Development of a pH-responsive polymer blend for FDM 3D Printing in delayed-release drug delivery

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Introduction

In recent years, thermal-based 3D printing techniques, such as fused deposition modelling (FDM), have been extensively explored for producing personalized medicines, including site-specific controlled-release dosage forms. These formulations aim to target specific regions of the gastrointestinal tract, such as the intestine and colon, while preventing drug release in the stomach [1].

In most studies, active pharmaceutical ingredients (APIs) are incorporated into the filaments before printing [2]. However, this approach poses a risk of thermal degradation, as APIs are subjected to high temperatures first during filament extrusion and again during the FDM printing process.

An alternative strategy involves 3D printing only the shell of a tablet and subsequently filling it with the API, thereby avoiding direct thermal exposure of the drug. For this approach to be effective in achieving site-specific drug release within the gastrointestinal tract, the formulation of the filament used to print the shell is critical.

Objectives:

- Develop a pH-responsive polymer blend filament capable of delaying drug release until it reaches intestinal pH.
- Investigate the effects of shell thickness and structural dimensions on drug release kinetics.

Methods and materials

HPMCAS-based filaments were extruded using the HAAKE MiniLab II, as shown in Figure 1. To evaluate the likelihood of filament breakage within the FDM printer's printhead, a modified feedability test using texture analyser was conducted [3]. In this test, filament samples (N=3) were compressed to simulate the pushing behaviour between the extruder gears and the nozzle. Three commercially available filaments made from different materials were used as benchmarks for comparison. The filament (N=3) were characterised used a range of thermal, microscopic and spectroscopic methods.

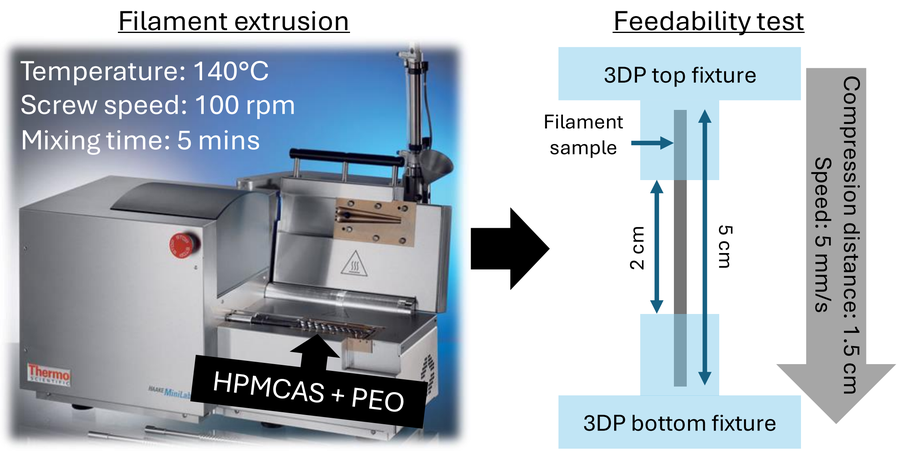

Figure 1. *The method to prepare the HPMCAS-based filaments and the experimental setup of the feedability test .*

To investigate the effects of shell thickness and dimensions on the delay of drug release, a simplified testing model was created to determine the time required to dissolve HPMCAS-based discs (representing a single side of the shell wall), allowing the indicator, fluorescein sodium salt (FSS) to release (Figure 2). Discs (N=3) with varying thicknesses (0.5 - 2 mm) with a 9 mm diameter and varying diameter (6 - 12 mm) with a 1mm thickness were printed using a Prusa MK3 printer (400 µm nozzle diameter) set at a nozzle temperature of 190 °C and a bed temperature of 60 °C. The disc was then attached to the device using ethyl cyanoacrylate before testing.

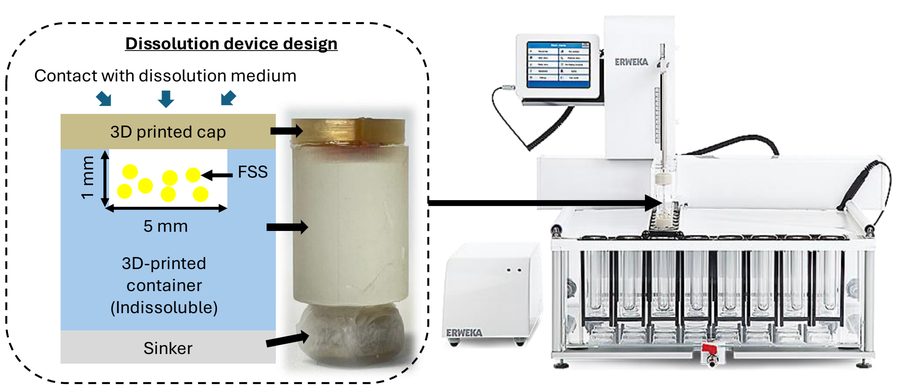

Figure 2. *The dissolution device created to measure polymer dissolution time in relation to shell thickness.*

The release time of the FSS from the device was monitored using a digital camera, while dissolution test was conducted with a USP Apparatus 3 set to 15 dips per minute in 200 ml of dissolution medium. Samples (N=3) were initially placed in a HCl pH 1.2 solution for 2 hours, then transferred to phosphate buffer solution at pH 6.8 (intestinal pH) until FSS release was observed. Images of the device were taken at each time point to record the release of FSS.

