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A Dynamic-Dose Dispenser for Immediate and Extended Release 3D Printed Tablets

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Abstract

The advances in personalised medicine increased the demand for a fast, accurate and reliable production method for tablets that can be digitally controlled by healthcare staff. Here we present a dynamic dose tablet system that proved to be suitable for immediate and extended release tablets with a realistic drug loading and an easy-to-swallow tablet. The method bridges the affordable, digitally controlled Fused Deposition Modelling (FDM) 3D printing with a standard pharmaceutical manufacturing process, Hot Melt Extrusion (HME). The reported method was universal for methacrylic polymers as well as cellulose based one. The use of HME based pharmaceutical filament preserved the linear relationship between the mass and printed volume and was utilized to digitally control the dose via an input from computer software with dose accuracy in the range of 91-95%. Higher resolution printing quality doubled the printing time but offered a little effect on *in vitro* release pattern and weight accuracy. Physical characterizations indicated that a potential amount of theophylline remained in a crystal form in the 3D printed tablet. Owing to the small size and the highly adjustable nature of the FDM 3D printer that can be controlled by a healthcare network, the method hold promise for future individualised treatment.

Key words: Rapid prototyping; Fused filament fabrication; FFF; Personalized; Patient-specific; 3D printing

1. Introduction

Personalised medicine provides patients with a superior treatment that takes into consideration their pharmacogenetic, anatomical and physiological particulars (Hamburg and Collins, 2010). One major clinical aspect of personalised medicine is individualizing the dose to suit an individual patient's need at a time. In the United States, 30 million prescriptions are prepared annually by 3000 compounding pharmacies (website, 2014). The most common therapeutic problems facing these pharmacies are prescribed combinations and strengths that were commercially unavailable (Martin et al., 2009). It is of significant importance to develop a dynamic dispensing system that can respond to different patient's needs rapidly and effectively.

For a tablet preparation method to perfectly suit the demands of personalised method, a safe easily adjustable dispensing station should be created. The station can be operated via a simple user interface with minimal training to the operator and can be connected to a wider healthcare network (Skowyra et al., 2015). Clearly, such criteria cannot be fulfilled by conventional tableting methods, where multiple processing stages, large batches, use of costly facilities and experienced labour are common practice (Khaled et al., 2014). This renders tailoring standard tablet manufacturing systems for an individual patient who continuously needs to change his/her medicines dose impractical and too expensive.

The use of 3D printing as a flexible alternative technique to conventional tableting techniques started with the use of powder-based printing (Katstra et al., 2000; Ursan et al., 2013; Yu et al., 2009; Yu et al., 2007). Other printing techniques such as inkjet printing (Gu et al., 2012), thermal inkjet printing (Buanz et al., 2011), piezoelectric inkjet printing system (Lee et al., 2012), stereolithography (Melchels et al., 2010) and syringe/extrusion 3D printing (Rattanakit et al., 2012) have also been investigated.

Fused deposition modelling (FDM) is a widely used and affordable bench top 3D printing technique (Lim, 2010). AN FDM based 3D printer uses a pre-prepared polymeric filament e.g. Poly Vinyl Alchohol (PVA) and guide it to pass through a heated nozzle to be extruded at a semi-solid state into fused 3D structure in a layer-by-layer fashion. The potential of FMD based 3D printers to incorporate drug molecules have been previously using commercially available PVA filaments (Goyanes et al., 2014a; Goyanes et al., 2014b; Masood, 2007). Our

research group showed the potential of this printing technology to provide a mini-dispensing dose controlling station via manipulating the volume of the printed design through input on software (Skowyra et al., 2015). However, previous attempts suffered several limitations such as limited encapsulation efficiency (<2.5%), the use of non-pharmaceutical grade ingredients, high temperature (Goyanes et al., 2014a; Goyanes et al., 2014b; Skowyra et al., 2015; Weisman et al., 2015), simplistic tablet designs, the use of and were confined to extended drug release systems (Goyanes et al., 2014a; Goyanes et al., 2014b; Sandler et al., 2014; Skowyra et al., 2015; Water et al., 2015).

In this work, we present a combined approach of manufacturing 3D printed tablet based on FDM 3D printing and hot melt extrusion (HME). We explored the potential of this approach to accurately control the dose of a model drug using a number of immediate and extended release polymers. The study was also carried out using a realistic drug loading with a challenging easy-to-swallow capsule-shaped tablet design.

2. Materials and methods

2.1. Materials

Theophylline was purchased from Arcos (UK). Eudragit® RL100 and Eudragit® RS100 formulation were donated by Evonik Industries (Darmstadt, Germany). Hydroxypropyl cellulose SSL grade was donated by Nisso Chemical Europe GmbH (Dusseldorf, Germany). Triethyl citrate (TEC) and triacetin were supplied by Sigma-Aldrich (UK). Scotch blue painter's tape 50 mm was supplied by 3M (Bracknell, UK).

2.2. Preparation of theophylline loaded filaments via hot-melt extrusion

MakerBot Replicator® 2X Experimental 3D Printer (MakerBot Industries, LLC, New York, USA) was utilized to print theophylline tablets. In order to obtain the new formulation hot melt extrusion method was implemented using Thermo Scientific HAAKE MiniCTW (Karlsruhe, Germany).

The compositions and the ratio of drug, polymer plasticizer mixtures are shown in Table 1. About 6 g of total blend was accurately weighed and added gradually to counter flow twin-screw extruder. The molten mass was allowed to mix for at least 5 min to allow homogeneous distribution of drug and polymer. The specific temperature of initial feeding and extrusion for

each filament are shown in table 1. The extrusion was carried out through a die nozzle with cylindrical shape and 1.5 mm diameter using a torque control of 0.6 Nm. Filaments were stored in sealed plastic bags at room temperature before 3D printing.

2.3. Tablet design and printing process

Blank and theophylline loaded tablets were designed in prolonged typical capsule shape using Autodesk® 3ds Max® Design 2012 software version 14.0 (Autodesk, Inc., USA) and saved in STL format (Figs.1C). The design was imported to the 3D printer's software, MakerWare Version 2.4.0.17 (Makerbot Industries, LLC., USA) (Fig.1). A series of tablets with increasing volumes were printed by modifying the dimensions of the design: length x width x heights (L, W, H) without altering the ratios between these dimensions (W=0.364 L, H=0.396 L).

