Effect of geometry on dissolution profiles of 3D printed tablets

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Key words

3D printing; controlled-release; fused deposition modeling; PVA; paracetamol; hot melt extrusion

Abstract

1. Introduction

The future of medicine design and manufacture is likely to move away from mass production of tablets/capsules of limited dose range towards extemporaneous fabrication of unit dosage forms of any dose, personalised to the patient. The factors driving this change include the development of low dose drugs with narrow therapeutic indices (for instance immunosuppressants and/or blood thinners), the increasing awareness and importance of pharmacogenomics (for instance in the drug sensitivity of cancer sufferers, Kim et al, 2012) and the need to formulate drug combinations. To face this challenge, the pharmaceutical industry needs to evaluate and embrace novel manufacturing technologies. One technology with such potential is 3D printing (3DP).

Of the many types of 3D printer commercially available, fused-deposition modelling (FDM) offers perhaps the most immediate potential to unit dose fabrication. In FDM 3DP an extruded polymer filament is passed through a heated tip. The heat softens the polymer and it is then deposited on a build plate. The temperature of the build plate can be controlled and is set so that the polymer hardens. The print head deposits polymer on the build plate in the x-y dimensions, creating one layer of the object to be printed. The build plate then lowers and the next layer is deposited. In this fashion, an object can be fabricated in three dimensions, and in a matter of minutes. The particular benefit of FDM 3DP to pharmaceutics is that the polymer filament can be loaded with a drug prior to printing, and so drug-loaded unit dosage forms can be manufactured. This principle has been demonstrated, for example, to tablets containing fluorescein (Goyanes et al, 2014), 4-aminosalicylate and 5-aminosalicylate (Goyanes et al, 2015) and (Skowyra et al, 2015).

A further potential benefit of FDM 3DP, currently unexplored, is that the printer can be used to fabricate tablets of any geometry, including shapes that would be impossible to create by powder compaction. Since in principle the shape of a tablet could control its dissolution profile, FDM 3DP would seem to offer a new route to design controlled-release or modified-

release dosage forms. The aim of this work, therefore, was to print tablets in a diverse range of geometries, many not attainable by powder compaction, and to correlate their geometric parameters with dissolution behaviour.

2. Materials and methods

Polyvinyl alcohol (PVA, a water-soluble synthetic polymer of molecular formula $(C_2H_4O)_n$) was purchased as an extruded filament (1.75mm diameter, print temperature 190-220°C, batch No: 2013-10-18, Makerbot Inc., USA). Paracetamol USP grade was obtained from (Sigma-Aldrich, UK). Salts for preparing buffer dissolution media were purchased from VWR International Ltd., Poole, UK.

2.1 Preparation of PVA filament loaded with drug

The commercial PVA filament (38g) was cut into small pieces (~1 mm) using a Pharma 11 Varicut Pelletizer (Thermo Fisher Scientific, UK) and mixed with paracetamol (2g, 5% drug w/w) for 10 minutes in a Turbula® T2F shaker-mixer (Glen Mills Inc., USA). The mixture was extruded using a single-screw FilaBot® hot melt extruder (Filabot, USA) at 180 °C through a 1.75 mm diameter nozzle (screw speed 35 rpm). The extruded filaments obtained were protected from light and kept in a vacuum desiccator until printing. The drug-loading of the filaments was determined by HPLC analysis.

2.2. Printing of paracetamol dosage forms

Tablets were fabricated with the drug-loaded filaments using a standard fused-deposition modelling 3D printer, MakerBot Replicator 2X Desktop 3D printer (MakerBot Inc, USA). The templates used to print the tablets were designed with AutoCAD 2014® (Autodesk Inc., USA) and exported as a stereolithography (.stl) file into MakerWare v. 2.4.1 (MakerBot Inc., USA). The .stl format encodes only the surface data of the object to be printed and requires the thickness of the surface to be defined in order to print the desired object. The printer settings were as follows: standard resolution with the raft option deactivated and an extrusion

temperature of 180 °C, speed while extruding (90mm/s), speed while traveling (150mm/s), number of shells (2) and layer height (0.20mm). The infill percentage was 100% in order to produce tablets of high density.The selected 3D geometries were cube, pyramid, cylinder, sphere and torus (Figure 1). The sizes of the shapes were varied using the scale function of the software to fabricate tablets of constant surface area (275 mm^2), surface area/volume ratio (1:1) or weight (500 mg), Tables 1-3. In all cases, however, the ratio of the length, width and height of each shape was kept constant.

