# Fused-Filament 3D Printing (3DP) for Fabrication of Tablets

Alvaro Goyanes[1], Asma B.M. Buanz[1], Abdul W. Basit[1,2] and Simon Gaisford[1,2*]

[1]UCL School of Pharmacy, University College London, 29-39 Brunswick Square, London, WC1N 1AX, UK

[2]FabRx Ltd, 3 Romney Road, Ashford, Kent, TN24 0RW

*Corresponding author

E-mail: s.gaisford@ucl.ac.uk

Tel: +44(0) 207 753 5853

Fax: +44(0) 207 753 5942

**Abstract**

The use of fused-filament 3D printing (FF 3DP) to fabricate individual tablets is demonstrated. The technology permits the manufacture of tablets containing drug doses tailored to individual patients, or to fabrication of tablets with specific drug-release profiles. Commercially produced polyvinyl alcohol (PVA) filament was loaded with a model drug (Fluorescein) by swelling of the polymer in ethanolic drug solution. A final drug-loading of 0.29% w/w was achieved. Tablets of PVA/Fluorescein (10 mm diameter) were printed using a 3D printer. It was found that changing the degree of infill percentage in the printer software varied the weight and volume of the printed tablets. The tablets were mechanically strong and no significant thermal degradation of the active occurred during printing. Dissolution tests were conducted in modified Hank's buffer. The results showed release profiles were dependent on the infill percentage used to print the tablet. The study indicates that FF 3DP has the potential to offer a new solution for fabricating personalized-dose medicines or unit dosage forms with controlled-release profiles. In addition, the low cost of FDM printers means the paradigm of extemporaneous or point-of-use manufacture of personalized-dose tablets is both feasible and attainable.

**Key words**

3D printing; controlled-release; fused filament printing; PVA; Fluorescein

## Introduction

The need to formulate drugs that have narrow therapeutic indices (for instance immunosuppressants or blood thinners), the increasing importance of proteomic and metabolomic analyses and the concomitant development of drugs and drug combinations personalised to the patient, are powerful drivers shaping the future of medicine design. In particular, the development of medicines personalised to the patient requires consideration of novel manufacturing technologies capable of fabricating small numbers of dosage forms, because current commercial technology only operates efficiently on a large scale. Printing technology has much potential in this area because it is possible to print drug solutions onto substrates (ink-jet printing) and to fabricate dosage forms directly (3D printing).

Ink-jet printing is particularly suited to deposition of drug solutions onto flat substrates, such as oral wafers (Buanz et al, 2011). The technology has been used to manufacture modified-release or personalized-dose medicines by printing dots of solution onto a substrate (Scoutaris et al 2011, 2012) and it has been shown possible to fabricate three-dimensional particles by printing aqueous droplets into liquid nitrogen and subsequently freeze-drying (Mueannoom et al, 2012; Sharma et al, 2013).

It is 3D printing (3DP) technology however that offers perhaps the greatest potential to revolutionize the future of pharmaceutical manufacturing (Yu et al, 2008; Wang, 2013). 3DP was developed as a tool for rapid prototyping. Typically a layer of a powdered substrate is spread over a build plate and a binding solution is deposited using an x-y printhead (analogous to ink-jet printing) to consolidate the powder. The object is then built up layer-by layer. This type of system has been widely employed to manufacture pharmaceutical dosage forms, including zero-order release tablets (Wang et al, 2006) and implants (Bbureck et al, 2007; Huang et al, 2007). The ability to change the powder and so manufacture multi-layer tablets has also been demonstrated (Katstra et al, 2000a,b; Yu et al, 2007). One limitation of this design is

that it cannot print hollow objects, because free powder will always be contained in the cavity, although even this effect has been exploited to fabricate fast-dissolving devices comprising powder contained in a polymeric shell (Yu et al, 2009a,b). An alternative technology is selective laser sintering (SLS), in which a laser is used to cure a photopolymer (this technology is used to print personalised medical devices, such as hearing aid shells).

The most recent 3DP technology is fused-filament (FF) printing, wherein a polymer strand is heated and extruded through a small tip (typically 50-100 μm) and then solidified on a build plate. FF technology has the significant advantages of cost (typical systems cost between £800-2000), the ability to fabricate hollow objects and the utility to print a range of polymers. The printer feedstock is an extruded polymer filament, typically 1.75 – 3 mm in diameter. One of the prime benefits of FF 3DP is that it is possible in principle to incorporate drug into the polymer filament so that the printed dosage form is drug loaded.