The volume of the rectangular prism that contains the tablet design (v) was calculated as:

$$\mathrm{V} = \mathrm{L}\,\mathrm{W}\,\mathrm{H} = \mathrm{L}\;0.364\mathrm{L}\;\;0.396\mathrm{L} = \;\;0.144144\;\mathrm{L}^3 \qquad \text{Equation 1}$$

In order to correlate between the volume of the design and the mass of the printed tablet (M), a series of tablets of increased volume were printed and accurately weighed. A linear equation was established:

$$\mathrm{M} = 0.7433\;\mathrm{V} - 9.8967 \qquad \text{Equation 2}$$

$$\mathrm{M} = 0.10714\;\mathrm{L}^3 - 9.8967 \qquad \text{Equation 3}$$

Since the theoretical loading of the filament is 50% of its mass, the dose D (mg) is calculated as:

$$\mathrm{D} = 0.5\;\mathrm{M} \qquad \text{Equation 4}$$

where M is the mass of the tablet. Therefore, the required dimension (L) to achieve a target dose (D) can be calculated as:

$$\mathrm{L} = \;\sqrt[3]{\frac{2\mathrm{D}+9.8967}{0.10714}} \qquad \text{Equation 5}$$

A series of tablets were printed according to equation 5 to achieve a target dose of 60, 120, 200, 250 and 300 mg. Table 2 provided details of dimensions, expected and measured mass of these tablets.

2.4. Modification of 3D printer

A MakerBot Replicator® 2X Experimental 3D Printer (MakerBot Industries, New York, USA) was utilized to print Eudragit RL tablets. Tablets were printed using modified settings of the software for PLA filament as follows: type of printer: Replicator 2X; type of filament: PLA; resolution: standard; temperature of building plate: 20 °C; speed of extruder 90 mm/s while extruding and 150 mm/s while traveling; infill: 100%; height of the layer: 200 µm. No supports or rafts were utilized in the printed model.

The following modifications were implemented:

i) Kapton tape layer (default) provided poor adhesion of the designs to the built plate. Blue Scotch painter's tape was applied to the surface of the printing board to improve adhesion to the surface layer.

ii) Changing extruder temperature during printing as specified in Table 1 was essential to maintain constant flow of theophylline loaded filaments.

2.5. Determination of drug content in 3D printed tablets

In order to assess theophylline content in the printed tablets, each tablet was weighed and sonicated in 1000 ml volumetric flask containing 0.1 M HCl. The sonication period were extended to 8 hours to ensure complete drug extraction. Theophylline drug concentration was determined via spectrophotometry (Jenway, Japan) at absorbance λ_{max} of 272 nm. For higher concentrations, the solution was diluted as suitable with 0.1 M HCl.

2.6. Scanning Electron Microscopy

The surface morphology of the printed tablet was assessed using a Quanta-200 SEM microscope at 20 kV. Samples were placed on metallic stubs and gold coated under vacuum for 2 min using JFC-1200 Fine Coater (Jeol, Tokyo, Japan), prior to imaging.

2.7. X-Ray Powder Diffraction

A powder X-ray diffractometer, D2 Phaser with Lynxeye (Bruker, Germany) was used to assess the crystallinity of theophylline in the drug loaded tablets. Samples were scanned from 2Theta (2θ)= 5° to 50° using 0.01° step width and a 1 second time count. The divergence slit was 1mm and the scatter slit 0.6mm. The wavelength of the X-ray was 0.154 nm using Cu source. The voltage used was 30kV. Filament emission was 10 mA using a scan type coupled with a two theta/theta scintillation counter over 30 min.

2.8. Differential Scanning Calorimetry (DSC)

A differential scanning calorimeter DSC Q2000 (TA Instruments, Elstree, Hertfordshire, UK) was utilized to perform thermal analysis. Samples (approximately 5 mg) were accurately weighed and placed in a 40 µL standard aluminium pan DSC analysis. Analysis was carried on under a nitrogen environment (50 mL/min). In order to exclude the effect of humidity and to get a clearer Tg, samples were cooled to -10°C, then heated to 100 °C. The temperature was kept isothermal for 5 min then cooled to -20 °C and left for 2 minutes. The heating and cooling of the samples were performed at of 10 °C/min. This was followed by a heat scan from -20 °C to 300 °C at the same rate. All measurements were carried out in triplicates. The data was analysed using a TA 2000 analysis software.

2.9. Thermo Gravimetrical Analysis (TGA)

A thermo gravimetrical analysis TGA Q5000 (TA Instruments, Elstree, Hertfordshire, UK) was used to measure the thermal decomposition profiles of the extruded filaments and printed tablets, in addition to the raw materials. Samples of approximately 5 mg were added to an aluminium pan in the TGA. Samples were heated from 25 °C to 600°C at a heating rate of 10°C/min. The data was analysed using a TA 2000 analysis software.

2.10 *In Vitro* drug release study via pH change USP II dissolution test

In vitro drug release studies for all gastro-resistant coating formulations used in this study were conducted in a USP II dissolution apparatus (AT 7 Smart, SOTAX, Switzerland). Each experiment was carried out in triplicate in dissolution medium at 37±0.5 °C with paddle speed of 50 rpm. The tablets were tested in 750 mL of a stimulated gastric fluid (0.1M HCl, pH 1.2) for 2 h, followed by 16-hour exposure to pH 6.8 phosphate buffer. Within all the experiment the amount of released theophylline was determined at 5 min intervals by UV/VIS spectrophotometer (PG Instruments Limited, UK) at the wavelength of 272 nm and path length of 1 mm. Data was analysed using IDISis software (Automated Lab, 2012).

3. Results and discussion

Here we present a strategy for the production of tablets via 3D printing with immediate and extended release properties that allows the using of a realistic high loading of a model drug (50%). The process is schematically illustrated in Fig.1. Firstly, theophylline loaded filaments were produced via processing a physical mixture of drug and polymer through hot-melt extrusion. Computer software is utilized to design a capsule-shaped tablet with different dimensions. The theophylline loaded filaments are utilized as a feed filament for FDM based 3D printer. SEM images of 3D printed tablets showed that tablets are made of staked layers of 200 µm thickness (Fig. 1E). The process takes approximately 5 min and is filmed in Video S1 (Supplementary data).

