

An Investigation into Fused Filament Fabrication for Pharmaceutical Manufacturing

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INTRODUCTION

In a modern world, what is the best way to deliver medicines to the patient? Human beings are an extremely diverse species with many different factors that can influence the behaviour of a drug within the body. Children are a perfect example of such variety. Doses are often prescribed based on body weight, and can vary greatly from infants to adolescents. With current 'traditional' manufacture of oral dose pharmaceuticals, generally only a limited number of doses are produced, leading to difficulties with accurate dosing. The ability to manufacture personalised doses for these patients would be of great benefit both practically and financially, and may even lead to 'point of care' manufacture.

Fused Filament Fabrication (FFF) is an emerging technique which has gained increased interest in recent years. An example of a tablet produced by this technique is shown in Figure 1. When considering this for pharmaceutical manufacture, two possible routes are available – loading of drug prior to filament fabrication (via hot-melt extrusion)¹ or loading of drug by submerging a suitable filament in a solution containing the selected drug.² Experiments were carried out, using the latter technique, in order to investigate the drug loading that can be achieved by submerging a poly(vinyl alcohol) (PVA) filament in a methanolic solution of the chosen drug. High performance liquid chromatography (HPLC) was used to determine the drug content of both the filament prior to printing, and the tablet after printing. Powder X-ray diffraction (xRPD) was used to investigate the crystallinity of the drug and scanning electron microscopy (SEM) was used to investigate the surface morphology of samples. Initial investigation into the drug distribution within the filament was carried out using time-of-flight secondary ion mass spectrometry (TOF-SIMS), however further investigation is still required.



Figure 1 - 3D Printed Tablet

DRUG LOADING

In order to determine drug loading of a PVA filament submerged in a methanolic solution of drug for 24 hours, HPLC analysis was used. Five calibration standards were analysed, along with three samples of drug loaded filament. The data produced a very good linear correlation, and the calculated drug loading was $3.58 \%w/w \pm 0.06$. When this was used for printing, tablets containing approximately 9mg of API were produced. Doses were within 0.5mg of those calculated and are in the middle of the dosage range already on the market for the API used.

API PHYSICAL FORM

As mentioned earlier, xRPD was used to investigate the physical form of the drug used in this piece of work. Samples of pure API, blank PVA filament, drug loaded PVA filament and drug loaded 3D printed tablet were analysed and the results are shown in Figure 2.

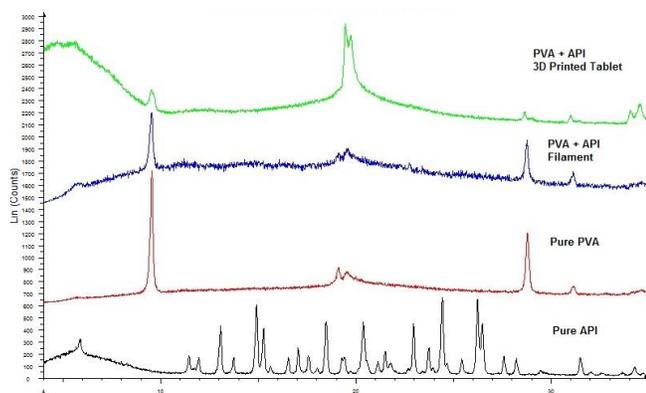


Figure 2. xRPD data

From this data, it would appear that the drug is present in an amorphous form. There are no clear peaks on either the drug loaded filament, or the drug loaded 3D printed tablet that would suggest any crystalline API is present. This could be the case, but it is also likely that the drug may be present in such a small amount that detection is difficult.

The API used for this piece of work was also classified as a BCS Class II drug therefore, if the API is present in an amorphous form, it is likely that improvements to the dissolution rate will be seen.

SURFACE MORPHOLOGY

SEM was used in order to investigate the surface of both the blank and drug loaded filaments, and the blank and drug loaded 3D printed tablets. An image of the edge of a drug loaded tablet can be seen in Figure 3.

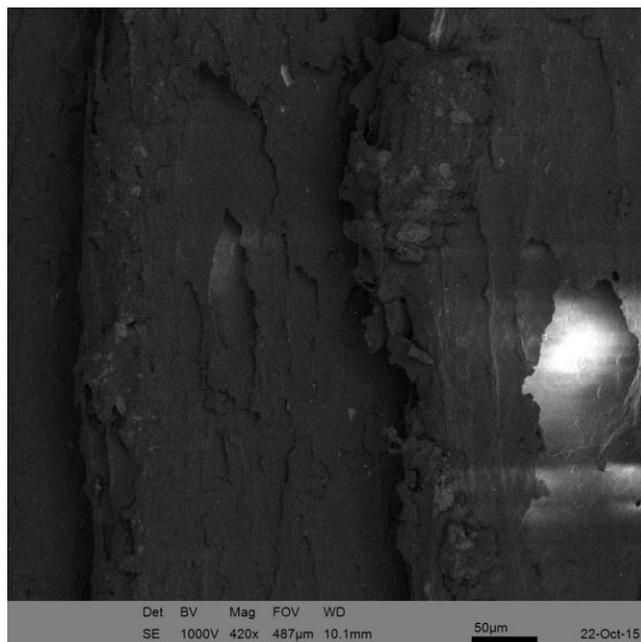


Figure 3. SEM image of 3D printed tablet

From the image, it is possible to see roughened edges, at the curved edge of the tablet, which appear to have small pores present. These pores are likely due to rapid evaporation of residual solvent when the filament is exposed to temperatures of approximately 200°C during printing. These observed pores and rough surfaces are less when compared to images from a blank 3D printed tablet, which could suggest a more efficient drying process is required. Further investigation could provide insights into whether this has any effect on dissolution.

DRUG DISTRIBUTION

Drug distribution throughout the PVA filament has been investigated using TOF-SIMS. Initial results suggest that the API is present in higher concentrations near the surface of the filament, which gradually decrease as analysis further beneath the surface is carried out. Further studies will look at how the distribution changes with the length of time the filament is submerged in a methanolic solution of drug.

CONCLUSION

While fused filament fabrication is still in its infancy, it is clear that there is potential for this technique to be used as a way of manufacturing personalised medicine. The work presented here only demonstrates doses which can be achieved by printing one particular size of tablet with an infill percentage of 30%. By altering the size of this tablet, or the infill percentage, a larger range of doses could potentially be manufactured in a reproducible manner. Varying the length of time for submersion of the filament not only alters the drug distribution, but could provide increased or decreased doses compared to those reported here. If the drug is present in an amorphous state, this technique also offers the benefit of potentially improving the dissolution rate of a BCS Class II drug. Further studies will focus on increasing and decreasing the size and infill percentage of printed tablets in order to further investigate the reproducibility.

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