Influence of Geometry on the Drug Release Profiles of Stereolithographic (SLA) 3D Printed Tablets

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Abstract

Additive manufacturing (3D printing) permits the fabrication of tablets in shapes unattainable by powder compaction and so the effects of geometry on drug release behavior is easily assessed. Here, tablets (printlets) comprising of paracetamol dispersed in polyethylene glycol were printed using stereolithographic 3D printing. A number of geometric shapes were produced (cube, disc, pyramid, sphere and torus) with either constant surface area (SA) or constant surface area/volume ratio (SA/V). Dissolution testing showed that printlets with constant SA/V ratio released drug at the same rate, while those with constant SA released drug at different rates. A series of tori with increasing SA/V ratio (from 0.5 to 2.4) were printed and it was found that dissolution rate increased as the SA/V ratio increased. The data show that printlets can be fabricated in multiple shapes and that dissolution performance can be maintained if the SA/V ratio is constant or that dissolution performance of printlets can be fine-tuned by varying SA/V ratio. The results suggest that 3D printing is therefore a suitable manufacturing method for personalized dosage forms.

Key words:

3D printing; additive manufacturing; Paracetamol; tablets; stereolithographic

Introduction

The development of new actives with high potencies and narrow therapeutic indices combined with the increasing desire for personalisation of medicines (in terms of dose strength and/or drug combinations) are driving factors changing the landscape of pharmaceutical manufacturing, compelling the pharmaceutical industry to consider new methods of pharmaceutical production. The advent of 3D printing (3DP), and the range of technologies developed, has resulted in a new era of additive manufacturing approaches in which material is deposited layer-by-layer to fabricate solid objects. 3DP offers many qualities ideally suited to meet the challenges facing the pharmaceutical sector; small production runs, infinite variability of dose and/or drug combinations and the possibility to use a wide range of excipients to solubilise, target or control drug release (1).

The kinetics of drug release from oral dosage forms can be influenced by different parameters including dimension and shape (2-4). Karasulu et al (5) found that the dissolution rate from erodible polymeric tablets containing theophylline was affected by the geometrical shape, polymer ratio and inclusion of diluents in the formulation, concluding that geometry played an important role in determining drug release rates. Raju et al (6) also reported that the drug release from hydrophilic polymeric tablets was directly related to the surface area to volume ratio (SA/V) of the tablets.

One limitation of these studies is that to create multiple tablet geometries requires production of specific molds. In this aspect, 3D printing offers great potential, because it allows the fabrication of varied and complex shapes, designed with computer-aided design (CAD) software (1, 7-9). Previously (10), we investigated the effect that geometry had on the drug release of paracetamol-loaded (4% wt./wt.) polyvinylalcohol (PVA) 3D printed tablets (Printlets®). Using a fused deposition modeling (FDM) 3D printer we fabricated printlets in 5 geometric shapes that would have been difficult to achieve with traditional powder compaction. The results showed surface area to volume ratio (SA/V) was the dominant

factor influencing drug release. However, variations in drug release rates between geometries were seen because erosion of the tablet occurred during dissolution.

In this work, we explore the effect of geometry on drug release from cross-linked polymeric printlets, created with stereolithography (SLA) 3D printing. With this technology a laser is focused into a resin tank, causing photopolymerization of the resin. By moving the laser in a raster pattern, objects can be created in a layer-by-layer fashion. To enhance the speed of photopolymerization a photoinitiator (PI) is used. A PI absorbs energy to produce an initiating species (often a free radical) which is then able to first attack a monomer and then add consecutively other monomers to this growing polymer chain (11). Since this process occurs in three dimensions, it yields a crosslinked network. Additional excipients (not involved in the photopolymerization process) can become entrapped in the crosslinked network, enabling the possibility of fabricating drug-loaded tablets.

Materials and methods

Polyethylene glycol diacrylate (PEGda, average MW 700), diphenyl(2,4,6-trimethylbenzoyl) phosphine oxide (TPO) and paracetamol were purchased from Sigma Aldrich Ltd (UK). The salts for preparing the buffer dissolution media were purchased from VWR International Ltd., Poole, UK. All materials were used as received.

Resin preparation: PEGda was used as the photopolymerizable resin, TPO was used as the photoinitiator (2% wt./wt.) and paracetamol was used as a model drug (4% wt./wt.). Briefly, TPO was added to PEGda and kept protected from light with constant stirring until complete dissolution (approximately 45 min). Paracetamol was added next and stirring continued until complete dissolution (approximately 25 minutes), the mixture was then transferred into the resin tray of the printer to begin the fabrication of the tablets.

