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Printing T_3 and T_4 oral drug combinations as a novel strategy for hypothyroidism

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ABSTRACT

Hypothyroidism is a chronic and debilitating disease that is estimated to affect 3% of the general population. Clinical experience has highlighted the synergistic value of combining triiodothyronine (T_3) and thyroxine (T_4) for persistent or recurrent symptoms. However, thus far a platform that enables the simultaneous and independent dosing of more than one drug for oral administration has not been developed. Thermal inkjet (TIJ) 2D printing is a potential solution to enable the dual deposition of T_3 and T_4 onto orodispersible films (ODFs) for therapy personalisation. In this study, a two-cartridge TIJ printer was modified such that it could print separate solutions of T_3 and T_4. Dose adjustments were achieved by printing solutions adjacent to each other, enabling therapeutic T_3 (15–50 μg) and T_4 dosages (60–180 μg) to be successfully printed. Excellent linearity was observed between the theoretical and measured dose for both T_3 and T_4 (R^2 = 0.982 and 0.985, respectively) by changing the length of the print objective (Y-value). Rapid disintegration of the ODFs was achieved (< 45 s). As such, this study for the first time demonstrates the ability to produce personalised dose combinations by TIJ printing T_3 and T_4 onto the same substrate for oral administration.

1. Introduction

Hypothyroidism is the most common thyroid ailment, estimated to affect around 3% of the general population (Vaidya and Pearce, 2008). This condition is characterised by a deficiency of the thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4), which normally aid in controlling a number of essential physiological processes, including brain development, skeletal maturation, oxygen consumption, heat production and heart contractility (Kirsten, 2000). As such, hypothyroid states often create debilitating symptoms for patients, such as chronic fatigue, weight gain and cold intolerance, making the regulation and maintenance of T_3 and T_4 levels of critical importance.

The 'active' thyroid hormone (T_3) mediates the vast majority of normal physiological processes and is predominantly (~80%) derived from the metabolism of T_4 by iodothyronine deiodinases (Wartofsky, 2013). Despite this, the mainstay of hypothyroid treatment involves levothyroxine (T_4) only, with the assumption that sufficient T_3 is regenerated from T_4 in the peripheral tissues (Celi et al., 2011; Collier et al., 2011; Saravanan et al., 2005). However, persistent or recurrent hypothyroidism has been reported in approximately 10–20% of patients taking T_4 monotherapy (Appelhof et al., 2005; Walsh, 2002; Wartofsky, 2013; Wiersinga, 2009). These patients complain of feeling unwell despite normal thyroid function tests, raising doubts about the deiodination of T_3 from circulating T_4 (Appelhof et al., 2005; Biondi and Wartofsky, 2012; Wartofsky, 2013). As such, individualized combination T_3 and T_4 therapy may be required to represent endogenous hormonal rhythms in a more physiological manner.

The value of combining T_3 and T_4 in hypothyroid patients has been widely researched and as the clinical condition of the patient evolves, frequent dose changes are common (Bunevičius et al., 1999; Escobar-Morreale et al., 2005; Mortoglou, 2004). It is apparent that there is a clinical need for individualised combination T_3 and T_4 therapies within certain patient populations. Current tablet forms of T_3 and T_4 contain synthetic derivatives of the naturally occurring hormones (liothyronine and levothyroxine, respectively) and exist in separate dosage forms of a limited number of discrete strengths (e.g. levothyroxine strengths: 25 μg, 50 μg and 100 μg); this often requires patients to take more than one tablet strength and/or to split tablets to achieve their target dose (BNF, 2017). These inherently complex dosage regimes can cause patient confusion, dose variation and hence medication errors (Shah et al.,

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2010; Trenfield et al., 2018a).

As such, there is a major clinical need for the development of a novel platform that is capable of simultaneously and independently dosing more than one drug to create personalised dose combinations of T_3 and T_4 therapy. One technique that offers great potential is thermal inkjet (TIJ) printing, a form of two-dimensional (2D) printing. This process involves a drug being dissolved in a liquid carrier to create a 'drug ink', which is contained within a cartridge attached to a print head nozzle. A current is then pulsed through a resistive element in the print head, causing an internal temperature rise, followed by vaporisation, nucleation and expansion of a bubble; this produces the necessary energy required to eject a small droplet (2–180 μL) onto a solid substrate (Buanz et al., 2011; Meléndez et al., 2008).