2.3 Scanning electron microscopy (SEM)

Surface and cross-section images of the filaments were taken with an SEM (JSM-840A Scanning Microscope, JEOL GmbH, Eching, Germany). All samples for SEM testing were coated with carbon (~30–40 nm).

2.4 Thermal analysis

Filaments were characterised with differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). DSC measurements were performed with a Q2000 DSC (TA instruments, Waters, LLC, USA) at a heating rate of 10°C/min. Calibration for cell constant and enthalpy was performed with indium (Tm = 156.6°C, ΔHf =28.71 J/g) according to the manufacturer instructions. Nitrogen was used as a purge gas with a flow rate of 50 mL/min for all the experiments. Data were collected with TA Advantage software for Q series (version 2.8.394), and analysed using TA Instruments Universal analysis 2000. All melting temperatures are reported as extrapolated onset unless otherwise stated. TA aluminium pans and lids (Tzero) were used with an average sample mass of 8-10mg.

For TGA analysis, samples were heated at 10°C/min in open aluminium pans with a Discovery TGA (TA instruments, Waters, LLC, USA). Nitrogen was used as a purge gas with a flow rate of 25 mL/min. Data collection and analysis were performed using TA Instruments Trios software and % mass loss and/or onset temperature were calculated.

2.5 Characterisation of tablet morphology

The physical dimensions of the tablets were measured using a digital calliper. Pictures of the tablets were taken with a Nikon CoolpixS6150 with the macro option of the menu. The surface areas and volumes of the tablets were calculated based on these dimensions. The surface area to volume ratio was obtained dividing these values.

2.6 Determination of drug loading

A tablet or a section of drug-loaded strand (approx. 0.3g) was placed in a volumetric flask with deionized water (1L) with magnetic stirring until complete dissolution. Samples of solution were then filtered through 0.45 μm filters (Millipore Ltd, Ireland) and the concentration of drug determined with HPLC (Hewlett Packard 1050 Series HPLC system, Agilent Technologies, UK). The validated high performance liquid chromatographic assay entailed injecting 20 μL samples for analysis using a mobile phase, consisting of methanol (15%) and water (85%), through a Luna 5μm C8 column, 25 x 4.6 cm (Phenomenex, UK) maintained at 40 °C. The mobile phase was pumped at a flow rate of 1 mL/min and the eluent was screened at a wavelength of 247 nm. All measurements were made in duplicate.

2.7 Dissolution testing

Dissolution profiles were obtained using a USP-II apparatus (Model PTWS, Pharmatest, Germany). In each assay, the tablets were placed at the bottom of the vessel in phosphate buffer (pH= 6.8, 900 mL) under constant paddle stirring (50 rpm) at 37°C. During the dissolution test, samples of paracetamol were automatically removed and filtered through 10μm filters and drug concentration was determined using an in-line UV spectrophotometer (Cecil 2020, Cecil Instruments Ltd., Cambridge, UK) operated at the wavelength of maximum absorbance of the drug in phosphate buffer (243 nm). Data were processed using Icalis software (Icalis Data Systems Ltd, Berkshire, UK). Tests were conducted in triplicate under sink conditions.

3. Results and discussion

The first important result was that it was possible to fabricate all of the shapes with 3DP, Figure 2. Manufacture of such complex and intricate shapes by powder compaction would be extremely challenging and so the study immediately suggests that 3DP offers a route of manufacture of dosage forms of novel geometries not previously possible. As found in our previous studies (Goyanes et al, 2014, 2015), 3DP tablets were not friable and so easy to handle.