To our knowledge, there has been no demonstration on the use of FF printing to manufacture drug-loaded unit dosage forms, although recent work using a similar system to print a paste has been reported (Khaled et al, 2014). Hence, the specific aims of this work were evaluate a method to load drug into the polymer filament, to print drug-loaded tablets using an FF 3DP and to explore whether varying the print settings enabled control over the dissolution kinetics of the final tablet and so offer a new method of manufacturing controlled-release dosage forms. Fluorescein was selected as a model drug because of its thermal stability and ease of quantification.

## Materials and Methods

Polyvinyl alcohol (PVA, a water-soluble synthetic polymer of 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). Absolute ethanol was of analytical grade. Fluorescein sodium salt was obtained from Sigma-Aldrich, Poole, UK. Salts for

preparing buffer dissolution media were purchased from VWR International Ltd., Poole, UK.

*Preparation of PVA filament loaded with fluorescein*: PVA filaments (~5 m in length) were placed in an ethanolic solution of fluorescein (2% w/v) with magnetic stirring for 24h. The drug-loaded filaments were removed and dried in an oven to constant weight (1.5h at 60°C) and stored in a vacuum desiccator until printing. The drug-load was determined with HPLC (see below).

*Printing of Fluorescein tablets:* Tablets were fabricated with a MakerBot Replicator 2x Desktop 3D printer (MakerBot Inc, USA). The templates used to print the tablets were designed with MakerWare Software (v. 2.2.2). The selected size for the tablet was X=10 mm, Y=10 mm and Z=3.6 mm (Figure 1). The printer settings that were found to produce the best tablets were standard resolution without the raft option activated, extrusion temperature (220 °C), speed while extruding (90mm/s), speed while traveling (150mm/s), number of shells (2) and layer height (0.20mm). The infill percentage was varied (0%, 10%, 25%, 50% or 90%, 100%) in order to produce tablets of different weights and infill patterns (Table 1 and Figure 2)

*Determination of tablet morphology:* The diameter and thickness of the tablets were measured using a digital calliper. Pictures were taken with a Nikon CoolpixS6150 with the macro option of the menu. Additional pictures of fluorescein tablets were taken in a dark room under UV light (Mineralight® Lamp UVGL-58, USA) at a wavelength of 365nm to evaluate the distribution of fluorescein in the tablets.

*Determination of fluorescein concentration:* One tablet or a drug-loaded strand before printing (approx. 0.3g) was placed in a 1L volumetric flask containing bicarbonate buffer with magnetic stirring until complete dissolution. Samples were then filtered

through 0.22 µm filters (Millipore Ltd, Ireland). Concentrations of fluorescein were determined at 490nm with a Cary 100 UV-VIS spectrophotometer (Agilent Technologies, UK). Measurements were performed in duplicate.

*Dissolution testing:* Drug release profiles from printed tablets were determined with a USP-II apparatus (Model PTWS, Pharmatest, Germany). In each assay, tablets were placed at the bottom of the vessel and were stirred (50 rpm) in dissolution medium (900 mL) at 37°C. Tests were conducted in triplicate under sink conditions. During the dissolution test, samples were automatically removed and filtered through 0.1mm filters and fluorescein concentration was determined using an in-line UV spectrophotometer (Cecil 2020, Cecil Instruments Ltd., Cambridge, UK) operated at 490nm. Data were processed using Icalis software (Icalis Data Systems Ltd, Berkshire, UK). Experiments were conducted in a dark room to avoid photo-degradation of fluorescein.

Dissolution tests were performed in a modified bicarbonate buffer (pH 6.8) controlled by an Auto pH System™ (Merchant et al, 2012). The bicarbonate buffer was chosen because of its better resemblance to the physiological characteristics of gastrointestinal fluid than phosphate buffers (Fadda et al, 2005; Liu et al, 2011). The medium, adapted from Hank's buffer, is primarily a bicarbonate buffer, in which bicarbonate ($HCO_3^-$) and carbonic acid ($H_2CO_3$) co-exist in equilibrium, along with dissolved $CO_2$, resulting from the dissociation of the latter (Equation 1).

$$\begin{array}{c} CO_2\,(g) \\ \Updownarrow \\ H_2O + CO_2(aq) \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \end{array}$$