Due to the capability for the precise spatial control of drug deposition, TIJ printing has received increasing attention in pharmaceuticals. Favourably, this technology is well suited to the field of personalised medicines by depositing precise dosages of highly potent and/or narrow therapeutic index drugs onto edible substrates, such as orodispersible films (ODFs) (Scoutaris et al., 2011; Vuddanda et al., 2018). A major driver for printing technologies lie in the possibility of depositing separate drugs as a single formulation to produce dose combinations. Such advancements have been made with 3D printing, whereby tablets containing multiple drugs (termed 'polypills') have been printed (Alhnan et al., 2016; Awad et al., 2018a,b; Goyanes et al., 2015; Khaled et al., 2015a,b; Maroni et al., 2017; Trenfield et al., 2018a,b). Despite a number of reviews highlighting the potential for inkjet printing to produce drug combinations (Alomari et al., 2015; Daly et al., 2015; Preis et al., 2015; Scarpa et al., 2017; Scoutaris et al., 2011), to date, limited research has explored this concept for oral administration. Thus far, studies have mainly focussed on depositing single drugs onto separate substrates (Buanz et al., 2011; Edinger et al., 2018; Genina et al., 2013a,b; Kollamaram et al., 2018; Montenegro-Nicolini et al., 2018; Planchette et al., 2016; Sandler et al., 2011; Vakili et al., 2017), which is likely due to the unsuitability of current unmodified printers to deposit more than one drug in the same print pass.

As such, this study describes the modification of a commercial TIJ printing system to produce customised ODFs containing dose combinations of T_3 and T_4. The printer used both the black and colour cartridges (each containing either T_3 or T_4 'ink') and dose modification was performed by printing two distinct colours adjacent to each other. The resulting ODFs were characterised for morphology, disintegration, solid-state properties and drug content.

2. Method and materials

2.1. Materials

Levothyroxine sodium (T_4, > 98.4%, Kemprotec Ltd, UK); liothyronine sodium (T_3, > 95%, Sigma Aldrich, UK); sodium hydroxide (NaOH, 98%, Fischer Scientific, UK); acetonitrile (ACN, 99.9%, Fischer Scientific, UK); sodium acetate (99%, Sigma Aldrich, UK); hydroxypropyl methylcellulose (HPMC 6cp, Pharmacoat 606, Shin-Etsu, Japan); propylene glycol (PG, 99%, Sigma Aldrich, UK); ethanol (analytical grade, Fischer Scientific, UK); dimethyl sulfoxide (DMSO, Fischer Scientific, UK). The water used in all experiments was ultrapure water.

2.2. Substrate preparation

The substrate film gel was composed of HPMC (70% w/w) and glycerol (30% w/w). Glycerol (3% w/v) was dissolved in water at room temperature, followed by gradual addition of HPMC (20% w/v) 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.

Substrate films were cast 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 cast 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; RH). The resulting films were used as substrates for printing.

2.3. 'Ink' preparation

The printing 'ink' comprised solutions of levothyroxine sodium and liothyronine sodium. No viscosity enhancers or surface tension modifiers were needed to make the solutions printable by TIJ. T_3 or T_4 (20 mg) was dissolved in a mixture of ethanol:DMSO:PG (45:45:10 v/v) at room temperature. The resultant solution was used for printing onto the film substrates.

2.4. Printer modification

An HP 5940 (Hewlett Packard Inc., USA) thermal inkjet printer was modified and used for printing). The printer was modified such that rather than the substrate passing through the printer's rollers during operation, instead printing was performed on a stage mounted underneath the cartridge print head. Printer modification involved removing certain physical parts of the printer to make space for a stationary stage under the cartridge print head. Key sensors were also identified, carefully isolated and manually activated appropriately to ensure normal printer functioning.

In the unmodified printer, two key sensors require activation to start the printing process: the printer lid sensor and the paper feed sensor. During the 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 was removed and printing was 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 was also manually activated by removing a bar which is placed between the sensors when the printer is idle. More information detailing the modification details are reported elsewhere (Vuddanda et al., 2018).