DSC and TGA analyses of the pure substances and extruded filament were performed in order to understand how the drug was incorporated in the polymer, Figures 3-5. It is apparent that paracetamol raw material melts around 168 ^{o}C, indicative of form I while PVA shows a glass transition around 135 ^{o}C and melting between 175-200 ^{o}C. Significant degradation of PVA is seen above 260 ^{o}C, but the printhead temperature used during tablet fabrication is 230 ^{o}C. The DSC data of the paracetamol-loaded PVA filament shows no evidence of melting around 168 ^{o}C, indicating that the drug is molecularly dispersed within the polymer matrix as a solid solution. A glass transition is seen in both experiments involving PVA (highlighted by the arrows in Figure 4), the temperature of which rises when paracetamol is present, suggesting the drug is acting as an anti-plasticiser. TGA data suggests that PVA is stable until 260 ^{o}C, consistent with the DSC data, while paracetamol degrades significantly above 200 ^{o}C. When paracetamol is incorporated into the PVA, no appreciable mass loss is seen, suggesting the polymer is stabilising the drug.

Percentage drug loadings were measured for the filament (3.95% ± 0.01) and printed tablets (3.78% ± 0.01), indicating little degradation of the drug during printing, consistent with the thermal stability of paracetamol above its melting point seen by DSC. Electron micrographs show little evidence of paracetamol crystallites within the polymer filaments, Figure 7, consistent with the DSC data. Images of the cross-section of the printed torus clearly show the individual strands deposited by the printer. The strands are ca. 100 μm in diameter,

consistent with the nozzle diameter of the printhead, and there is some evidence of fusion of strands, leading to the strength of the tablet noted earlier.

Dissolution tests reveal that the geometry plays an important role in defining drug release profiles, Figure 7. When the surface area of the tablets was kept constant, drug release rates were in the following order (fastest first); pyramid > torus > cube > sphere and cylinder. The time to 90% release (t_{90}) varied from just under 2h (pyramid) to nearly 12 h (sphere and cylinder). When tablets were prepared with a constant surface area/volume ratio, the order of release rates was (fastest first); sphere and cube > torus > cylinder > pyramid. Less differentiation was seen in the t90 values, with most shapes having a value between 2-3h. Only the pyramid gave noticeably slower release (9 h). Interestingly, when tablets were prepared to constant weight, dissolution behavior was similar for all geometries. Since PVA releases drug via erosion, it seems that the controlling factor is simply the mass of polymer present. The data do show, however, that it is possible to design a tablet with a controlled-release profile (varying over 10h) by careful selection of shape and/or size.

Shape	Surface area (mm^2)	Volume (mm^3)	SA/V ratio	Weight (mg)	Density (mg/mm^3)
Cube	287.9 ± 2.1	332.3 ± 3.6	0.866 ± 0.003	268.2 ± 15.7	0.81 ± 0.05
Pyramid	270.4 ± 0.4	231.3 ± 0.5	1.169 ± 0.001	187.5 ± 3.9	0.81 ± 0.02
Cylinder	268.5 ± 3.9	314.4 ± 6.5	0.854 ± 0.005	355.3 ± 23.7.5	1.13 ± 0.05
Sphere	280.8 ± 1.4	442.3 ± 3.2	0.634 ± 0.002	505.3 ± 36.0	1.14 ± 0.08
Torus	266.8 ± 1.0	266.4 ± 1.9	1.002 ± 0.004	276.0 ± 19.6	1.04 ± 0.08

Table 1: Physical parameters for tablets with similar surface areas

Shape	Surface area (mm^2)	Volume (mm^3)	SA/V ratio	Weight (mg)	Density (mg/mm^3)
Cube	212.1 ± 2.2	210.1 ± 3.3	1.009 ± 0.005	186.9 ± 19.3	0.89 ± 0.11
Pyramid	356.1 ± 2.7	353.7 ± 5.2	1.007 ± 0.008	451.2 ± 12.0	1.28 ± 0.05
Cylinder	200.8 ± 3.2	202.3 ± 4.0	0.992 ± 0.004	197.6 ± 4.0	0.97 ± 0.18
Sphere	111.5 ± 1.2	110.7 ± 1.9	1.007 ± 0.006	98.5 ± 0.9	0.89 ± 0.05
Torus	266.8 ± 1.0	266.4 ± 1.9	1.002 ± 0.004	276.0 ± 19.6	1.04 ± 0.08

