequent vaporisation, nucleation and expansion of a bubble, which imparts sufficient energy to eject a droplet. The droplet is then precisely deposited onto a solid substrate; this has enabled inkjet printing to find numerous pharmaceutical applications. To date, this technology has been used to coat and load drug-eluting stents (Tarcha et al., 2007), to coat transdermal microneedles (Uddin et al., 2015) and to manufacture drug-loaded microparticles (Lee et al., 2012; Palmer et al., 2017).

In the context of personalised medicines, TIJ could be used to print a variety of individualised dosages onto an edible substrate, such as orodispersible films (ODFs). This concept was demonstrated by Buanz. et al., whereby a highly potent drug (salbutamol sulphate; 40 μg/cm^2 per print pass) was printed onto an edible potato starch film (Buanz et al., 2011). However, commercially available TIJ printers are only able to deposit very low doses (approximately a maximum of 35 μg/print cycle). As such, this technology is currently only suitable for formulating highly potent drugs (Alhnan et al., 2016).

This provides a challenge when attempting to formulate narrow therapeutic index drugs that typically require dosing within the milligram range, such as warfarin. Researchers have attempted to increase drug deposition via a number of approaches, for example by using multiple printing cycles (Genina et al., 2013) and higher feed concentrations (Raijada et al., 2013). However, challenges surrounding non-linearity of drug deposition and crystallisation of active pharmaceutical ingredient were found. To extend the applications of TIJ, it is clear that a novel method to increase the amount of drug deposition is required.

As such, this study describes the modification of a commercial TIJ printing system to formulate customised warfarin ODFs (up to milligram dosages). The resulting ODFs were characterised and evaluated for drug content and stability.

2. Materials and Methods

2.1. Materials

Sodium warfarin was obtained from LKT Labs, UK; hydroxypropyl methylcellulose (HPMC) 6cp, i.e., Pharmacoat® 606 was obtained from Shin-Etsu, Japan; glycerol was from VWR chemicals, UK; and the fluoropolymer coated polyester film, Scotch pack release liner 1022, was from 3 M Inc., US. Fast Green dye was purchased from Alfa Aesar, UK. The water used in all experiments was ultrapure water.

2.2. Printer Modification and Evaluating Robustness

A Hewlett-Packard printer (HP 5940 Deskjet, USA, Fig. 1) was used in this work. This printer was modified such that rather than the substrate (generally paper in the unmodified printer) passing through the printer's rollers during operation, printing was done onto a stage mounted underneath the cartridge print head. Briefly, the modification process involved the careful removal of some physical parts of the printer to make room for fixing a stationary stage under the cartridge print head as shown in Fig. 1. Key sensors were also identified, carefully isolated so as not to damage these, and manually activated appropriately to ensure normal printer functioning.

In the unmodified printer, two key sensors require activation for the printing process to take place: the printer lid sensor and the paper feed sensor. During a normal printing process, the lid sensor is engaged with a bar attached to the printer lid and the paper feed sensor is activated by disengaging a bar which is required for paper to be fed into the printer.

In the modified printer, the printer lid is removed and printing is performed onto a stationary substrate without a paper rolling mechanism. These activations are manually performed by placing a bar between the lid sensor to mimic a closed printer lid; a requirement for printing functionality. The paper feed sensor is also manually activated by removing a bar which is placed between the sensors when the printer is idle.

HP 337 black cartridges were used in this work: these were modified by cutting off the top, draining the ink, and rinsing several times with deionised water until clear. The cartridge nozzles were then submerged in deionised water: ethanol solution (2:1) for 5 min.

An experiment to evaluate any potential inter- or intra-cartridge variations due to the modification was conducted. Three modified HP 337 black cartridges were used for this experiment. 1 mg/mL Fast Green dye solution was used as the "ink" for printing. 1 cm × 1 cm squares were printed in triplicate for each cartridge onto the clear acetate sheets. The print-outs were then carefully cut and immersed in 1 mL deionised water to dissolve the dye. The dye solutions were vortexed to ensure complete dissolution after which high-performance liquid chromatography (HPLC) analysis was conducted.

The liquid chromatographic system used was Agilent Technologies 1200 series with quaternary pump and degasser. The column used was a Phenomenex C_{18} column (150 mm × 3.90 mm, 5 μm). A gradient system was adopted with acetonitrile HPLC grade as the organic phase and 55 mM acetate buffer (pH 5 ± 0.02) as the aqueous phase at a flow rate of 1 mL/min for 10 min. The gradient system consisted of 15% acetonitrile and 85% buffer for 6 min then 60% acetonitrile and 40% buffer for a minute after which 15% acetonitrile and 85% buffer run again for 3 min. An injection volume 10 μL was used with the column temperature set at 30 °C. A wavelength of 600 nm was used for detection.

2.3. Film Preparation

The placebo film gel was composed of HPMC and glycerol. Glycerol (3% *w*/w) was first dissolved in water at room temperature, followed by gradual addition of HPMC (20%w/w) under continuous stirring at room temperature. The resulting viscous solution (10 g) was stirred for 4 h until a homogenous gel was formed. The gel was left to stand for 2 h to eliminate any air bubbles trapped.

Placebo films were casted on a fluoropolymer coated polyester sheet using an automated film applicator (Coatmaster 510, Erichsen, Sweden) equipped with an adjustable coating blade. A fixed wet film thickness (1000 μm) and casting speed (5 mm/s) were used. The casted films were dried in an oven for 40 min at 60 °C (Binder, Sweden), followed by storage in a desiccator (23 °C/40% relative humidity). The resulting film sheets were used as substrates for printing.

2.4. Printing of Warfarin onto Films

Amounts of warfarin deposited onto a substrate can generally be varied by using different cartridge concentrations or by modifying the dimensions of the templates to be printed. In modifying the dimensions of the templates, a series of rectangles having the same width but variations in their height were deposited onto the same unit area. This resulted in an increase in the amount of material deposited and the concept is referred to as "Y-value". An example of the Y-value concept is illustrated in Fig. 2, where three black rectangles have the same width