3D printing: All printlets were fabricated with a Formlabs 1+ SLA 3D printer (Formlabs Inc, USA). The printer is equipped with a 405nm laser and can fabricate objects with a resolution of 300 microns and a layer thickness of 25, 50, 100 or 200 microns. The electronic shapes (Figure 1) were designed with AutoCAD® 2017 and exported as a stereolithography file (.stl) into the 3D printer software (PreForm Software v. 2.11.1 Formlabs Inc.). The parameters of the printer were set to flexible resin (version 01) with a layer thickness of 0.05 mm. The dimensions of the printlets were measured using an ellectronic calliper (0.150 mm PRO-MAX, Fowler, mod S 235 PAT).

Scanning electron microscopy (SEM): Surface and cross-section images of the printlets 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).

Drug loading: To determine drug concentrations of the printlets, they were crushed using a mortar and pestle and then dissolved in 1 L of deionized water with constant magnetic stirring for 24 h. Samples of the solutions were then filtered through 0.45 µm filters (Millipore Ltd., Ireland). The amount of drug in solution was determined using HPLC (Hewlett Packard 1050 Series HPLC system, Agilent Technologies, UK). The assay entailed a mobile phase consisting of water (85%) and methanol (15%), through an Eclipse Plus C18 5µm column, 15 x 4.6 cm (Agilent, USA). The mobile phase was pumped at a flow rate of 1 ml/min and the eluent was screened at a wavelength of 247 nm. The injection volume was 20 µL and the temperature was kept at ambient. The measurements were made in triplicate.

Dynamic dissolution testing conditions: Drug dissolution profiles for the 3D printed tablets were obtained with a USP-II apparatus (Model PTWS, Pharmatest, Germany). The hydrogels were placed in 750 mL of 0.1 M HCl for 2 h to simulate the gastric compartment, and then transferred into 950 mL of modified Hanks (mHanks) bicarbonate physiological medium for 35 min (pH 5.6 to 7); 3) and then in modified Krebs buffer (1000ml) (pH 7 to 7.4 and then to 6.5). The modified Hanks buffer based dissolution medium (12) forms an in-situ

modified Kreb's buffer (13) by addition of 50 mL of pre-Krebs solution to each dissolution vessel. These conditions mimic transit through the small intestinal and colonic environments. The buffer capacity and ionic composition of the physiological bicarbonate buffers also closely match the buffer capacities of the intestinal fluids collected from different parts of the gut in humans (12-15). The paddle speed of the USP-II was fixed at 50 rpm, and the tests were conducted at 37 +/-0.5 °C (n=3). The percentage of drug released from the formulations was determined using HPLC, using the same method as described above.

Satistical analysis was performed using IBM SPSS Statistics 22 software. Comparison of means of drug release during 10 h was analysed using one-way ANOVA repeated measures, followed by Tukey HSD Post Hoc Test. $P < 0.05$ was considered as a significant level. To evaluate the relationship between drug release with weight and SA/V, simple and multiple regression analysis were performed.

SA/V change: the change in SA/V ratio was calculated by measuring the initial dimensions of the printlets and after placing them in 0.1 M HCl for 2 h, then in modified Hanks (mHanks) bicarbonate physiological medium during 22 h at 37 °C to simulate the dissolution test conditions. The final SA/V ratio was calculated using equation 1.

$$Final\ \frac{SA}{V}(\%) = \frac{SA/V_s}{SA/V_i} \times 100 \qquad \text{Eq 1}$$

Where:

SA/V_s = SA/V for the swollen tablets (after 24 h).

SA/V_i = Initial SA/V.

Swelling ratio (SR): Printlets were blotted with filter paper to remove any uncured liquid formulation on the surface immediately following printing, then they were weighed (Wi). After this, printlets were placed into HCl (0.1 M) for 2h then into modified Hanks (mHanks)

bicarbonate physiological medium for 8 h; after this, the excess water was carefully wiped off and the tablets were weighed (Ws). The SR was calculated using equation 2.

$$SR = \frac{W_s}{W_i} \qquad \text{Eq 2}$$

Where:

W_s = weight of the swollen tablet (after 24 h).

W_i = initial weight of the tablet.

Results.