The use of high temperature during FDM 3D printing can lead to the degradation of thermo-labile drugs and polymers (Goyanes et al., 2014c). The temperatures of the 3D printing of different polymer mixtures were in the range of 140-170°C (Table 1). This is significantly lower than the recommended temperature by the 3D printer manufacturer (230°C)(Makerbot, 2013). However, further lowering temperature is likely to result in nozzle blockage due to increased viscosity of semisolid drug-polymer mixture in the print nozzle during 3D printing.

It is also noticeable that the printing ultimate temperature is approximately 40-50 °C higher the ideal HME processing (Table 1). This can be explained by the heating time of the two processes. While the processing temperature lasts approximately 10 min under shear mixing during the preparation of the filament via HME. In contrast, to enable successful completion of FDM 3D printing process, the filament has to be rendered in a semi-solid state via elevating its temperature by passing through the nozzle in a much shorter time (extrusion speed of 90-150 mm/sec).

When tablets with increasing dimensions has been used to fabricate tablets, a good correlation between the volume and tablet mass was achieved ($R^2 = 0.9997$) (Supplementary data, Fig. S1). This indicated the ability of this system to maintain an efficient control of the printed tablet mass using the newly fabricated filaments. The relevant equation was utilized to fabricate tablets with increasing tablet mass as in equation 3. Table 2 and Figure 2 demonstrated the fabrication of different tablets with therapeutic dose of theophylline: 60, 120, 200, 250 and 300 mg. The tablets demonstrated a good ecstatic shape and high physical

resistance (crushing strength >368N). The accuracy of dose was in the range of 91.34-95.92% with small variation co-efficient in the range of 0.8-3.4%. The printing method demonstrated a high correlation between the target and achieved dose (R^2 = 0.9995) (Fig.2B). This illustrate the potential of FDM 3D printer to function as a mini-dispenser for tablets that can accurately control the dose through an input from software.

The *in vitro* drug release pattern for theophylline from Eudragit RL was extended over 16 hours. It is likely that theophylline diffused out of water-insoluble Eudragit RL matrix leaving ghost matrix of Eudragit RL in the dissolution medium. Faster release pattern is demonstrated in smaller size tablets (60mg and 120 mg) compared to larger ones e.g. 300 mg. This is likely to increased surface/mass ration with the smaller tablets which promotes water imbibition and drug diffusion. A similar trend in prednisolone was also noted with PLA based 3D printed tablets (Skowyra et al., 2015).

The choice of 3D printing speed appeared to have significant impact of the external appearance of the tablet and the thickness of deposited layer (Fig. 3A-C). SEM images indicated that low, standard and high printing resolutions (corresponding to faster printing speeds) resulted in the formation layer thicknesses of 400, 200 and 100µm respectively. However, the printing speed appeared not to have significant influence on the variation of tablet weight or pattern of drug release for Eudragit RL based 3D printed tablets (Fig. 3D, E). Also, standard and low resolution took similar printing time while higher resolution appeared to significant increase the printing time. Such a difference may have major implication when optimizing the printing process to minimize dispensing time while maintaining the quality of the 3D printed tablets.

In order to test the applicability of this method to tailor drug release from 3D printed tablets, different individual polymers or mixture of polymers were used in replacement of Eudragit RL. The details of the formulation and preparation method are available in Table 1. Two polymers commonly used for immediate release products (HPC SSL and Eudragit E) were applied. The majority of theophylline *in vitro* release took place within 25 min from both filaments Fig.3A. However, it is obvious in Fig.3B that drug release was slowed down following 3D printing (compared to the corresponding non-printed filament). This might be attributed to the loss of surface area of the polymeric filament upon fusion following 3D printing. It is

also possible that further thermal treatment of drug-polymer filament (during 3D printing process) has increased the drug-polymer interaction within polymeric matrix and hence reduced chances of water imbibition upon introduction to dissolution medium.

To test the possibility of tailoring the pattern of drug release, mixtures of Eudragit RL with less permeable polymethacrylic polymer (Eudragit RS) or acid soluble polymer (Eudragit E) were also investigated (Fig.3 B-C). The process was tolerant to change of polymer composition. It was possible to slow down theophylline release following the addition of Eudragit RS. However, the incorporation of Eudragit E appeared to have a little influence on drug release from Eudragit RL:E 3D printed tablet. It is possible that the acid soluble polymer was entrapped in the polymeric network of water-insoluble Eudragit RL.

In order to compare the thermal decomposition pattern of the 3D printed tablet to that of the extruded filaments, thermo-gravimetric analysis were carried out (Fig. 5A). Eudragit RL lost around 3% of its weight up to 110 °C probably due to the evaporation of the moisture content of the polymer. The degradation pattern of the physical mixture revealed two degradation steps (Fig. 5B). The first (200 °C) represents the degradation of theophylline while the (340°C) indicated the degradation of the Eudragit RL. It can be also noticed that the degradation of the theophylline in the physical mixture has a steeper fashion compated to that of the filament or the 3D printed tablet which can be related to the distribution and interaction of theophylline particles with the polymeric matrix.

DSC thermographs showed that the glass transition temperature (Tg) of Eudragit RL has shifted from about 70°C for the pure polymer to approximately 46°C for the extruded filaments and the 3D printed tablet due to the plasticizing effect of theophylline (Fig. 5B). The thermal treatment of the filament during 3D printing appeared to have minimal effect on Tg of the polymer. Theophylline crystals have the melting point of pure theophylline can be noticed at 272°C (Fig. 5C). However, the impurity effect of the polymer caused a slight negative shift in the melting endotherm. The presence of such peak in the DSC thermograph of filament and 3D printed tablets indicated that a potential amount of theophylline remained in crystalline form following HME and the further thermal treatment of 3D printing. This was confirmed using XRPD analysis (Fig. 5D), where the spectra of drug-polymer filament and 3D printed tablets and tablets revealed a diffraction peaks at 2Theta = 7, 12, 14 and 24 that

match the diffraction pattern of theophylline (Räsänen et al., 2001). Similar trends were also noted when cellulose based (HPC SSL) 3D printed tablets were assessed (Supplementary data, Fig. 2S).