Table 2: Physical parameters for tablets with similar surface/volume ratios

Shape	Surface area (mm^2)	Volume (mm^3)	SA/V ratio	Weight (mg)	Density (mg/mm^3)
Cube	341.4 ± 0.5	429.2 ± 1.0	0.795 ± 0.001	477.9 ± 11.9	1.11 ± 0.03
Pyramid	393.0 ± 15.2	406.2 ± 23.4	0.968 ± 0.019	494.8 ± 16.6	1.22 ± 0.03
Cylinder	335.0 ± 15.7	438.3 ± 29.3	0.765 ± 0.016	480.0 ± 11.0	1.10 ± 0.06
Sphere	280.8 ± 1.4	442.3 ± 3.2	0.634 ± 0.002	505.3 ± 36.0	1.14 ± 0.08
Torus	387.0 ± 3.0	479.5 ± 4.3	0.807 ± 0.001	509.9 ± 29.0	1.06 ± 0.05

Table 3: Physical parameters for tablets with similar weights

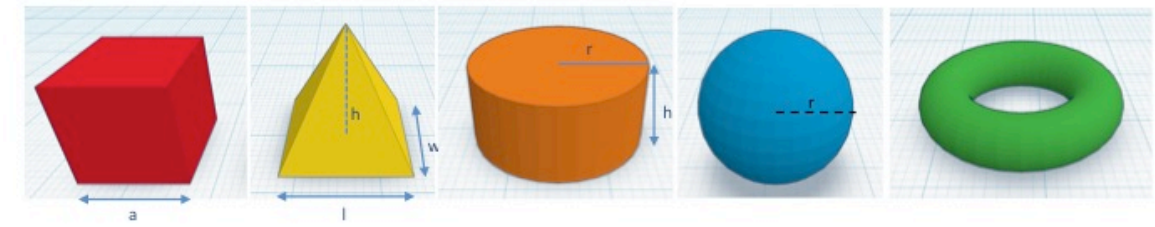


Figure 1. 3D representation of the 3D geometries printed (left to right; cube, pyramid, cylinder, sphere and torus)