Paracetamol was readily dissolved in PEGda, yielding a clear solution similar to the results obtained by Wang et al and Martinez et al (16-17), and the laser was able to photocure the resin. Figures 2-4 show the various printlets produced and it is apparent that the SLA printer was able to fabricate them with good resolution. Tables 1 and 2 quantify the physical dimensions of the printlets, all of which were close to the target values set in the CAD designs. SEM images of the printlets (Figure 5) do not show any visible pores, indicating that the resin photocured with a high crosslinking density.

The average drug content in the printlets was 3.82 ± 0.12 % w/w (the expected content based on the resin formulation was 4% w/w) and no degradation peaks were seen in the HPLC chromatograms. This result suggests that there is little drug degradation during printing, which was to be expected since SLA printing involves no significant rise in temperature and paracetamol does not degrade under light. This is a potential benefit of SLA printing compared with fused deposition modelling (FDM) printing; the latter involves appreciable rises in temperature and has been shown to cause significant drug degradation when used to fabricate polymeric tablets (18). The slightly lower than expected concentration

might be due to incomplete drug extraction from the crosslinked printlet prior to HPLC analysis; this is an issue seen previously by Wang et al (16).

Figures 6 and 7 show the drug release profiles from the printlets with similar SA and SA/V ratios. Printlets with similar initial surface areas did not show similar drug release profiles; statistical analysis of the data showed that drug release was significantly different for the sphere (which had the lowest value for SA/V) compared with almost all of the other shapes, except the cylinder. Drug release from the cylinder was significantly different only from the pyramid (which has the highest SA/V ratio). In the case of printlets with similar initial SA/V ratios, the results showed that the percentage of drug released from any shape were not significantlly different (p= 0.05).

In our previous work (10) it was also noted that the mass of the tablets could influence the drug release kinetics. In this work we performed simple and multiple regression to compare the relation and possible influence that both the SA/V and weight may have on the drug release kinetics. The multiple regression equation is:

$$\textit{Drug release 10h} = -1.573 + 60.9.SA/V - .014weight$$

This means that drug release increases on average by 60.9 units as the SA/V value increases by one, after adjusting for weight. The coefficient for weight is -.055 in the simple regression and -.014 in the multiple regression, hence adjusting for SA/V decreases the effect of weight on drug release. Weight is significant in the simple regression (p-value= .002) but not in the multiple regression (p-value= .350). The coefficient for SA/V is 67.9 in the simple regression and 60.9 in the multiple regression, hence adjusting for weight decreases the effect of SA/V on drug release. SA/V is significant in both, the simple and the multiple regression (p-value= 0.000 on both). Therefore, SA/V is an important characteristic to predict the speed of drug release after adjusting for weight. The adjusted R square is

0.604, suggesting that approximately 60% of the variation in drug release is explained by its linear relationship with weight and SA/V.

The physical parameters of the printlets are shown in Tables 1 and 2. The results show that as the SA/V increases, the speed of drug release does as well. This is in agreement with other studies; Parojcić et al (19) reported that the drug release kinetics from carbomer matrix tablets can be controlled by modifying the type and content of polymer and the geometry of tablets. In particular, they concluded that the relative surface area (absolute surface area/absolute volume) is a reliable parameter to compare the drug release kinetics from tablets of different shapes. Tablet surface area/volume has also been found to be the most relevant parameter determining the rate of drug release from hydroxypropylmethylcellulose (HPMC) matrix tablets and lipid tablets (2, 20).

Since SA/V ratio has an important influence on the speed of drug release from 3DP tablets, a group printlets with a range of different initial SA/V ratios were printed, in order to compare their speed of drug release. All the printlets for this section of the study were tori, as this is the geometry that can be altered to give the widest range of SA/V ratios. Additionally, as noted by Wang et al (16), a torus is a complex shape that would be difficult to fabricate using conventional techniques and it is a shape that has been studied for the possibility to produce tablets with a zero-order release (21-22). To achieve a SA/V ratio greater than 1.4 it was necessary to print a tablet comprised of multiple tori; Table 3 shows the physical parameters of the printlets. Again, the flexibility of 3D printing facilitates the simple manufacture of these very complex shapes.

Figure 8 shows the results of drug dissolution for the printlets with different SA/V ratios. The data show that drug release becomes faster as the SA/V increases, confirming the observation reported above that among the parameters affecting drug release kinetics, SA/V plays an important role. It is also clear from these data that 3D printing is a new approach to

pharmaceutical manufacturing that allows precise tailoring of dissolution profiles through changing geometry rather than by altering the composition of the formulation.