In summary we have reported a new approach for production of a flexible dose system based on combined approach of FDM 3D printing and HME. The realistic loading of the tablet, versatile control of dosing and in vitro drug release and the finishing quality of the 3D printed tablets hold the potential for a significant solution for personalised medicine.

4. Conclusion

FDM based 3D printing process proved to be compatible with drug-loaded fabricated through HME. Bridging 3D printing with HME process required a 40-50 °C elevation of the temperature of 3D printing above the HME processing temperature of the corresponding filament. The reported method proved to be universal for methacrylic polymers such as Eudragit RL, RS and E. It was also possible to print tablets using a cellulose based polymer such as HPC SSL. The use of HME based pharmaceutical filament preserved the linear relationship between the mass and printed volume and was utilized to digitally control the dose (R^2=0.9995) via an input on the software. The dose accuracy was in the range of 91-95%. Thermal analysis indicated that a potential amount of theophylline remained in a crystal form in the 3D printed tablet. Because of the low cost, minimal size, the wide-availability of FDM 3D printers and ease of its incorporation into healthcare network systems, these 3D printers hold a promise for clinical applications.

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List of Figures

List of tables

Supplementary Data

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Table 1 Processing parameters for filament production using HME and subsequent 3D printing

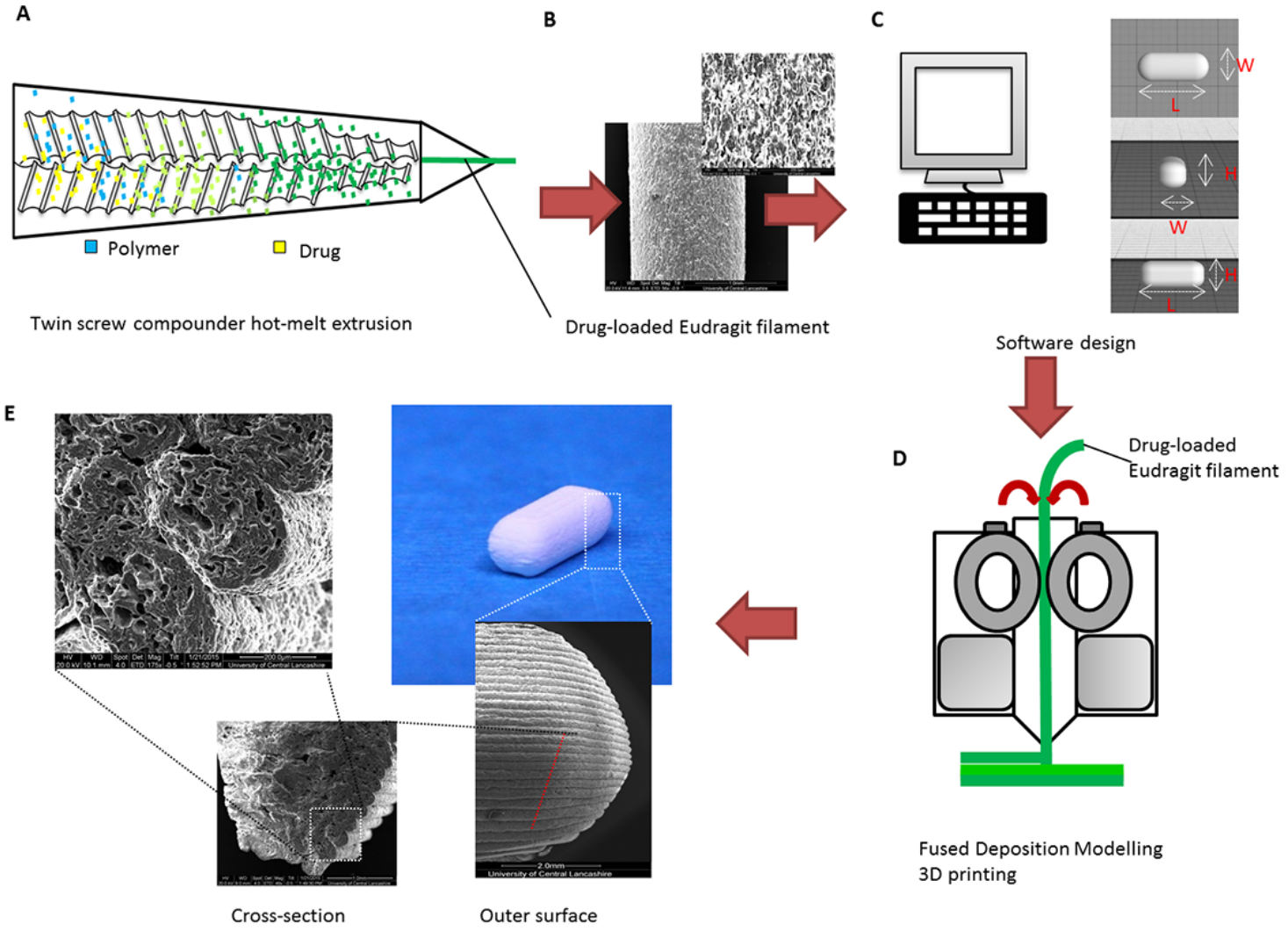
Formulation (Weight ratio)	HME process		3D Printing process	
	Initial temperature (°C)	Extruding temperature (°C)	Extruding temperature (°C)	Platform temperature (°C)
Eudragit RL/Theophylline/TEC 45/50/5	130	120	170	90
Eudragit RS/ Theophylline /TEC 42.5/50/7.5	130	110	150	60
Eudragit E/ Theophylline /TEC 46.5/50/3.5	130	110	140	60
Eudragit RL/Eudragit E/ Theophylline /TEC 22.5/22.5/50/5	130	115	140	90
Eudragit RL/Eudragit RS/ Theophylline /TEC 22.5/22.5/50/5	130	120	150	90
HPC SSL/ Theophylline /Triacetin 46/50/4	125	110	160	20

Table 2 Target and actual tablet mass, volume and dimensions.