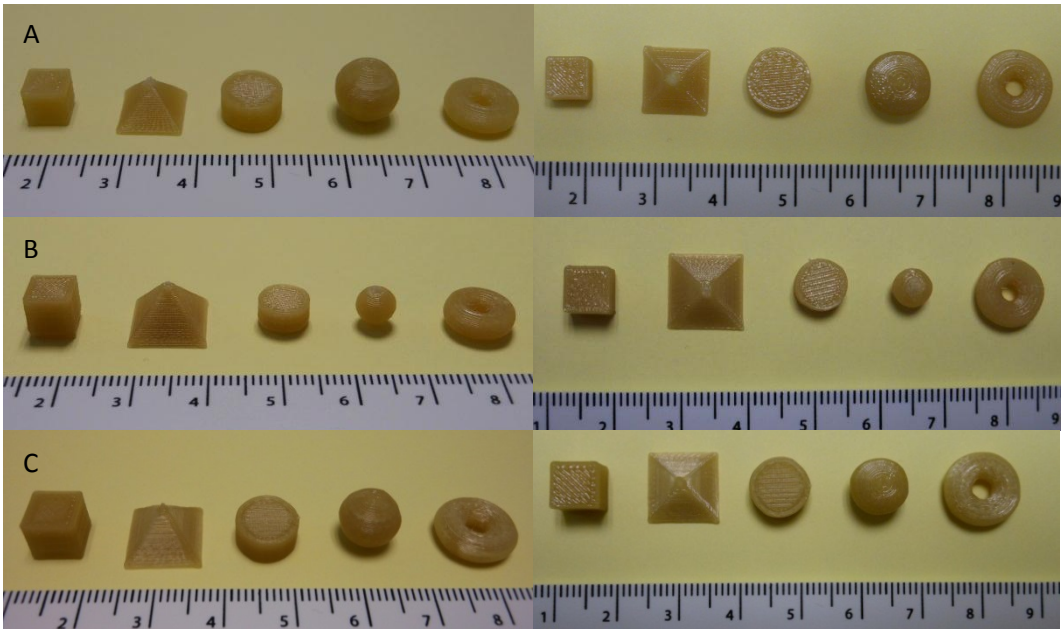
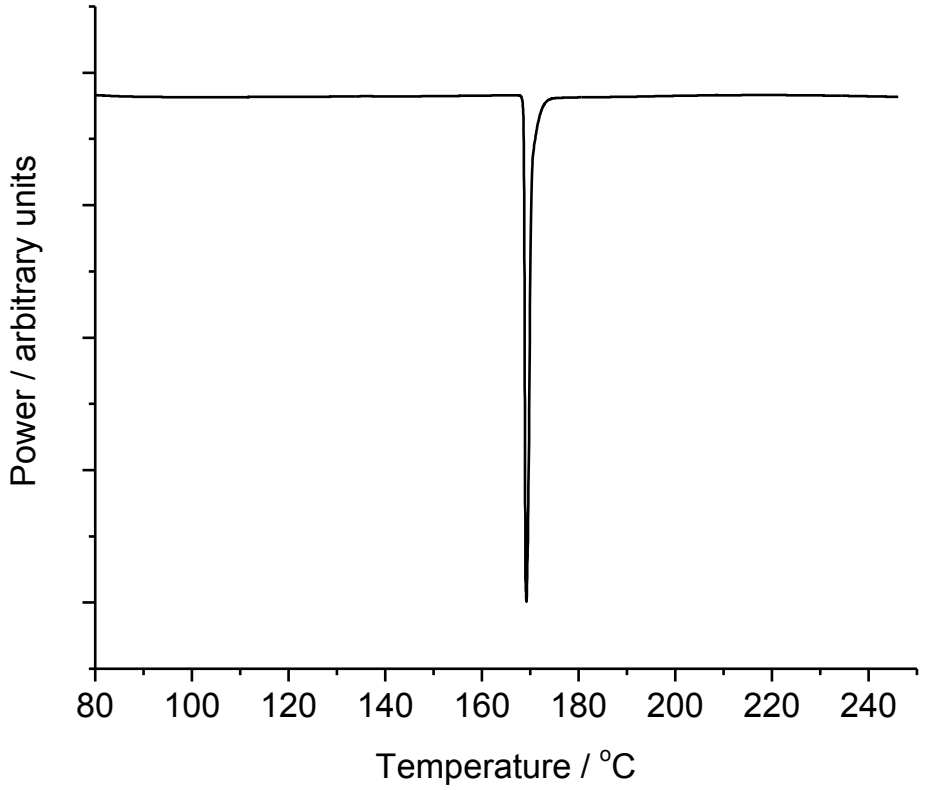


Figure 2: Images of the 3DP fabricated tablets at constant (A) Surface area, (B) surface area/volume ratio and (C) mass.



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237 Figure 3. DSC thermal trace for paracetamol raw material, showing melt of the stable form I

238 at 168 °C.