Conclusion

SLA 3DP is suitable for fabricating complex drug-loaded tablets with a good resolution. The results from this work show that of all the geometric parameters, SA/V ratio has the greatest influence on the drug release kinetics from PEGda printlets. One immediate benefit of this outcome is that it will be possible to adjust the dose of printlets so that they are tailored to the needs of an individual patient, but that by changing SA/V ratio the specific drug release profile can be maintained.

References

(1) Trenfield SJ, Awad A, Goyanes A, Gaisford S, Basit AW. 3D Printing Pharmaceuticals: Drug Development to Frontline Care. Trends Pharmacol Sci 2018. doi:10.1016/J.TIPS.2018.02.006.

(2) Gökçe EH, Özyazici M, Ertan G. The effect of geometric shape on the release properties of metronidazole from lipid matrix tablets. J Biomed Nanotechnol. 2009;5:421–427. doi:10.1166/jbn.2009.1052

(3) Karasulu HY, Ertan G. Different geometric shaped hydrogel theophylline tablets: statistical approach for estimating drug release. Farmaco. 2002;57:939–945.

(4) Skoug JW, Borin MT, Fleishaker JC, Cooper AM. In Vitro and in Vivo Evaluation of Whole and Half Tablets of Sustained-Release Adinazolam Mesylate. Pharm Res. 1991;8:1482–1488. doi:10.1023/A:1015834114359

(5) Karasulu HY, Ertan G, Köse T. Modeling of theophylline release from different geometrical erodible tablets. Eur J Pharm Biopharm. 2000;49:177–182.

(6) Raju PN, Prakash K, Rao TR, Reddy BCS, Sreenivasulu V, Narasu ML. Effect of Tablet Surface Area and Surface Area / Volume on Drug Release from Lamivudine Extended Release Matrix Tablets. Int J Pharm Sci Nanotechnol. 2010;3:872–876.

(7) Ventola CL. Medical Applications for 3D Printing: Current and Projected Uses. Pharmacy Therapeutics. 2014;39:704–11.

(8) Fina F, Goyanes A, Gaisford S, Basit AW. Selective laser sintering (SLS) 3D printing of medicines. Int J Pharm. 2017;529:285-293. doi: 10.1016/J.IJPHARM.2017.06.082

(9) Goyanes A, Scarpa M, Kamlow M, Gaisford S, Basit AW, Orlu M. Patient acceptability of 3D printed medicines. Int J Pharm. 2017;530:71–8. doi:10.1016/j.ijpharm.2017.07.064.

(10) Goyanes A, Martinez PR, Buanz A, Basit A, Gaisford S. Effect of geometry on drug release from 3D printed tablets. Int J Pharm. 2015;494:657-663. doi:10.1016/j.ijpharm.2015.04.069

(11) Fouassier JP, Lalevée J. Photopolymerization and Photo-Cross-Linking, in: Photoinitiators for Polymer Synthesis. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2012 p. 3–9. doi:10.1002/9783527648245.ch1

(12) Liu F, Merchant HA, Kulkarni RP, Alkademi M, Basit AW. Evolution of a physiological pH 6.8 bicarbonate buffer system: application to the dissolution testing of enteric coated products. Eur J Pharm Biopharm. 2011;78:151–157. doi:10.1016/j.ejpb.2011.01.001

(13) Fadda HM, Merchant HA, Arafat BT, Basit AW. Physiological bicarbonate buffers: stabilisation and use as dissolution media for modified release systems. Int J Pharm. 2009;382:56-60. doi:10.1016/j.ijpharm.2009.08.003

(14) Goyanes A, Hatton GB, Basit AW. A dynamic in vitro model to evaluate the intestinal release behaviour of modified-release corticosteroid products. J Drug Deliv Sci Technol. 2014;25:36–42. doi:10.1016/j.jddst.2014.12.002

(15) Goyanes A, Hatton GB, Merchant HA, Basit AW. Gastrointestinal release behaviour of modified-release drug products: dynamic dissolution testing of mesalazine formulations. Int J Pharm. 2015;484:103–108. doi:10.1016/j.ijpharm.2015.02.051

(16) Wang J, Goyanes A, Gaisford S, Basit AW. Stereolithographic (SLA) 3D printing of oral modified-release dosage forms. Int J Pharm. 2016;503:207–212. doi:10.1016/j.ijpharm.2016.03.016

(17) Martinez PR, Goyanes A, Basit AW, Gaisford S. Fabrication of Drug-Loaded Hydrogels with Stereolithographic 3D Printing. Int J Pharm. 2017;532:313–7. doi:10.1016/j.ijpharm.2017.09.003.