Expected tablet mass (mg)	Volume (mm^3)	Dimensions (mm) X x Y x Z	Average tablet mass ±SD (mg)	Weight accuracy ±SD (%)
150	210.14	11.34 x 4.13 x 4.49	149.77±3.15	99.84±2.10
300	420.27	14.29 x 5.20 x 5.66	300.53±4.23	100.18±1.41
450	630.42	16.35 x 5.95 x 6.48	455.17±1.84	101.15±0.41
600	840.55	18.00 x 6.55 x 7.13	613.43±4.69	102.24±0.78
750	1050.69	19.39 x 7.06 x 7.68	774.43±8.71	103.26±1.16

Table 3 Target and actual theophylline dose in 3D printed Eudragit RL based tablets.

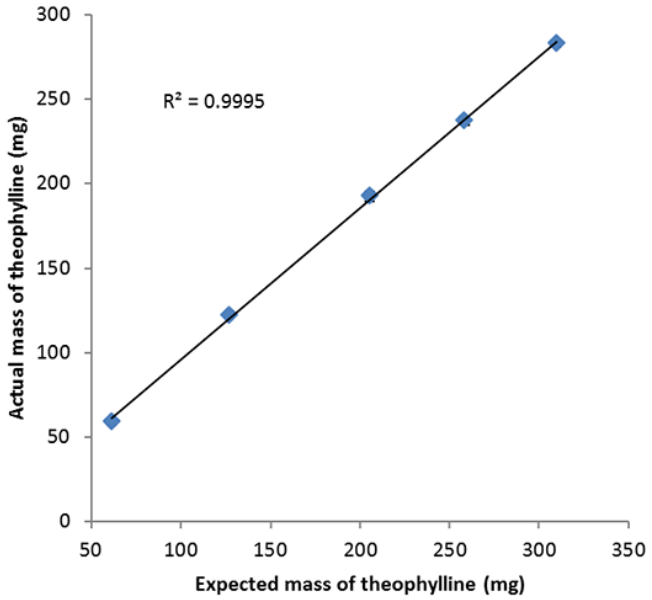
Target dose (mg)	Tablet mass± SD (mg)	Theoretical dose ±SD (mg)	Achieved dose ±SD (mg)	Dose accuracy ±SD (%)
60	123.0±1.1	61.5±0.57	58.8±0.8	95.56±2.03
125	253.7±4.5	126.9±2.26	121.7±2.3	95.92±0.80
200	411.2±5.9	205.6±2.97	192.4±4.0	93.62±3.39
250	516.6±10.7	258.3±5.35	237.1±1.3	91.83±2.63
300	618.9±6.3	309.5±3.13	282.6±3.0	0-±2.01


A
Polymer
Drug
Twin screw compounder hot-melt extrusion
B
Drug-loaded Eudragit filament
C
W
L
H
W
H
L
Software design
D
Drug-loaded
Eudragit filament
Fused Deposition Modelling
3D printing
E
Cross-section
Outer surface

A

3D printed theophylline tablets with increased strength

B



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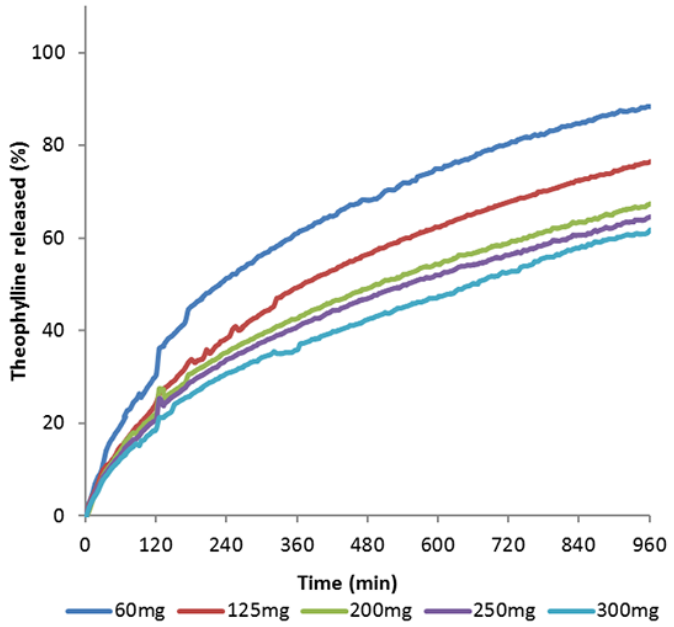