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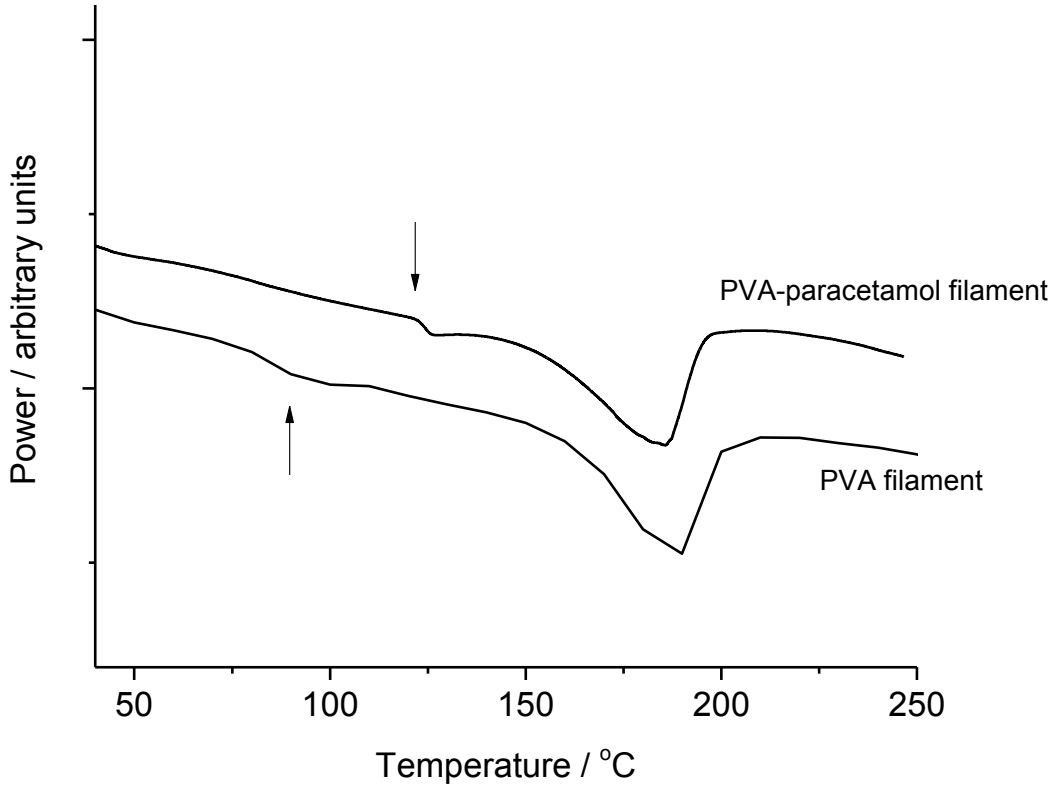

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243 Figure 4. DSC thermal traces for PVA and PVA-paracetamol filaments. The PVA melts

244 between 175-200 °C and the arrows indicate glass transition temperatures.

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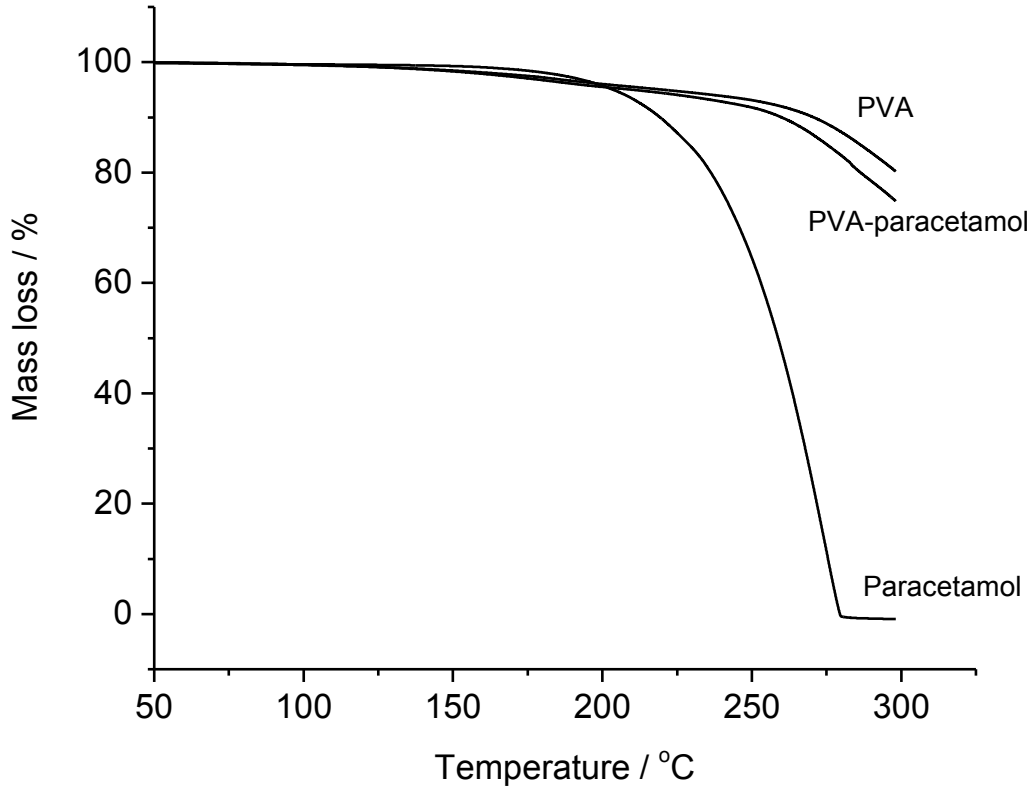