(18) Goyanes A, Buanz ABM, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. Eur J Pharm Biopharm. 2014;89:157–62. doi:10.1016/j.ejpb.2014.12.003

(19) Parojcić J, Durić Z, Jovanović M, Ibrić S. An investigation into the factors influencing drug release from hydrophilic matrix tablets based on novel carbomer polymers. Drug Deliv. 2004;11:59–65. doi:10.1080/10717540490265379

(20) Reynolds TD, Mitchell S, Balwinski KM. Investigation of the effect of tablet surface area/volume on drug release from hydroxypropylmethylcellulose controlled-release matrix tablets. Drug Dev Ind Pharm. 2002;28:457–66. doi:10.1081/DDC-120003007

(21) Kim C. Compressed Donut-Shaped Tablets with Zero-Order Release Kinetics. Pharm Res. 1995;12:1045–1048. doi:10.1023/A:1016218716951

(22) Kim C. Release kinetics of coated, donut-shaped tablets for water soluble drugs. Eur J Pharm Sci. 1999;7:237–242.

Shape	Surface area (mm^2)	Volume (mm^3)	SA/V ratio	Weight (mg)	Density (mg/mm^3)
Cylinder	284.0 ± 6.8	321.1 ± 13.3	0.885 ± 0.016	403.0 ± 3.8	1.26 ± 0.05
Sphere	260.2 ± 6.0	394.7 ± 13.7	0.659 ± 0.008	559.0 ± 13.4	1.42 ± 0.02
Pyramid	253.4 ± 0.9	220.3 ± 1.6	1.150 ± 0.004	346.1 ± 4.5	1.57 ± 0.01
Torus	278.4 ± 3.6	276.1 ± 7.4	1.009 ± 0.015	358.7 ± 2.3	1.30 ± 0.04
Cube	292.6 ± 2.1	340.6 ± 3.7	0.859 ± 0.003	404.7 ± 6.9	1.19 ± 0.02

Table 1. Various physical parameters for printlets with similar surface areas

Shape	Surface area (mm^2)	Volume (mm^3)	SA/V ratio	Weight (mg)	Density (mg/mm^3)
Cylinder	210.8 ± 3.4	222.8 ± 7.0	0.946 ± 0.017	274.7 ± 1.4	1.23 ± 0.05
Sphere	116.9 ± 1.9	118.9 ± 2.9	0.984 ± 0.008	142.0 ± 4.0	1.19 ± 0.01
Pyramid	283.5 ± 11.1	281.3 ± 16.6	1.009 ± 0.019	424.7 ± 35.4	1.51 ± 0.04
Torus	278.4 ± 3.6	276.1 ± 7.4	1.009 ± 0.015	358.7 ± 2.3	1.30 ± 0.04
Cube	213.6 ± 4.6	212.5 ± 6.8	1.006 ± 0.011	268.4 ± 6.2	1.26 ± 0.02

Table 2. Various physical parameters for printlets with similar initial SA/V ratios

Physical Parameter					
SA (mm^2)	1263.3	575.8	276.4	278.6	190.5
V (mm^3)	2526.6	823.4	276.4	197.8	78.0
SA/V	0.5	0.7	1	1.4	2.4
Weight (mg)	3388.0 (RSD 4.1%)	1029.8 (RSD 3.6%)	358.7 (RSD 0.6%)	490.3 (RSD 2.0%)	102.3 (RSD 1.5%)

Table 3. Various physical parameters of the group of tori with different SA/V ratios

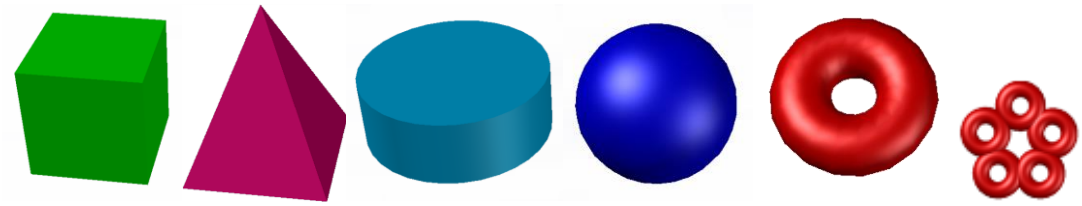

Figure 1. CAD drawings of the printlets used to explore the effect of geometry on drug release