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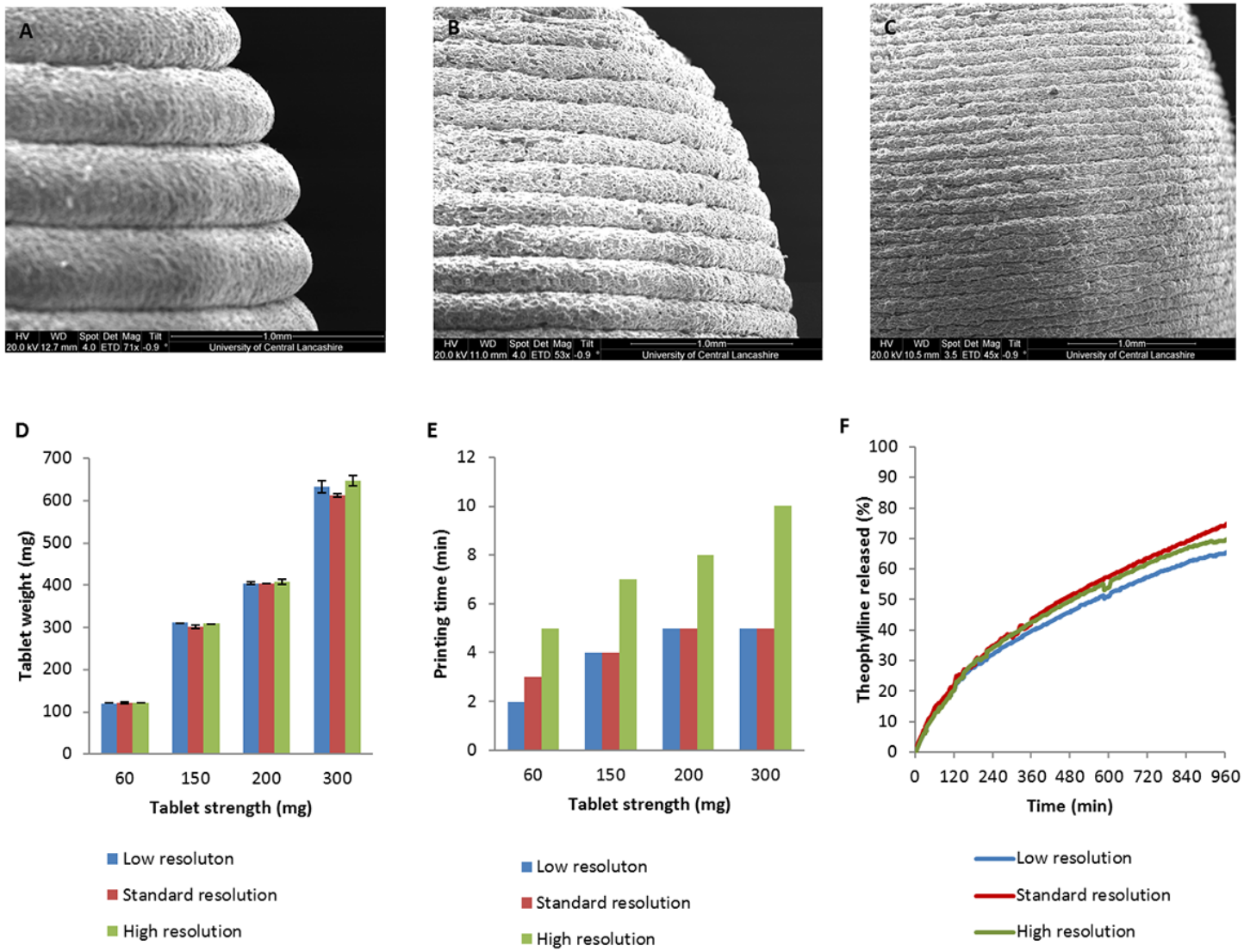
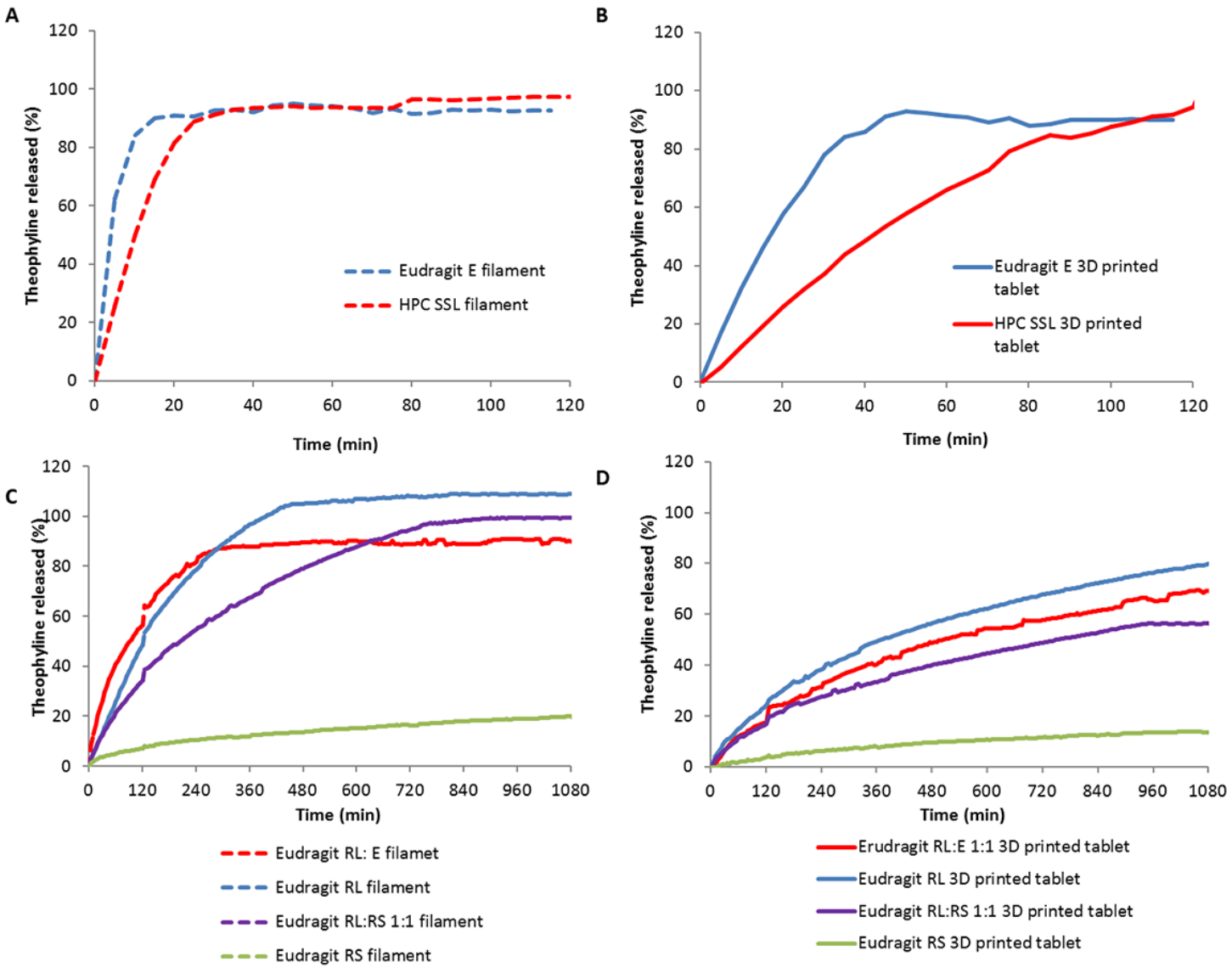
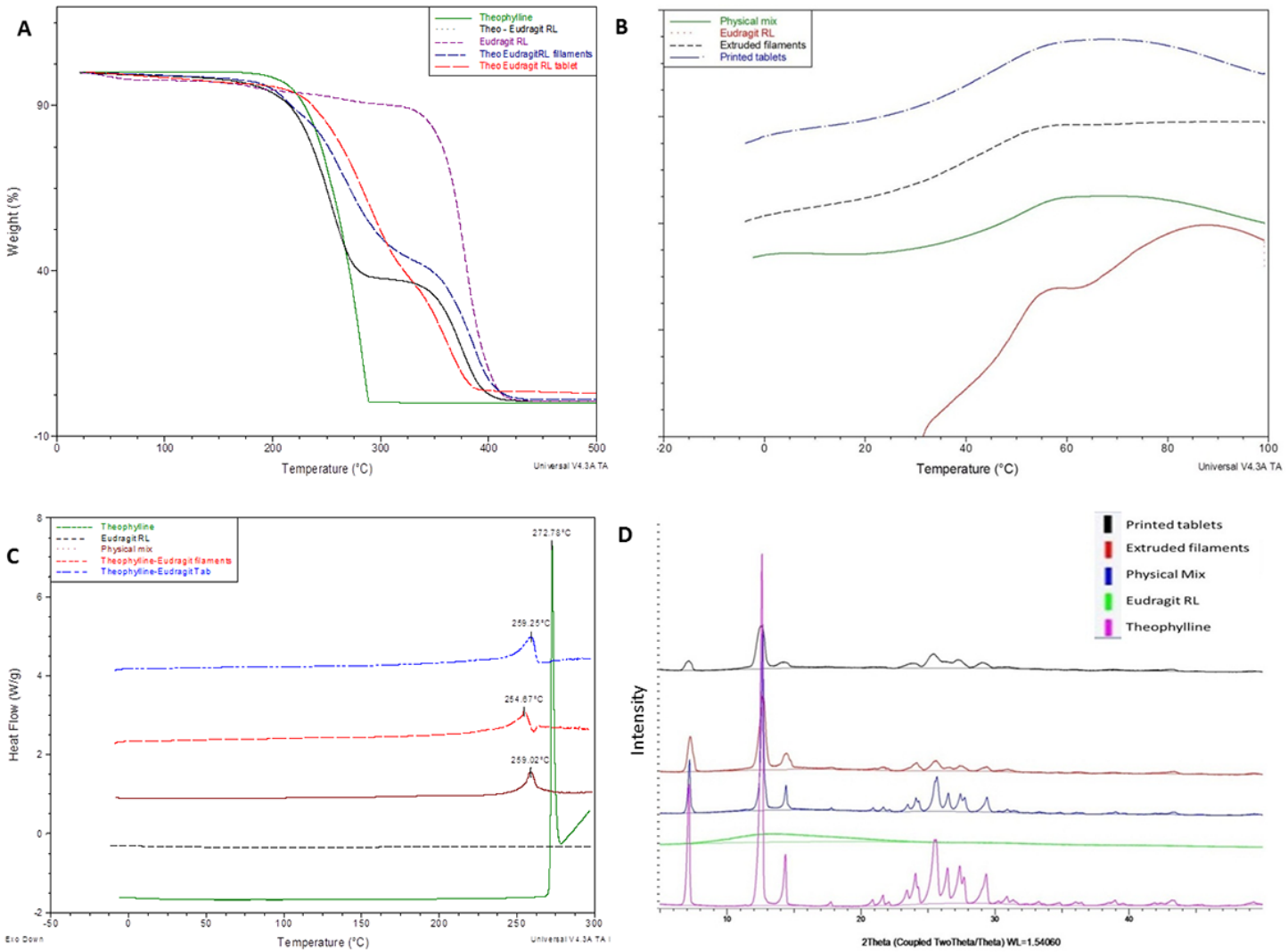