Equation 1

Adjusting the concentration of carbonic acid ($H_2CO_3$) and bicarbonate ($HCO_3^-$) in accordance with the Henderson-Hasselbalch equation (Equation 2) allows control of the buffer pH.

$$pH = pKa + \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

Equation 2

Purging the solution with carbon dioxide, which promotes the formation of carbonic acid, increases the carbonic acid concentration. Similarly, purging with an inert gas (such as Helium) reduces the carbonic acid to bicarbonate ratio, which removes dissolved $CO_2$ from the solution and so pushes the equilibrium to the left. The purging of gases is regulated by an Auto pH System™, automatically triggered by a pH feedback from solution. Controlling the pH of the medium to pH 6.8 simulates the pH conditions of the small intestine. Additionally, other components are added to simulate the ionic strength and composition of gastrointestinal fluid (136.9 mM NaCl, 5.37 mM KCl, 0.812 mM $MgSO_4.7H_2O$, 1.26 mM $CaCl_2$, 0.337 mM $Na_2HPO_4.2H_2O$, 0.441 mM $KH_2PO_4$, 4.17 mM $NaHCO_3$, $CO_2$ quantity sufficient to maintain the pH at 6.8).

**Results and discussion**

Tablets were fabricated initially using the commercially available extruded PVA polymer, prior to any drug loading, in order to assess the suitability and capability of the printer. Tablets were produced with a high degree of repeatability of weight and physical dimension (Table 1 and Figure 2). Tablets were mechanically strong enough to handle without damage and, although they are not discussed in this paper, it was possible to create tablets of varying size using the scaling factor in the printer driver software. This immediately indicates that FF 3DP has the potential to offer a new

manufacturing solution for fabricating personalized-dose medicines, since scaling the tablet to the appropriate volume or weight would permit fabrication of specific doses. In addition, the low cost of FF printers means the paradigm of extemporaneous or point-of-use manufacture of personalized-dose tablets would appear to be both feasible and attainable.

Of course, to fabricate pharmaceutically relevant tablets it is necessary to incorporate a drug into the polymer filament, prior to the fabrication step. Fluorescein was selected as it has a low molecular weight, good solubility in a range of solvents and a convenient UV chromophore for analysis. Additionally, its fluorescence under UV light meant it was possible to image the filament before and after printing and so determine the location of the drug in the polymer. Since the PVA polymer used here is commercially available pre-extruded for the printer, drug was loaded into the polymer from solution. In this method, the polymer filament is swelled in a solution of drug for a period of time before removal and drying. In principle, and assuming no chemical interaction between the drug and polymer, the drug should passively diffuse into the polymer matrix and be trapped following the drying phase. The method has the considerable advantage that the diameter of the polymer filament is the same before and after drug loading, which means the printer easily extrudes it. It is also cheap, versatile and requires little method development, save selection of a suitable solvent.

It was not possible to load the drug into the polymer from aqueous solution, because the PVA filament started to dissolve with 10 min and did not return to its original geometric size and morphology on drying. This was not unexpected because the polymer was not chemically cross-linked. Drug loading from ethanol was found to be more successful, because the polymer filament did not dissolve, even after 24h. However, the final drug-loading was relatively low 0.29 ± 0.01 % w/w. Further, the fluorescein is seen mainly towards the surface of the strands (Figure 3), indicating relatively slow diffusion of the drug into the polymer. It is important to note here that

208 the main aim of this work was to assess the feasibility of 3DP as a method to
209 fabricate unit dosage forms and so while the loading efficiency was low, sufficient
210 drug was present to enable dissolution analysis. Clearly, loading drug from other
211 solvents may result in higher encapsulation and/or greater diffusion into the polymer
212 strands.
213 One further point of interest is that analysis of the printed tablets showed a drug
214 content of 0.28 ± 0.02 % w/w. This demonstrates that the drug was not degraded as
215 it passed through the heated extruder of the printer (fluorescein melting temperature,
216 320 $^{o}$C). It is important to recognise, however, that the relatively high extrusion
217 temperature of PLA means 3DP may not be universally suitable for thermally labile
218 drugs.
219 The tablet template was imported into the Makerware software prior to printing as a
220 stereolithography (.stl) file. This file type encodes only the surface data (or shell) of
221 the object to be printed. It is necessary for the 3DP software to define the thickness
222 of the shell (so that there is an object of some physical size to be printed) but in
223 essence a hollow object will be printed. To increase the mechanical strength of the
224 object, the user can select an infill percentage to be used during printing (the infill
225 percentage is the degree to which the printer will pack the void space with polymer
226 and will vary from 0, empty, to 100, solid). Greater infill percentages will result in
227 stronger objects. It follows that there is the potential to use the infill percentage to
228 modulate the physical properties of the 3DP tablet, and so the dissolution profile.
229 Here, tablets were printed with six different infill percentages (0, 10, 25, 50, 90 and
230 100%). Tablets with 0% infill were hollow because only the shell was printed. Tablets
231 with 10%, 25% and 50% infill showed different internal patterns. These patterns got
232 more dense as the infill value increased. 90% infill tablets showed no cavities and
233 appeared as a compact mass. Photographs of selected tablets are shown in the
234 cross-section images in Figure 4.