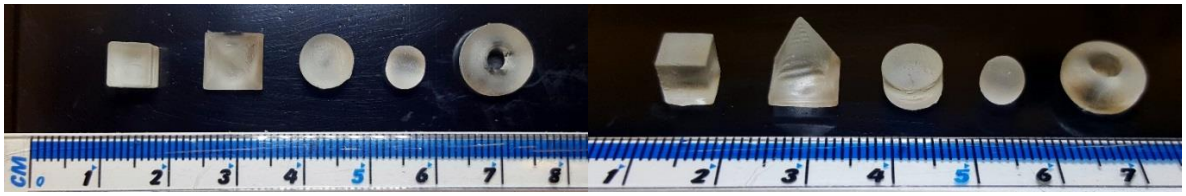

Figure 2. Printlets with similar initial SA/V ratios

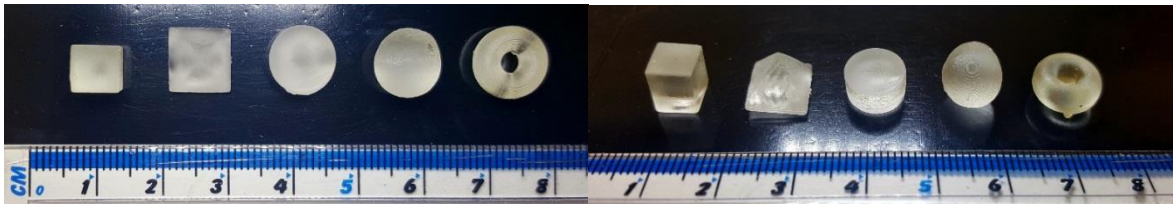

Figure 3. Printlets with similar initial surface areas

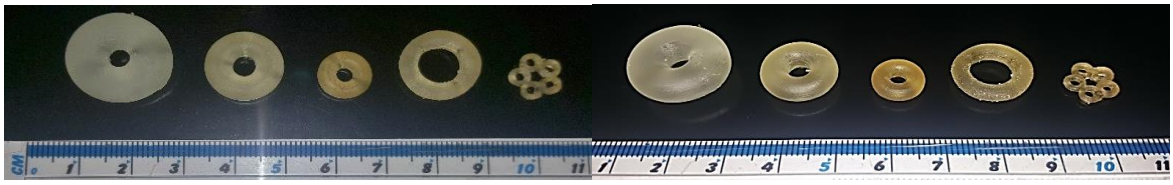