Figure 5. TGA thermal traces for paracetamol raw material and PVA and PVA-paracetamol filaments.

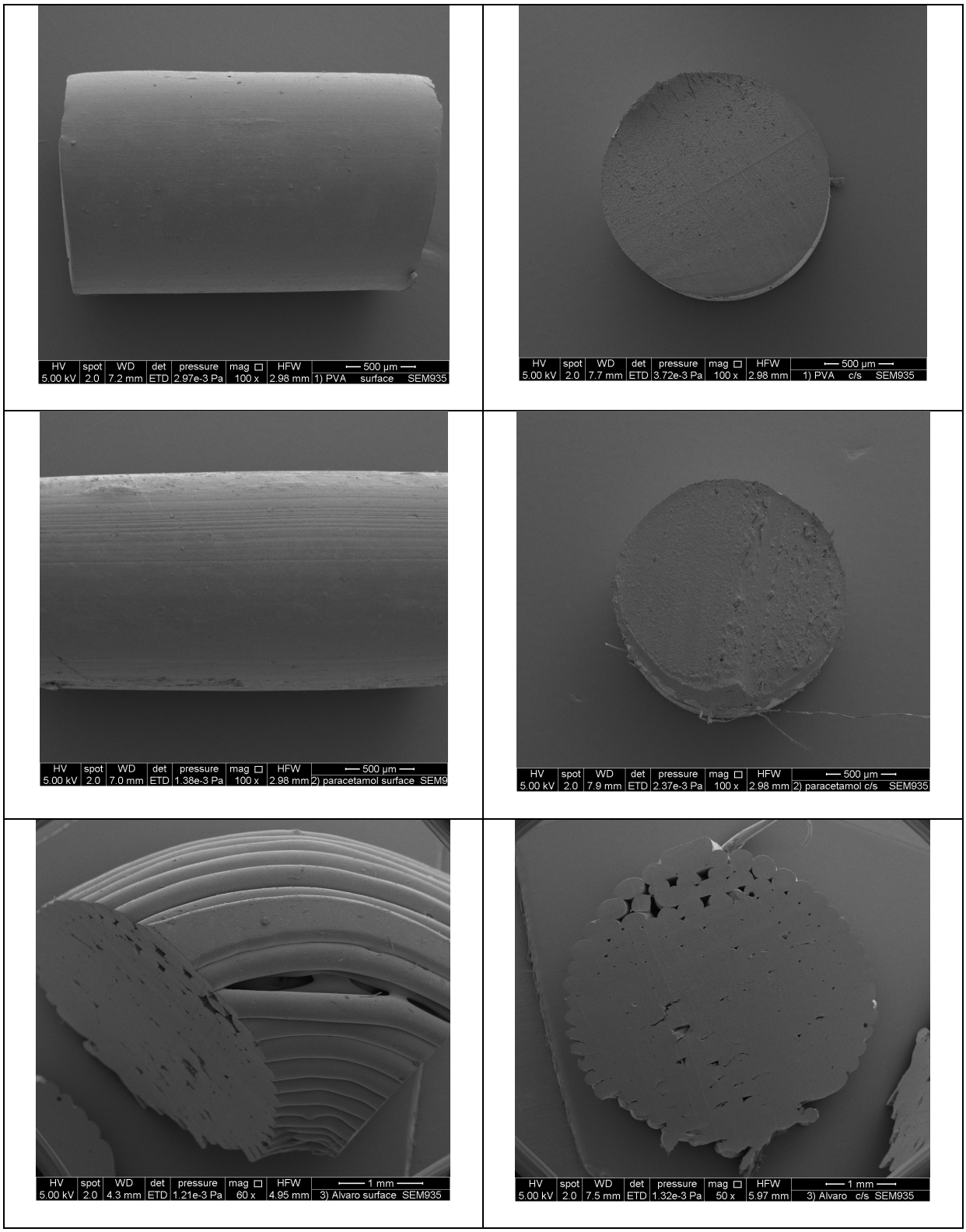
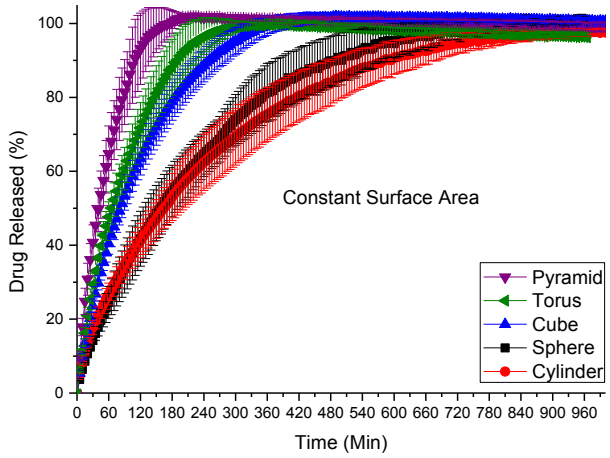


