Semi-solid extrusion 3D printing of starch-based soft dosage forms for the treatment of paediatric latent tuberculosis infection

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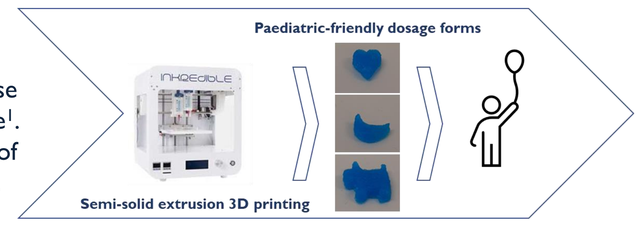
Introduction

An ideal paediatric formulation should consist of non-toxic excipients, enable ease of administration and flexible and accurate dose titration over a wide age and weight range, while at the same time its production should be easy, cost-effective and commercially viable[1]. This study aims to address these requirements from both a material and manufacturing method perspective, describing the fabrication of starch-based soft dosage forms for paediatric tuberculosis treatment with isoniazid (ISO) using semi-solid extrusion (SSE) 3D printing[2,3,4].



Materials and Methods

Corn starch was used for ink preparation using ISO as model drug. The inks were characterized physicochemically and their viscoelastic properties were assessed with rheological analysis. Starch tablets were fabricated using the CELLINK INKREDIBLE printer (Gothenburg, Sweden) and the morphology of the printed dosage forms was visualized with scanning electron microscopy. Texture profile analysis (TPA) was used to evaluate the hardness, cohesiveness, springiness, gumminess and adhesiveness of blank and ISO printed tablets. Dose accuracy was verified before in-vitro swelling and dissolution studies in simulated gastric fluid (SGF) at 37 °C.

Results

Fabrication and characterization of 3D printed starch tablets

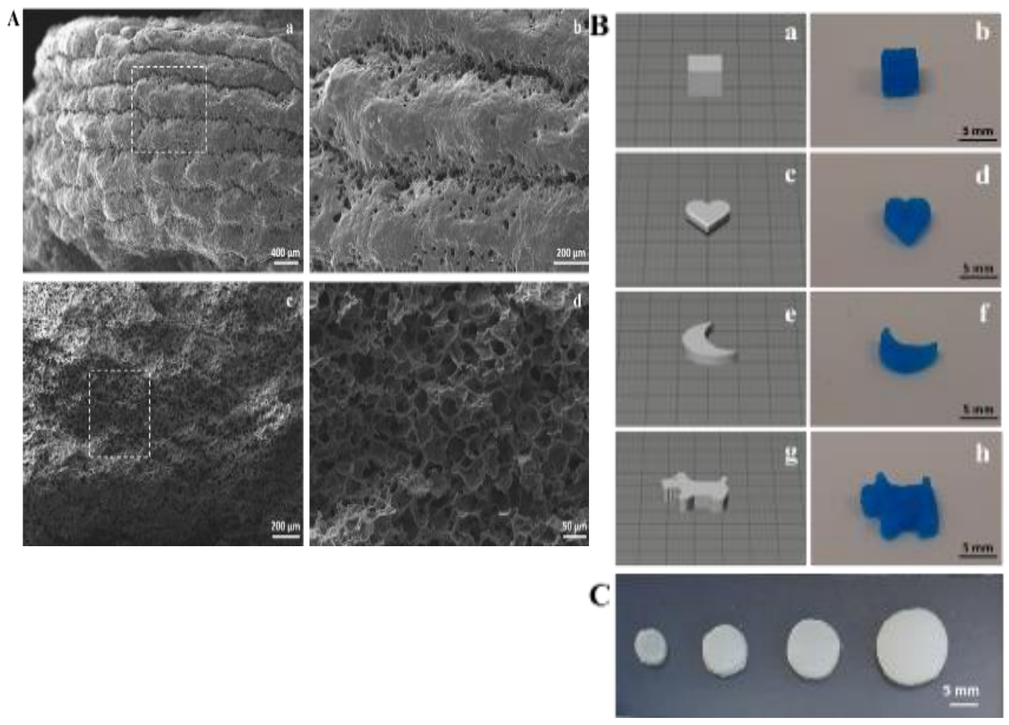


Figure 1. A. Scanning electron microscopy images of the (a, b) external and (c, d) internal morphology of the 3D printed starch tablets. The dotted rectangles correspond to the higher magnification images on the right. **B.** Schematic representation of (a, c, e and g) the .stl files and (b, d, f and h) the respective 3D printed dosage forms in the shape of (a, b) cube, (c, d) heart, (e, f) moon and (g, h) dog. **C.** The starch-based tablets printed in different sizes.

Table 1. Texture profile analysis (TPA) parameters of the blank and ISO printed tablets (n=3 ± S.D.).