Figure 4. Torus printlets with different SA/V ratios

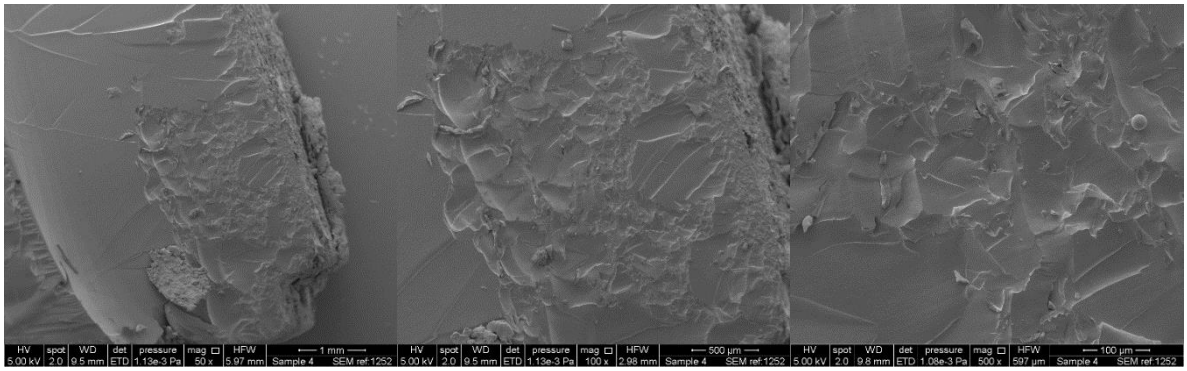

Figure 5. SEM images of the printlets, showing surface detail

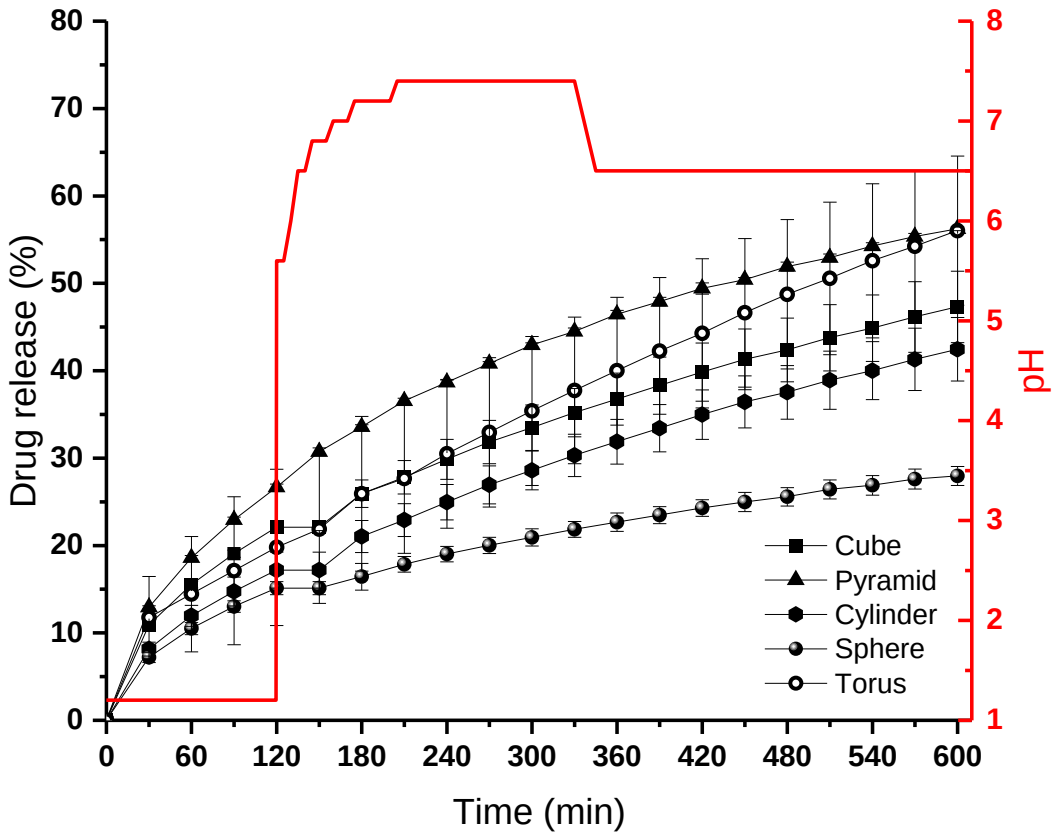

Figure 6. Dissolution profiles for printlets with similar surface areas