Black (HP 337) and colour (HP 343) cartridges were modified by cutting off the top, draining the ink, and rinsing several times with deionised water until clear. Cartridges were then rinsed with ethanol and dried in air. Printing templates were designed and consisted of solid yellow rectangles (1 cm width) alongside non-overlapping rectangles of solid black (1 cm width), as shown in Fig. 1. The height of each of these rectangles determined the dose deposited. The yellow compartment of

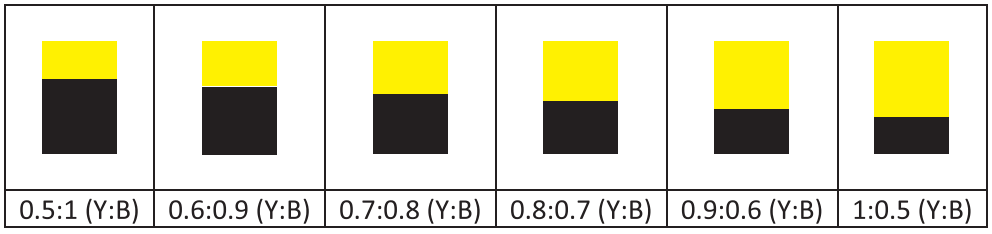

Fig. 1. The representation of Y-values to be printed in order of increasing yellow and decreasing black linearly. Y = Yellow colour (T_3), B = Black colour (T_4). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

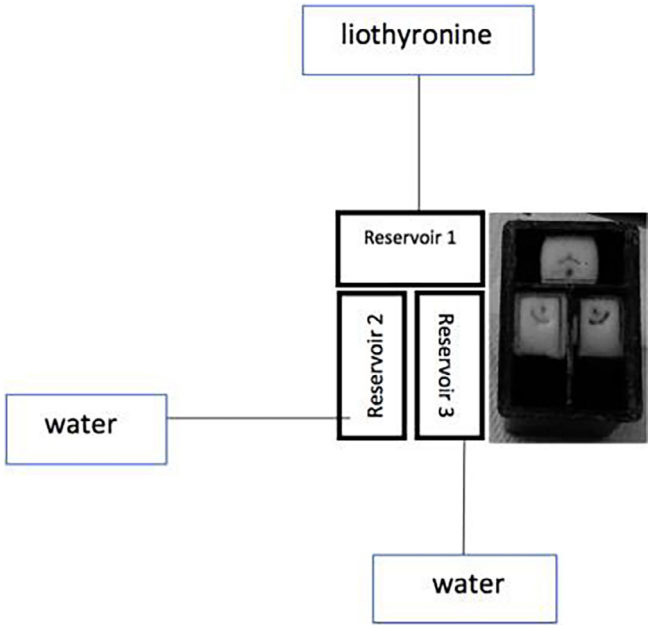

Fig. 2. Top view of colour inkjet reservoirs (left); print cartridge with sponges covering reservoirs (right).

the colour cartridge (reservoir 1) was filled with T_3 solution whilst the other two compartments were filled with deionised water, as shown in Fig. 2. The black cartridge was filled with the T_4 solution.

2.5. Drug content

The printed substrates were carefully cut using scissors without touching the printed areas. Samples (1 cm^2) were then dissolved in mixture of ethanol:DMSO:H_2O (30:30:40 v/v). Drug concentrations were determined using high performance liquid chromatography (HPLC) using the method described elsewhere (Samanidou et al., 2000). An ODS-3, 150 × 4.0 mm, 5 mm analytical column was used with a mixture of methanol and 2% acetic acid, at a ratio of 65:35 v/v with a flow rate of 1 mL/min and injection volume of 20 µL. The detection was performed using a UV–visible detector at 240 nm. The total run time for each sample was 10 min. Method validation was undertaken by evaluating inter- and intra-day precision, method accuracy, limit of detection (LOD) and the limit of quantification (LOQ).

2.6. Attenuated total reflection-Fourier transform infrared spectroscopy (ATR-FTIR)

ATR-FTIR was performed with a Perkin-Elmer Spectrum 100 FTIR Spectrometer (PerkinElmer, UK) using the universal diamond ATR attachment. The spectra were collected in the range of 4000–650 cm^{-1} at ambient conditions using a minimum number of four scans per sample. Spectra were analysed with Spectrum Express software (version 6.3.4, PerkinElmer, UK).