It is worth noting that the fluorescein is distributed uniformly inside the tablets, the implication being that during printing the softening of the polymer allows uniform redistribution of the fluorescein.

It can be seen from Table 1 and the photographs in Figure 4 that the tablet weights and physical dimensions increased with increasing infill percentage. There is a very good linear relationship between the infill and the tablet weight ($r^2$ = 0.9741), suggesting that it could also be possible to control the drug dose by varying the infill percentage. The infill percentage also slightly increased the thickness of the tablets (the lengths remain almost constant).

For dissolution testing tablets were selected with low (10%), medium (50%) and high (90%) infill. Dissolution tests were conducted in modified Hank's bicarbonate buffer (pH 6.8), more representative of human small intestinal fluid. It is apparent that the dissolution profiles show different behaviours. Faster drug release was seen with a lower infill percentage (Figure 5). The 10% infill tablets show complete release after 6 h, while 50% and 90% tables release fluorescein over an extended time period (77% and 70% drug release after 6 h respectively). Complete drug dissolution took 15h for 50% infill tablets and 20h for 90% infill tablets. Gupta et al (2011) showed that the swelling ratio of PVA hydrogels was dependent on polymer concentration, higher concentrations resulting in reduced swelling ratios and this effect may be controlling the release profiles seen in this work.

Pictures of tables obtained after dissolution show a reduction of size and an apparently homogenous distribution of the drug inside the tablet during the dissolution process (Figure 6). According to the pictures, the release of the drug seems to be mediated mainly by an erosion process.

**Conclusion**

We have demonstrated the feasibility of using FF 3DP to fabricate drug-loaded tablets and have shown that the release profiles obtained can be modified by careful

selection of the printing parameters. The results immediately suggest that FF printng could offer a potential new method of manufacture for personalised-dose medicines and/or for tablets prepared at the point of dispensation/use. Our initial study loaded drug into polymer filament by passive diffusion from solution and while the percentage drug loading was low, it was sufficient to demonstrate proof-of-principle. It was possible to print tablets of varying physical size and density and it has been shown that infill percentage modulates the dissolution profile.

**Acknowledgement**

Alvaro Goyanes would like to thank Fundación Alfonso Martín Escudero for the post-doctoral fellowship.

## References


Buanz, A.B.M., Saunders, M.H., Basit, A.W., Gaisford, S., 2011. Preparation of personalized-dose salbutamol sulphate films with thermal ink-jet printing. Pharm Res. 28, 2386-2392.

Fadda, H.M., Basit, A.W., 2005. Dissolution of pH responsive formulations in media resembling intestinal fluids: bicarbonate versus phosphate buffers. J Drug Del Sci Tech. 15, 273-279.

Gbureck, U., Vorndran, E., Müller, F.A., Barralet, J.E., 2007. Low temperature direct 3D printed bioceramics and biocomposites as drug release matrices. J Cont Rel. 122, 173-180.

Gupta, S., Webster, T.J., Sinha, A., 2011. Evolution of PVA gels prepared without crosslinking agents as a cell adhesive surface. J Mater Sci: Mater Med, 22, 1763-1772.

Huang, W., Zheng, Q., Sun, W., Xu, H., Yang, X., 2007. Levofloxacin implants with predefined microstructure fabricated by three-dimensional printing technique. Int J Pharm. 339, 33-38.

Katstra, W.E., Palazzolo, R.D., Rowe, C.W., Giritlioglu, B., Teung, P., Cima, M.J., 2000a. Oral dosage forms fabricated by three dimensional printing. J Cont Rel. 66, 1-9.