Results and discussion

All filaments show a single glass transition temperature (T_g) as shown in Table 1, indicating a homogenous mix between HPMCAS and PEO 100kDa and confirming that the filaments are in an amorphous state. As the amount of PEO in the filament increased, the T_g gradually decreased, attributed to the plasticising effect of PEO.

Table 1. *Formulation of the HPMCAS-based filaments and their glass transition (T_g) measured by DSC.*

Filament	HPMCAS	PEO 100kDa	T_g (°C)
H1	90	10	85.6 ± 0.4
H2	80	20	59.8 ± 1.9
H3	70	30	27.7 ± 4.1

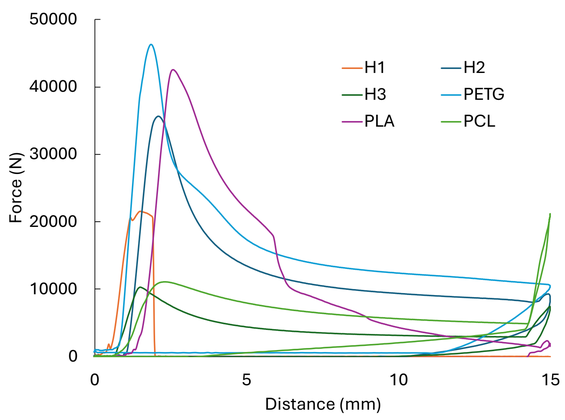

Figure 3. *Feedability test results of filaments.*

The feedability test helped evaluate the strength of filament formulations to prevent breakage inside the printhead, a common issue in FDM printing using pharmaceutical filaments. As shown in Figure 3, filament H1 fractured during the test, while H2 and H3 tolerated significant compression without breakage. However, during the printing process, H3 was prone to tangling within the printhead, likely due to its softness; therefore, H2 was selected for printing.

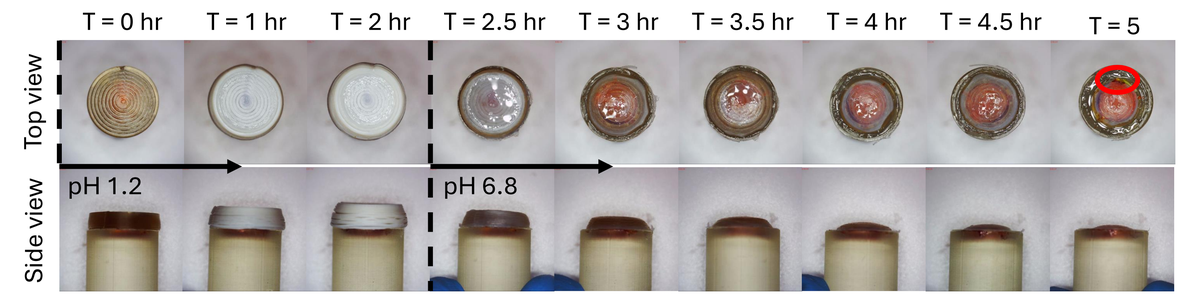

Figure 4. *Images of the dissolution process of the discs (FSS release highlighted by the red circle).*

A simple cylinder device with a non-dissolvable body and a disc-shaped cap made of the filament was 3D printed and was used to assess the release time of indicator. Figure 4 shows example images taken at various time points to monitor the dissolution of HPMCAS-based polymer and release of FSS.

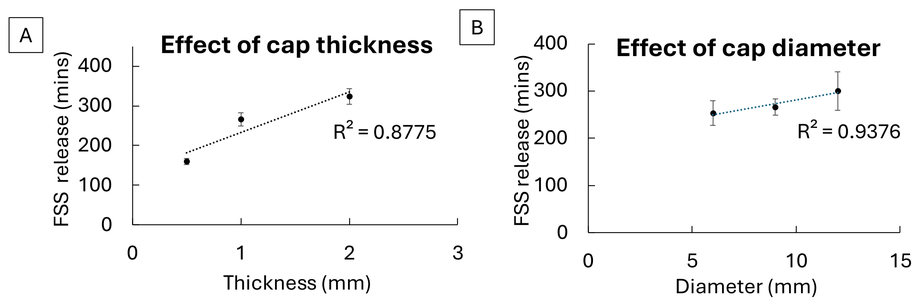

Figure 5. *(A) Release time of FSS for caps with 9 mm diameter and different thicknesses. (B) Release time of FSS for caps with 1 mm thickness and different diameters.*

Figure 5 shows the release time of FSS for different cap thicknesses and diameters. A positive trend is observed for both parameters, where R2 = 0.8775 and R2 = 0.9376 for cap thickness and diameter changes, respectively. The likely explanation for this trend is that a thicker or wider cap has more material, which requires a longer time to dissolve fully before the indicator releases. Additionally, thicker and wider cap have a lower surface area-to-volume ratio, which slows down the polymeric shell dissolution rate, further extending the release time.

Conclusions and future work

HPMCAS-based filaments were formulated and screened for feedability prior to printing. The H2 formulation was selected as the most stable filament, and a simple device was created to mimic the dissolution behaviour of the proposed personalised polypills. The dissolution test revealed a positive trend between cap thickness, cap diameter and release time, providing insights into how tablet shell thickness can be tailored to control drug release rates. The upcoming experiments will focus on printing hollow tablets that contain the FSS indicator to validate the result and develop a database for various drug release profiles.

References

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