2.7. Thermal analysis

Thermal measurements were made using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). DSC was performed using a differential scanning calorimeter (DSC Q1000, TA Instruments, USA) and each sample (> 5 mg) was placed in a hermetically-sealed aluminium pan with a pinhole lid. Pure samples of T_3 and T_4 were heated up to 300 °C at 10 °C/min. The printed films were subjected to the following heat-cool-heat cycles with a nitrogen purge gas (50 mL/min). Firstly, the sample was heated from 25 °C to 100 °C at 10 °C/min (to remove water content). The sample was then cooled from 100 °C to 0 °C. Finally, the sample was re-heated from 0 °C to 250 °C at 10 °C/min. An empty pan was used as a reference and the instrument was previously calibrated for temperature and heat capacities using indium and sapphire. DSC results were analysed using Universal Analysis software (version 4.5A, TA instruments, USA).

TGA measurements were performed using a Discovery instrument (TA instruments, USA). Approximately 5–8 mg of the film was heated from 25 °C to 150 °C at 10 °C/min using nitrogen as a purge gas (50 mL/min). Data collection and analysis were performed using Universal Analysis software (version 4.5A, TA instruments, USA).

2.8. Scanning electron microscopy (SEM)

Surface and cross-section morphology of films were captured with an FEI Inspect F50 Scanning Electron Microscope (SEM) (FEI, Hillsboro, OR, USA). Film cross-sections were immersed in liquid nitrogen; this fracture by freezing method ensured clean-cut edges and avoided plastic deformation. These films were then affixed on aluminium stubs by conductive carbon tape, and sputter-coated with gold (approx. 10–12 nm) in a high vacuum evaporator (108 Auto, Cressington Scientific Instruments Ltd, UK).

2.9. Film thickness and disintegration

The thickness of the films (1 cm^2) was measured using a digital micrometer (Cokraf$^{t®}$ Digital Caliper, Sweden) at three points of each sample and reported as the mean ± standard deviation (SD). The disintegration times of the films were then evaluated by using a modified Petri dish method (Garsuch and Breitkreutz, 2010). Samples (1 cm^2) were placed in a Petri dish containing 2 mL of water and were shaken at 60 rpm using an orbital shaker water bath at 37 ± 1 °C. The time until film disintegration was recorded.

3. Results and discussion

A standard HP 5940 Deskjet printer was modified to enable printing of multi-drug combination ODFs containing liothyronine (T_3) and levothyroxine (T_4). The printer was modified such that, rather than the substrate (paper in the unmodified printer) passing through the printer's rollers during operation, printing was performed on a stage mounted underneath the cartridge print head. In particular, the printer's sensors were identified and manually activated to begin the printing process when required. For printing of ODFs, HPMC substrates were loaded onto the stage mounted underneath the print head and the sensors that usually detect paper presence were manually activated.

To dispense two medicated liquids onto the HPMC substrate with high precision and dose flexibility, two cartridges were used: black and colour. The colour cartridge contains three separate ink chambers; reservoir 1 (Fig. 2) was used since this corresponds to the yellow compartment in the colour cartridge. Drug deposition was accomplished by printing rectangles of 1 cm width of solid yellow non-overlapping with 1 cm width rectangles of solid black. The height of each of these rectangles was the main determinant of the dose deposited since the width was kept constant; the so-called Y-value approach. This is similar to our previous work with warfarin that involved a single drug as compared with a combination of drugs here (Vuddanda et al., 2018).

When such a template is printed, the yellow reservoir of the colour cartridge will dispense a volume of liquid proportional to the height of the rectangle (assuming a fixed width across rectangles) and then the black cartridge will dispense on top of the volume deposited by the yellow reservoir, because the substrate is static. The second and third reservoirs in the colour cartridge should not be activated using this template, at least not significantly. Generally, empty reservoirs should not be activated since this will cause a burnout and potential electrical shorts of the reservoirs affected. Since the electrical connectors are

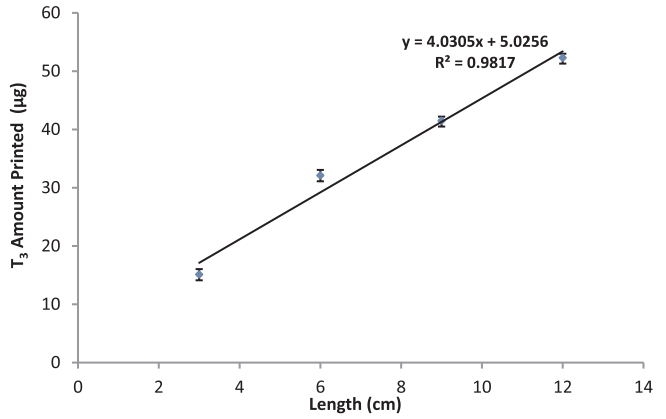

Fig. 3. Amount of T_3 printed onto free film substrates upon varying Y-values at constant initial feed concentration (20 mg/mL) (n = 3).