Katstra, W.E., Palazzolo, R.D., Rowe, C.W., Giritlioglu, B., Teung, P., Cima, M.J., 2000b. Multimechanism oral dosage forms fabricated by three dimensional printing. J Cont Rel. 66, 11-17.

Khaled, S.A., Burley, J.C., Alexander, M.R., Roberts, C.J., 2014. Desktop 3D printing of controlled release bilayer tablets. Int J Pharm. 461, 105-111.

Liu, F., Merchant, H.A., Kulkarni, R.P., Alkademi, M., Basit, A.W., 2011. Evolution of a physiological pH 6.8 bicarbonate buffer system: Application to the dissolution testing of enteric coated products. Eur J Pharm Biopharm, 78, 151-157.

304 Merchant, H.A., Frost, J., Basit, A.W., 2012. Apparatus and method for testing
305 medicaments, PCT/GB2013/051145.
306 Mueannoom, W., Srisongphan, A., Taylor, K.M.G., Hauschild, S., Gaisford, S., 2012.
307 Thermal ink-jet spray freeze-drying for preparation of excipient-free particles of
308 salbutamol sulphate for inhalation. Eur J Pharm Biopharm. 80, 149-155.
309 Scoutaris, N., Alexander, M.R., Gellert, P.R., Roberts, C.J., 2011. Inkjet printing as a
310 novel medicine formulation technique. J Cont Rel. 156, 179-185.
311 Scoutaris, N., Hook, A.L., Gellert, P.R., Roberts, C.J., Alexander, M.R., Scurr, D.J.,
312 2012. ToF-SIMS analysis of chemical heterogeneities in inkjet micro-array printed
313 drug/polymer formulations. J Mater Sci Mater Med. 23, 385-391.
314 Sharma, G., Mueannoom, W., Buanz, A.B.M., Taylor, K.M.G., Gaisford, S., 2013. In
315 vitro characterization of terbutaline sulphate particles prepared by thermal ink-jet
316 spray freeze drying. Int J Pharm. 447, 165-170.
317 Wang, C-C, Tejwani, M.R., Roach, W.J., Kay, J.L., Yoo, J., Surprenant, H.L.,
318 Monkhouse, D.C., Pryor, T.J., 2006. Development of near zero-order release dosage
319 forms using three-dimensional printing (3-DP$^{TM}$) technology. Drug Dev Ind Pharm.
320 32, 367-376.
321 Wang, L-N., 2013. Printing medicines: A new era of dispensing and drug
322 formulation? Pharm J. 291, 25-26.
323 Yu, D-G, Zhu, L-M, Branford-White, C.J., Yang, X-L., 2008. Three-dimensional
324 printing in pharmaceutics: Promises and problems. J Pharm Sci. 97, 3666-3690.
325 Yu, D-G, Branford-White, C., Yang, Y-C, Zhu, L-M, Welbeck, E.W., Yang, X-L.,
326 2009a. A novel fast disintegrating tablet fabricated by three-dimensional printing.
327 Drug Dev Ind Pharm. 35, 1530-1536.
328 Yu, D-G, Yang, X.L., Huang, W.D., Liu, J., Wang, Y.G., Xu, H., 2007. Tablets with
329 material gradients fabricated by three-dimensional printing. J Pharm Sci. 96, 2446-
330 2456.

331 Yu, D-G, Shen, X-X, Branford-White, C., Zhu, L-M, White, K., Yang, X-L., 2009b.
332 Novel oral fast-disintegrating drug delivery devices with predefined inner structure
333 fabricated by three-dimensional printing. J Pharm Pharmacol. 61, 323-329.
334
335

336 Table 1: Measured parameters of the printed fluorescein tablets as a function of infill

337 percentage (n=9)

338

| Infill (%) | Weight (mg) | Thickness (mm) | Major length (mm) | Minor length (mm) | Theoretical Volume ($mm^3$) |
|---|---|---|---|---|---|
| 0 | 216.5 ±3.1 | 3.48 ±0.01 | 10.67 ± 0.04 | 10.66 ±0.06 | 310.88 |
| 10 | 229 ±2.6 | 3.71 ±0.05 | 10.50 ±0.08 | 10.63 ±0.08 | 325.24 |
| 25 | 245.3 ±0.6 | 3.74 ±0.07 | 10.48 ±0.02 | 10.57 ±0.02 | 325.39 |
| 50 | 266.6 ±2.8 | 3.78 ± 0.05 | 10.45 ±0.04 | 10.58 ±0.05 | 328.25 |
| 90 | 285.7 ±7.7 | 4.03 ±0.15 | 10.48 ±0.07 | 10.63 ±0.06 | 352.62 |
| 100 | 293.6 ±8.0 | 4.34 ±0.04 | 10.55 ±0.04 | 10.59 ±0.07 | 353.98 |