A
B
C
1.0mm
University of Central Lancashire
D
Tablet weight (mg)
0
100
200
300
400
500
600
700
60
150
200
300
Tablet strength (mg)
Low resoluton
Standard resolution
High resolution
E
Printing time (min)
0
2
4
6
8
10
12
60
150
200
300
Tablet strength (mg)
Low resoluton
Standard resolution
High resolution
F
Theophylline released (%)
0
10
20
30
40
50
60
70
80
90
100
0
120
240
360
480
600
720
840
960
Time (min)
Low resolution
Standard resolution
High resolution

3


A
Theophyline released (%)
Time (min)
Eudragit E filament
HPC SSL filament
B
Theophyline released (%)
Time (min)
Eudragit E 3D printed tablet
HPC SSL 3D printed tablet
C
Theophyline released (%)
Time (min)
Eudragit RL: E filamet
Eudragit RL filament
Eudragit RL:RS 1:1 filament
Eudragit RS filament
D
Theophyline released (%)
Time (min)
Erudragit RL:E 1:1 3D printed tablet
Eudragit RL 3D printed tablet
Eudragit RL:RS 1:1 3D printed tablet
Eudragit RS 3D printed tablet

4


A
Theophylline
Theo - Eudragit RL
Eudragit RL
Theo EudragitRL filaments
Theo Eudragit RL tablet
Weight (%)
Temperature (°C)
Universal V4.3A TA
B
Physical mix
Eudragit RL
Extruded filaments
Printed tablets
Temperature (°C)
Universal V4.3A TA
C
Theophylline
Eudragit RL
Physical mix
Theophylline-Eudragit filaments
Theophylline-Eudragit Tab
272.78°C
259.25°C
254.67°C
259.02°C
Heat Flow (W/g)
Temperature (°C)
Exo Down
Universal V4.3A TA
D
Printed tablets
Extruded filaments
Physical Mix
Eudragit RL
Theophylline
Intensity
2Theta (Coupled TwoTheta/Theta) WL=1.54060

A Dynamic-Dose Dispenser for Immediate and Extended Release 3D Printed Tablets

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Supplementary data

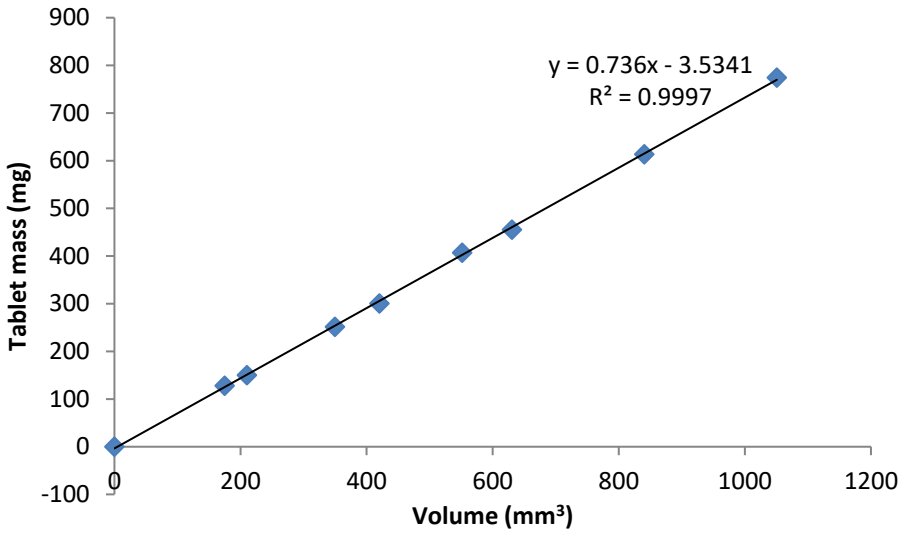
y = 0.736x - 3.5341
R² = 0.9997
Tablet mass (mg)
Volume (mm³)
900
800
700
600
500
400
300
200
100
0
-100
0
200
400
600
800
1000
1200