Figure 6. SEM images of the surface and cross-section of; Top) PVA filament, middle) PVA-paracetamol filament and bottom) a section of printed filament (in this case from the torus).



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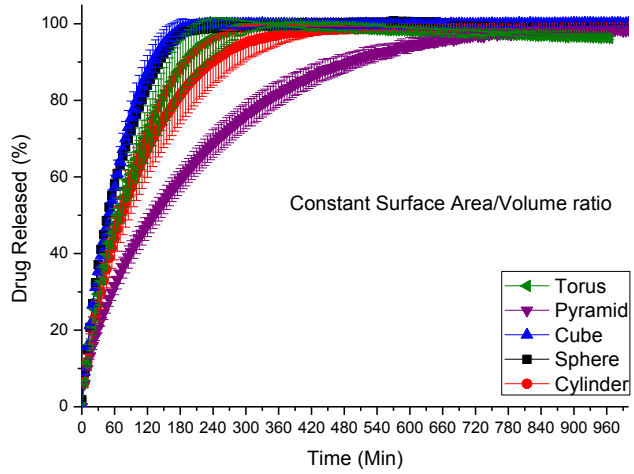

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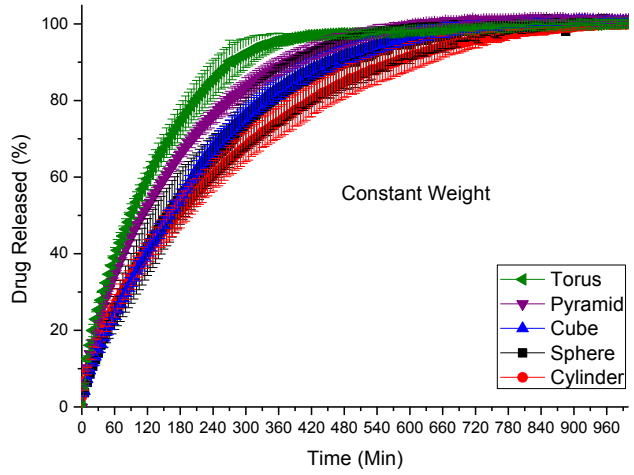

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259 Figure 7: Paracetamol dissolution profiles from 3DP solid dosage with A) surface area 275

260 mm^2, B) surface area/volume ratio 1 and C) 500 mg mass in phosphate buffer (pH 6.8)

Conclusions

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