339

340

341

342

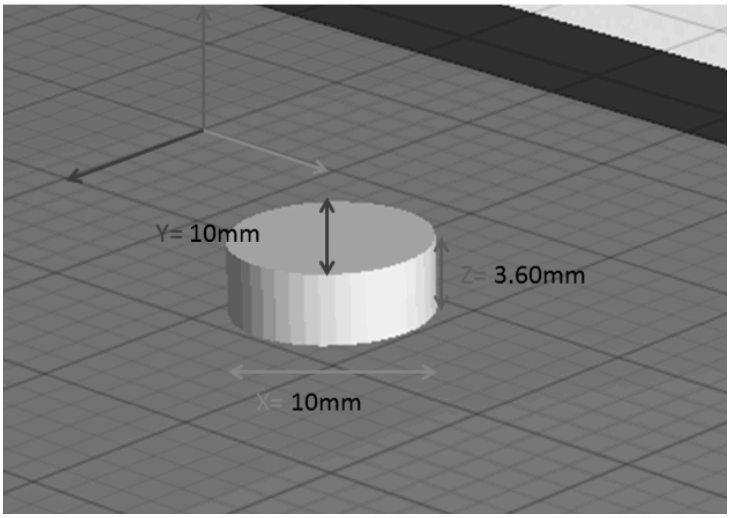



**Figure 1: The basic tablet design, rendered in Makerware v2.2.2.**

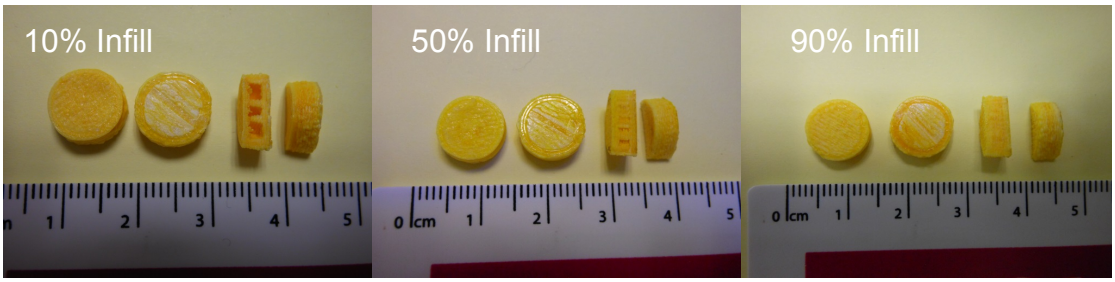



**Figure 2: Images of 3DP fabricated tablets as a function of infill percentage, showing (from left to right; top, base, internal and lateral views)**