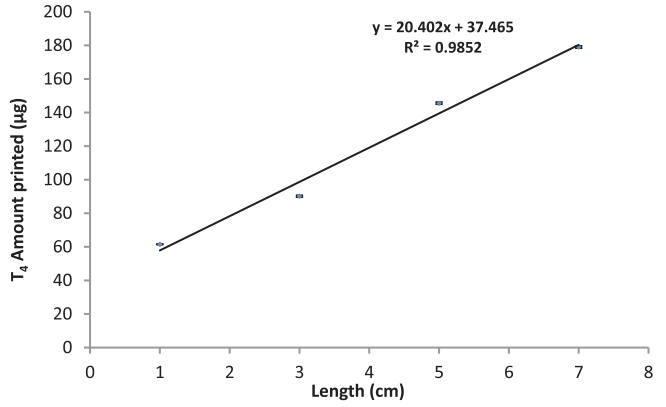

Fig. 4. Amount of T_4 printed onto free film substrates upon varying Y-values at constant initial feed concentration (20 mg/mL) (n = 3).

Table 1
Disintegration time of films (n = 3).

Films	Disintegration time (s)
T_3 printed film	43 ± 2
T_4 printed film	41 ± 1
Placebo film	40 ± 1

produced as a single circuit in which damage to one part could affect the connectors to another, deionised water was placed in reservoirs 2 and 3 during the experiment even though they were not used for printing purposes.

During printing, the height values of the two cartridges and their reservoir were set so that one increased while the other decreased; this was to eliminate the potential for cross-contamination between the cartridges and to show independent control of each for the purpose of independently dispensing different medicines. For T_3, the Y-values (with a width of 1 cm) were varied from 3 to 12 cm at a constant T_3 feed concentration (20 mg/mL). The correlation between the Y-values and dose deposited demonstrated excellent linearity (R^2 0.982), high precision and accuracy (demonstrated by the low SD values reported (Fig. 3)). For T_4, the Y-values (with a width of 1 cm) were varied from 1 to 7 cm at constant initial T_4 feed concentration (20 mg/mL). The correlation between the Y-values and dose deposited also demonstrated excellent linearity (R^2 = 0.985), high precision and accuracy (low SD) (Fig. 4). Importantly, it was observed that the substrate films were unable to retain their shape when attempting to print with Y-value lengths above 7 cm in the case of T_4 and 12 cm with T_3 solutions. This is likely due to the hydrophilic substrate film being unable to absorb the volume of solution printed.

During TIJ printing, the overall volumes (and hence doses) that can be dispensed are rather small. As such, this technology is well suited to drugs with high potency (and so a narrow therapeutic index) (Alomari et al., 2015). In previous studies drugs, such as salbutamol sulphate and theophylline, have been printed onto ODF platforms (Buanz et al., 2011; Sandler et al., 2011). To this end, T_3 and T_4 were considered to be ideally suited for printing onto ODFs, as therapeutic doses of levothyroxine range from 50 to 200 µg daily for adults, whereas liothyronine has been reported to fall within 10–20 µg daily (BNF, 2017, 2018). The lower dosing need of T_3 has been attributed to its high potency in exerting its clinical effects and, therefore, higher potential for toxicity (Biondi and Wartofsky, 2012). This small dose requires refinement at a much smaller scale than T_4, making T_3 a good candidate for use in the smaller colour reservoir, and the larger black cartridge for T_4. Moreover, the optimum dose is determined as a function of the patient's clinical response, as well as biochemical test outcomes such as monitoring of blood thyroid stimulating hormone (TSH) levels (Bernareggi et al., 2013), warranting the need for personalisation of dosages.

Despite being highly potent, to achieve deposition of meaningful therapeutic doses of T_3 and T_4 onto the ODFs, high concentrations of the initial feedstock are required in the printer cartridges. In both cases, concentrations of 20 mg/mL were prepared in mixtures of solvents (mentioned in the methods section) due to the low solubility of both drugs in water (DrugBank, 2005a,b). Therapeutic dosages of both T_3 (approx. 15–50 µg) and T_4 (approx. 60–180 µg) were successfully printed onto films. Many studies have reported the preparation of single drugs onto substrates. Buanz et al. demonstrated this concept, whereby a highly potent drug (salbutamol sulphate; 40 µg/cm^2 per print pass) was deposited onto an edible potato starch film (Buanz et al., 2011). Furthermore, Sandler et al. printed 78 µg of a narrow therapeutic index drug, theophylline, suitable for dosing in children aged 2–12 years old (Sandler et al., 2011). In the case of hypothyroidism, preparation of T_4 printed ODFs by piezoelectric inkjet printing technology has also been reported (Vakili et al., 2017; Wickström et al., 2018).