Figure S1

Table S1 Mass and 3D printing time using low, standard or high resolution of Eudragit RL based tablets

Target tablet mass (mg)	Low resolution		Standard resolution		High resolution	
	Tablet weight ± SD (mg)	Printing time (min)	Tablet weight ± SD (mg)	Printing time (min)	Tablet weight ± SD (mg)	Printing time (min)
120	119.3±0.2	2	120.5±2.5	3	121.0±1.4	5
300	311.9±2.7	4	300.5±4.2	4	308.4±1.4	7
400	404.1±3.5	5	404.2±1.4	5	407.3±6.4	8
600	632.4±14.8	5	611.9±4.7	5	646.8±13.1	10

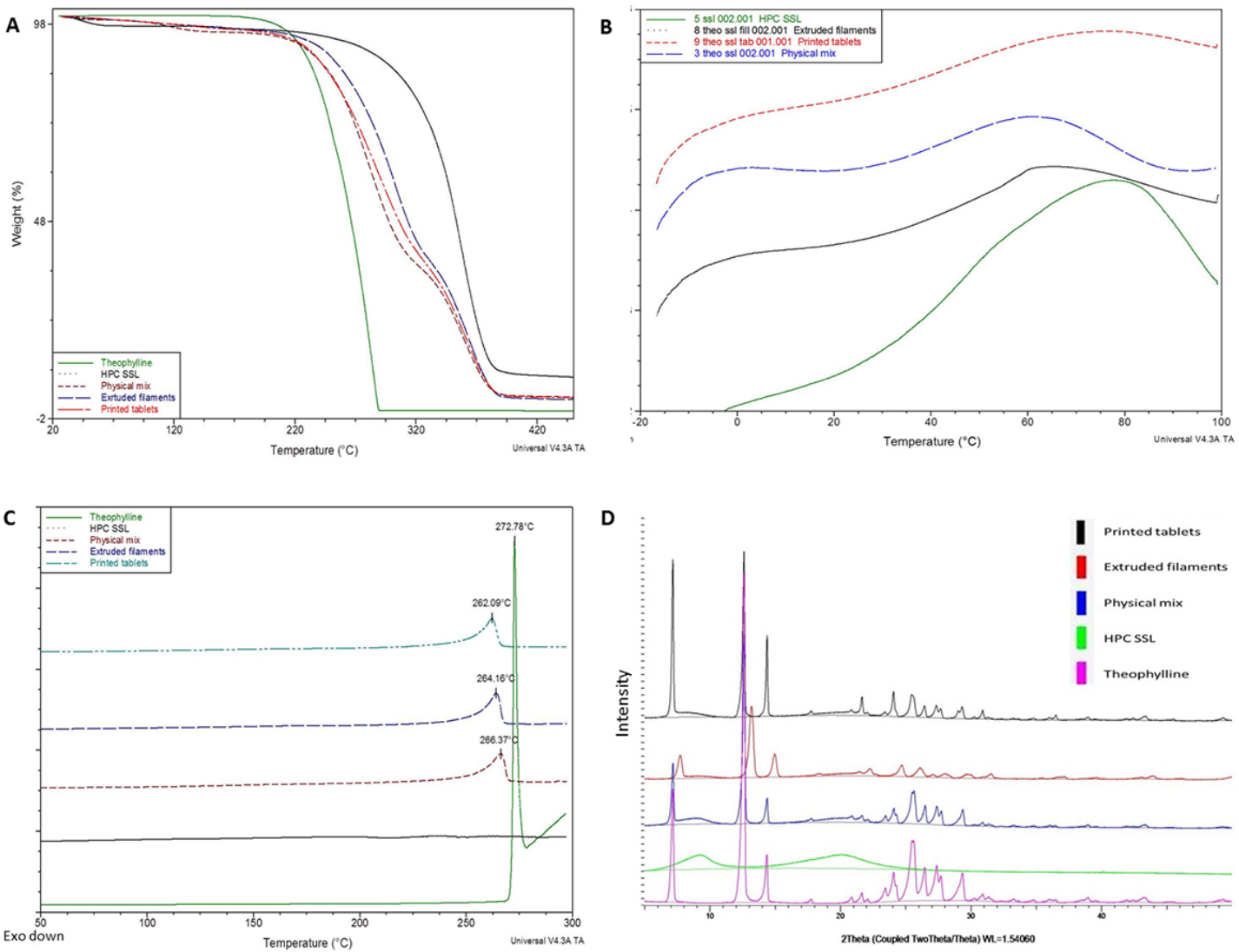
A
98
48
-2
Weight (%)
20
120
220
320
420
Temperature (°C)
Universal V4.3A TA
Theophylline
HPC SSL
Physical mix
Extruded filaments
Printed tablets
B
5 ssl 002.001 HPC SSL
8 theo ssl fill 002.001 Extruded filaments
9 theo ssl tab 001.001 Printed tablets
3 theo ssl 002.001 Physical mix
-20
0
20
40
60
80
100
Temperature (°C)
Universal V4.3A TA
C
Theophylline
HPC SSL
Physical mix
Extruded filaments
Printed tablets
272.78°C
262.09°C
264.16°C
266.37°C
50
100
150
200
250
300
Exo down
Temperature (°C)
Universal V4.3A TA
D
Printed tablets
Extruded filaments
Physical mix
HPC SSL
Theophylline
Intensity
10
20
30
40
2Theta (Coupled TwoTheta/Theta) WL=1.54060

Figure S2