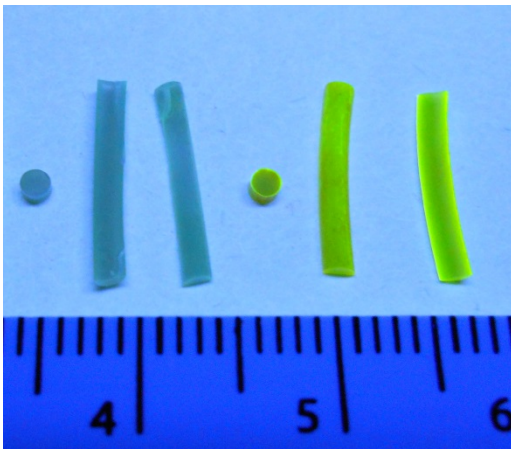



**Figure 3: Images of polymer filaments as received (left) and after loading with fluorescein (right) under UV light.**

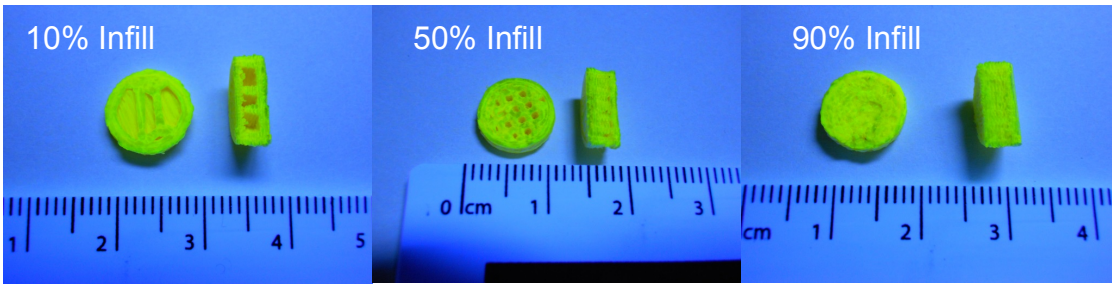



**Figure 4: Cross-sectional views of 3DP fabricated tablets containing fluorescein under UV light (top 10%, middle 50%, bottom 90%)**

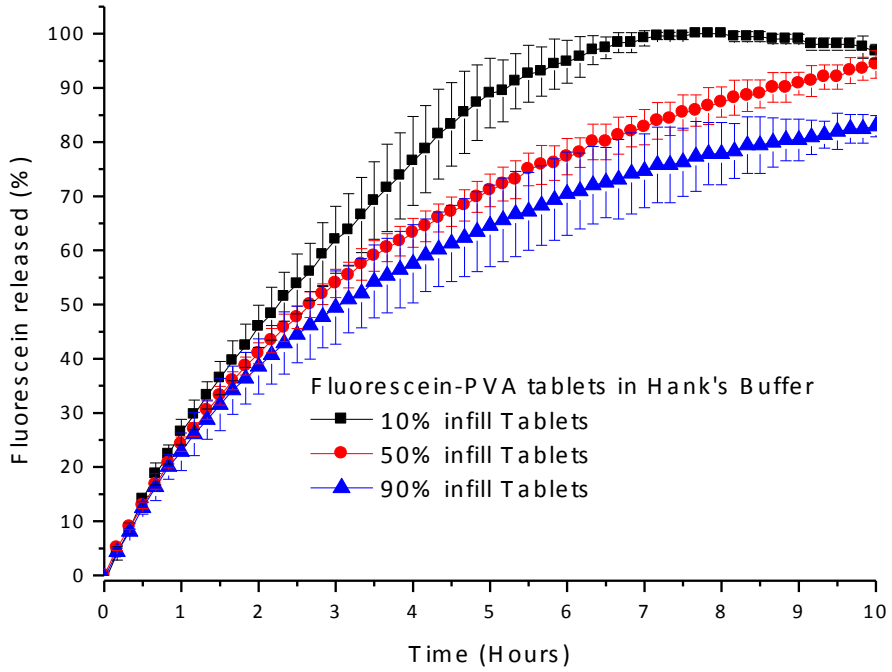
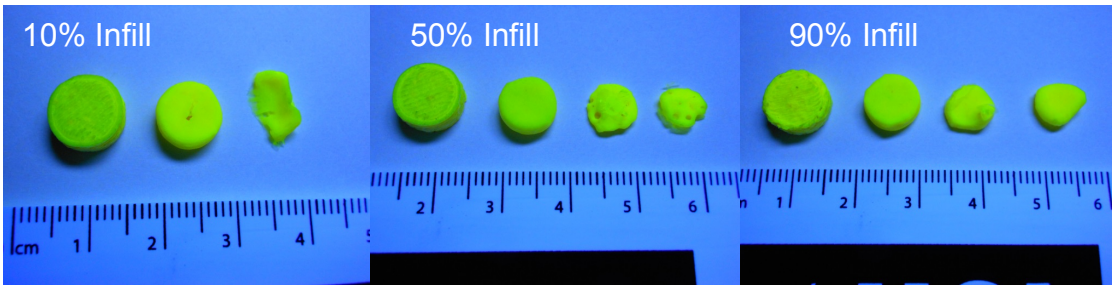



**Figure 5: Dissolution profiles of 3DP tablets with varying infill percentages in modified Hank's buffer (pH 6.8)**

374




375

376

377 **Figure 6: Tablet integrities as a function of dissolution time (2, 4, 6 and 8h)**

378 **showing fluorescein is released via erosion (top 10%, middle 50%, bottom 90%)**