A major benefit of TIJ printing lies in the possibility of depositing separate solutions onto a single substrate to produce dose combinations. Wickström et al. used inkjet printing to formulate a ODF dose combination of Vitamins B_1, B_2, B_3 and B_6 (Wickström et al., 2017). However, in that case, a single multicomponent solution was prepared and the vitamins were dispensed together from the same solution according to their set ratios. As such, using this method, the doses of each vitamin cannot be independently changed. Thabet et al. also produced an ODF dose combination by depositing enalapril solutions onto the surface of solvent-casted ODFs containing hydrochlorothiazide (HCT) (Thabet et al., 2018). Moreover, Kollamaram et al. reported inkjet printing two separate drugs (paracetamol and indomethacin), however this research focussed on printing onto separate substrates (Kollamaram et al., 2018).

A proposed method for producing flexible dose combinations involves more than one solution being independently dispensed from separate cartridges. This concept has been demonstrated for the preparation of bioadhesive films containing two anticancer agents intended for cervical administration (Varan et al., 2017). Within that study, doses of the two drugs were escalated by increasing the number of layers deposited. However, printing several layers through several printing cycles could lead to deformation of substrate and loss of drug. To avoid such complications, this current study utilised the Y-value concept to enable a greater amount of drug to be printed within a single printing cycle, reducing the risk of deformation whilst increasing dose accuracy. To the authors' knowledge, this study here is the first to report the development of an orally-disintegrating dose combination platform using TIJ printing, enabling two chemically-similar molecules (T_3 and T_4) to be independently dispensed onto the same substrate for single administration.

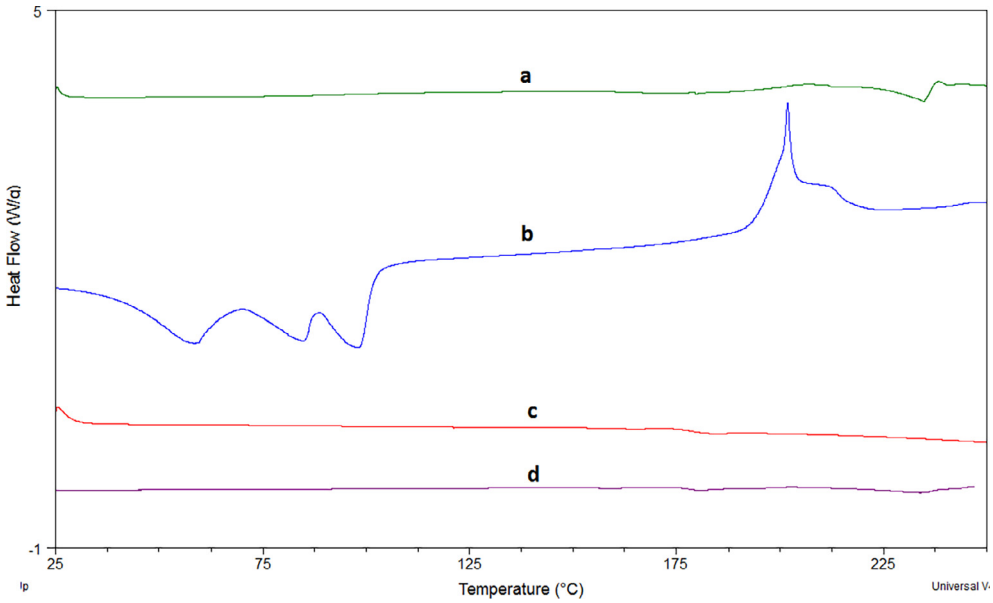

Fig. 5. DSC thermograms depicting: a) T_3 (pure), b) T_4 (pure) (c) T_3 printed films and (d) T_4 printed films.