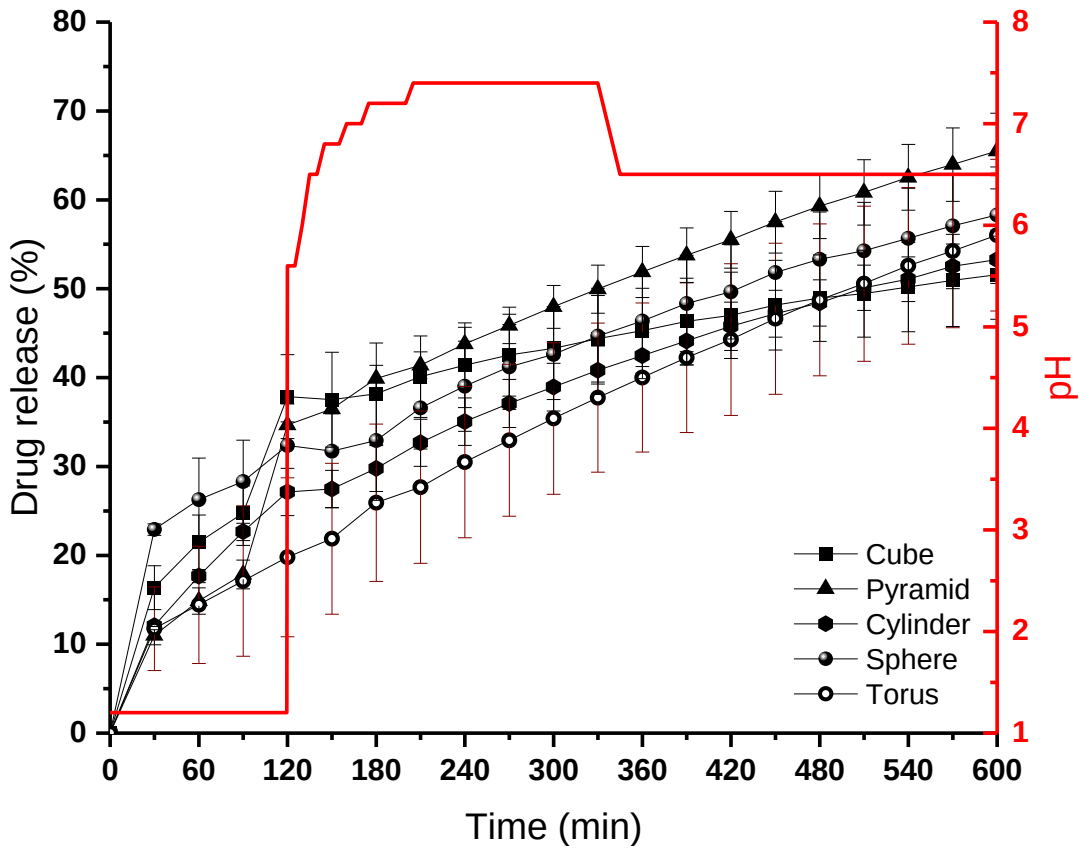

Figure 7. Dissolution profiles for printlets with similar SA/V ratios

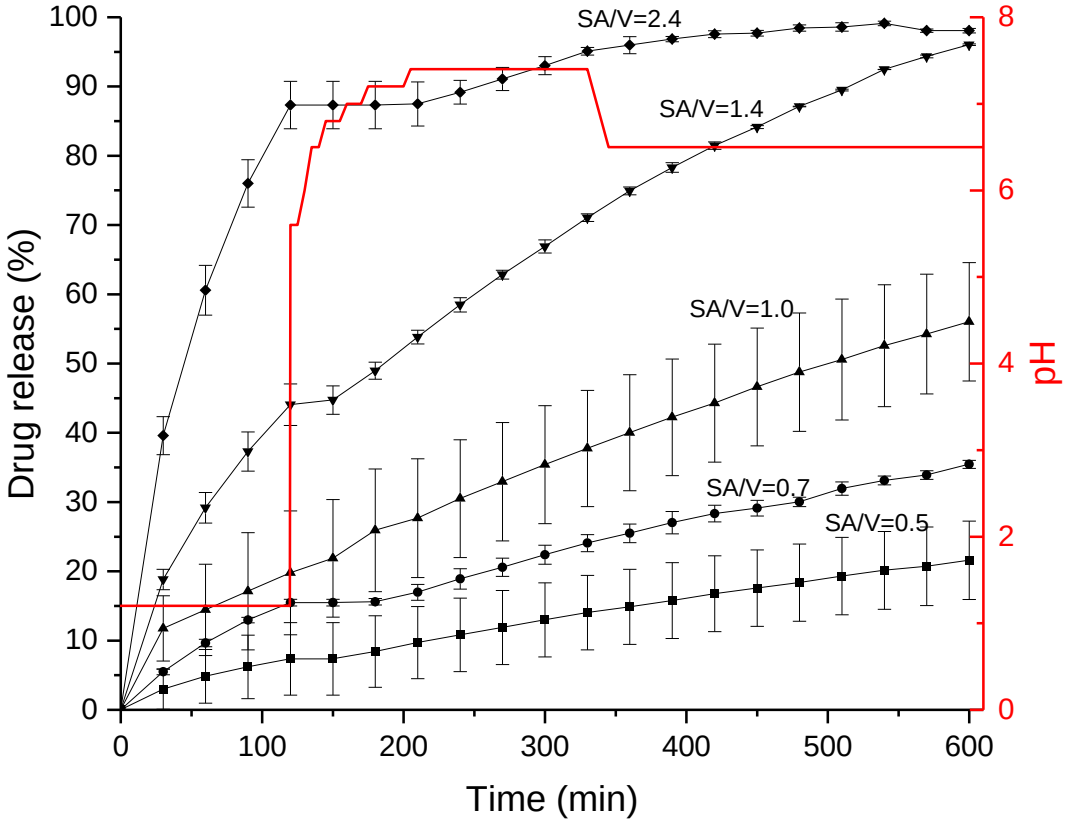

Figure 8. Drug release from torus printlets with different SA/V ratios