TPA parameters	Formulation	
	Blank 3D printed tablets	ISO 3D printed tablets
Hardness (N)	0.94 ± 0.00	0.87 ± 0.11
Cohesiveness (-)	0.53 ± 0.05	0.57 ± 0.00
Springiness (s)	0.63 ± 0.02	0.70 ± 0.12
Gumminess (N)	0.50 ± 0.05	0.50 ± 0.06
Chewiness (N·s)	0.32 ± 0.02	0.34 ±0.02
Adhesiveness (N·s)	0.03 ± 0.03	0.04 ± 0.01

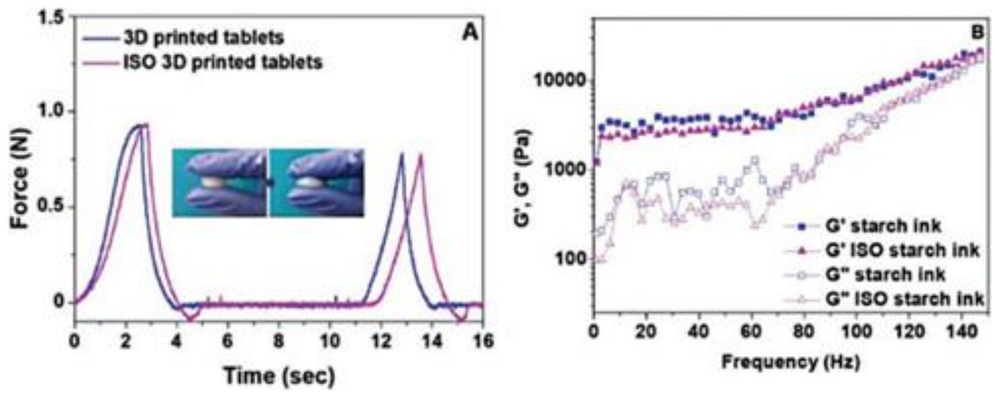


Figure 2. A. TPA of the blank and ISO 3D printed starch tablets (n = 3 ± S.D.). The inset shows (a) the handling of the 3D printed starch tablets even (b) after the application of slight pressure. **B.** Oscillation frequency sweep tests of the blank and ISO starch inks at a strain value of 0.1% and at the frequency range of 1-50 Hz (25°C).

In vitro studies

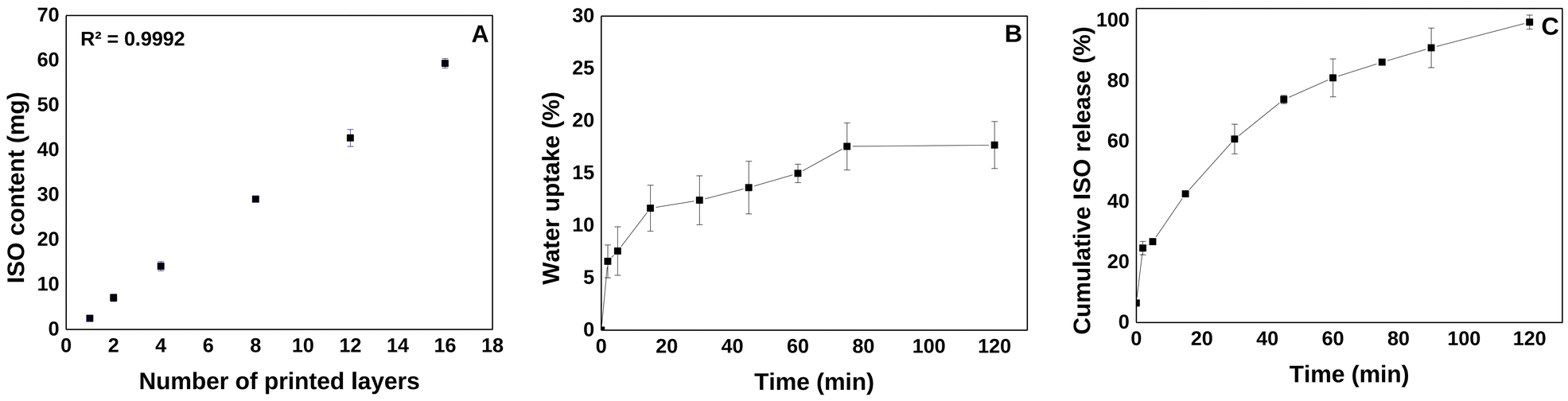


Figure 3. A. Assessment of dose accuracy with linear regression analysis in the ISO 3D printed starch tablets with increasing number of printed layers (n = 4 ± S.D.). **B.** Water uptake (%) of the 3D printed starch tablets after immersion in SGF for 2 h (n = 4 ± S.D.). **C.** Cumulative ISO release (%) from the minced 3D printed starch tablets to simulate the mastication process in SGF at 37°C (n = 3 ± S.D.).

Conclusion

In this study, we aimed to address the requirements from both a material and a manufacturing perspective. We used starch as a safe and cost-effective excipient that could be SSE 3D printed in soft dosage forms, enabling dose titration and accuracy. At the same time, we opted for a material that could be printed in a semi-solid state to overcome the swallowing difficulties commonly encountered with solid dosage forms but could additionally accommodate the use of sweeteners or flavors to potentially enhance palatability. SSE 3D printing of starch-based soft dosage forms could essentially provide a viable paediatric-friendly alternative to manual compounding in hospital settings and an applicable solution in low-resource settings.

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Published Article
https://doi.org/10.1093/jpp/rgab121

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