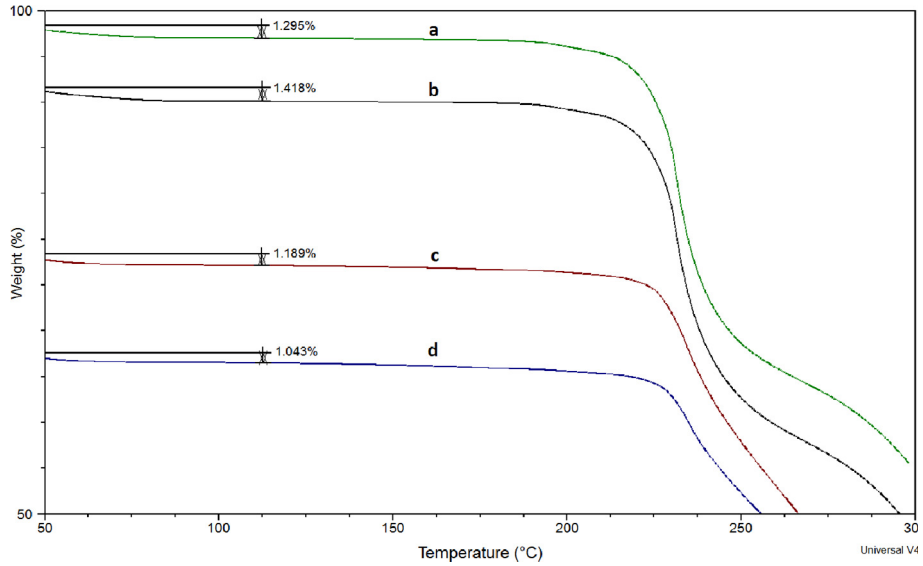

Fig. 6. TGA thermograms depicting: a) T_3 pure, b) T_4 Pure, c) T_3 printed film and d) T_4 printed films.

Rapid disintegration is considered a highly important characteristic for the performance of ODFs, with typical disintegration times ranging from 5 s to 180 s (FDA, 2008). In this study, the placebo substrate, and T_3- and T_4-printed films containing different doses (179 ± 0.6 and 52 ± 0.62 μg) were found to disintegrate within 43 s (Table 1). These results also indicate that disintegration was not significantly affected by the presence of T_3 or T_4, with disintegration times being in agreement with ODFs composed of HPMC reported in literature (Liew et al., 2012).

DSC thermograms of samples are shown in Fig. 5. The sodium salt of T_3 exhibited an endothermic peak at 234.7 °C and sodium salt of T_4 exhibited complex endothermic events at 58.8 °C, 84.6 °C and 97.1 °C, as well as an exothermic peak at 201.4 °C. The melting endotherms of T_3 and T_4 confirmed their crystalline state. The characteristic endothermic and exothermic events were not observed in T_3 and T_4 printed films. The slight change in the baseline observed at 145 °C corresponds with the glass transition temperature (T_g) of the HPMC polymer. These findings could be as a result of two reasons: either the printed drugs are amorphous after printing or the DSC was not sensitive enough to detect the heat changes due to the low doses of drug (T_3: 0.49% w/w and T_4: 1.69% w/w) available in sample films.

Water content and thermal stability were analysed based on the weight loss of films using TGA. It can be observed from the thermograms that T_3 and T_4 sodium salt pure samples contained 1.29% and 1.41% moisture and were stable up to 200 °C, followed by a rapid degradation (Fig. 6a and b). For freshly printed T_3 and T_4 films, the observed weight losses were 1.19% and 1.04%, respectively (Fig. 6). It was revealed that the solvents that were used in the feed printing solution were evaporated completely during printing and that no solvent residues were present within the printed films. The residual solvent peaks were not observed in the HPLC chromatograms of T_3 and T_4 printed films (Fig. 1). It was also noticed that the thermal stability of T_3 and T_4 printed films was improved compared with pure forms, which could be due to the existence of a single phase composite system of HPMC with T_3 or T_4 in printed films (as evident from DSC thermograms) or due to the presence of large quantities of polymer in printed films which has a relatively higher thermal stability.

The surface and cross-sectional morphologies of both the free film substrate and T_3- and T_4-printed films were observed using SEM

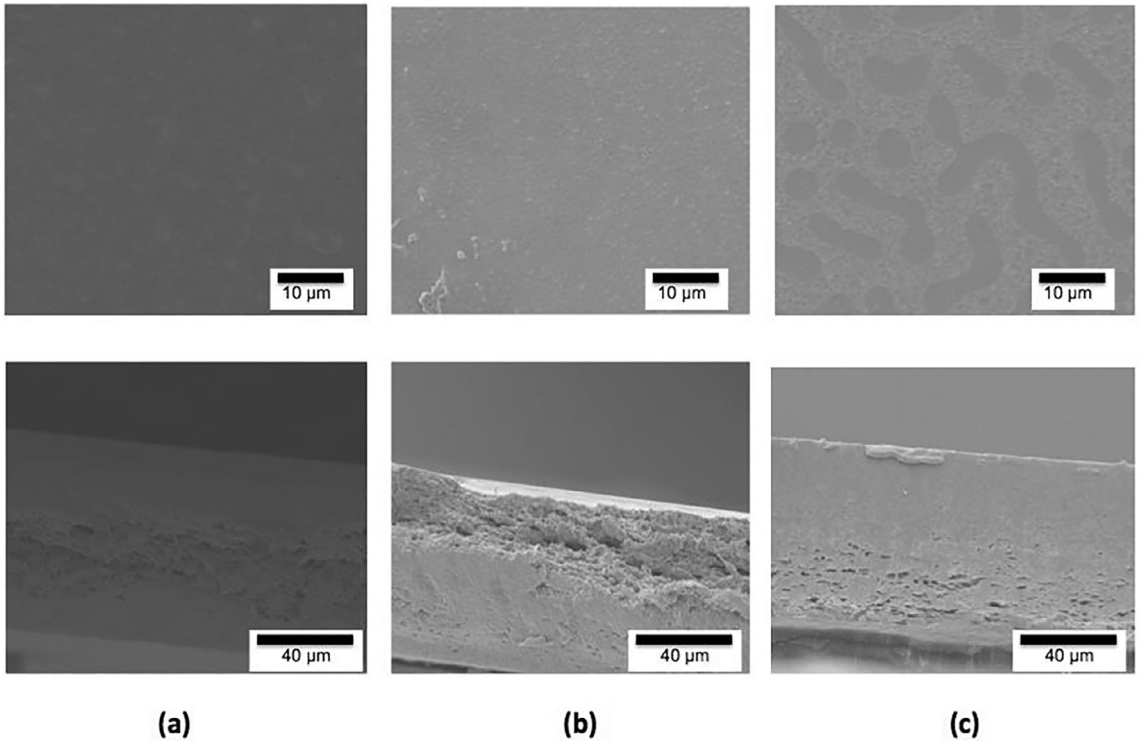

Fig. 7. SEM micrographs: a) Placebo substrate b) T_4 printed film c) T_3 printed film. Top view surface area (above) and cross sectional area (below). In the cross sectional pictures, drug deposition is shown on the upper exposed surface.

(Fig. 7). In both cases, drug was deposited onto the top surface of the HPMC substrate and the surface and cross-sectional micrograph of the substrate film revealed its microporous structure (Fig. 7a). In general, the surface micrographs confirmed the differences between the substrate and printed films but cross-sectional images did not show such clear evidence. However, it can be seen that marked differences in the surfaces of T_3 and T_4 films, with regards to printing pattern, is likely due to the difference in volumes of the printing solutions ejected from the nozzles of the black and colour cartridges. No drug particle residue was observed in the surface micrographs of T_3 and T_4 (higher Y-scale printed dose of T_3 and T_4 films). This could be due to the printing solution being absorbed uniformly into the porous structure of the film or due to the drug being adequately solubilised in the HPMC polymer, thereby preventing recrystallisation. In such cases, the drug could be present in the amorphous state on the films. It has been well documented that HPMC forms long chain networks that can prevent the recrystallisation and enhance the physical stability of drugs (Li and Taylor, 2018).

4. Conclusion

This study has demonstrated a novel approach of simultaneously and independently dosing more than one drug (T_3 and T_4) onto ODFs using TIJ printing. In particular, a commercial TIJ printer was modified, whereby the printer's sensors were manually activated and a stationary platform was installed to enable printing onto HPMC substrates. By containing T_3 and T_4 'inks' in separate black and colour cartridges, printing of both drugs onto the same substrate was attained. Dose modification was achieved by changing the length of their respective print objectives (Y-values), enabling multi-drug combinations containing therapeutic dosages to be successfully produced. The novel work explored here has the potential to revolutionise the way in which oral dose combinations are produced, expanding the applications of ink-jet printing within personalised medicine.

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