Transactions on Additive Manufacturing Meets Medicine
Trans. AMMM, Vol 3, No 1, 2021, Article ID 541

The development of hypromellose based semisolid 3D printing inks for drug delivery

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Abstract: 3D printing is a promising method for producing medicines to tailor individual patient's needs in the optimal dose and drug combinations which subsequently leads to enhanced therapeutic outcomes. Here, we developed semisolid ink formulations based on hydroxypropyl methylcellulose (HPMC). We investigated the effects of additives including PVP and SiO2 and a model drug, paracetamol, on the HPMC ink rheology behaviour and shape fidelity when produced using semisolid 3D extrusion printing. The formulations were extruded from the printing nozzle and laminated layer-by-layer. The current study presents novel drug-loaded HPMC-based inks for 3D construct fabrication for potential drug delivery applications.

I. Introduction

Research into 3D printing for the manufacture of personalised medicines has proliferated [1]. For solid dosage forms used in oral drug delivery, a wide range of 3D printing techniques have been explored to fabricate tablets and capsules [2]. Semisolid 3D printing has been less studied in comparison to other 3D printing methods. This is likely to be due to the requirement for drying after the printing. However, semisolid 3D printing is a promising method to produce fast-dissolving and disintegrating solid dosage forms which have clinical applications for patients with swallowing difficulties. Meanwhile, semisolid 3D printing is a non-heat method that enables the printing of thermolabile components. However, there is a limited understanding of ink development for solid dosage forms. HPMC is one of the most widely used excipients in oral solid dosage forms. In this study, (1) rheology of HPMC-based inks and (2) influence of polymer, additives and drug on the shape fidelity of the printed 3D construct were investigated.

II. Material and methods

Drug-loaded ink was formulated by dissolving 5%w/v paracetamol (PAC) in deionised water by magnetic stirring at 200 rpm for 2 hours at room temperature (Table 1). HPMC (90SH-4000) and Polyvinylpyrrolidone (PVP) were then added at 15% and 20%w/v, respectively. Silico dioxide (SiO_2) powder (50µm) was added as an additive to improve the printing shape fidelity. The formulated inks were followed by an hour of centrifuge mixing (4000 rpm) (Fig. 1(a)).

A piston extrusion-based 3D printer (BioX, Cellink Life Sciences, Gothenburg, Sweden) was used to fabricate the 3D construct. The G-code of the design was generated in accordance with the predesigned CAD model (20×20×3 mm) (Fig. 1 (b)). Each layer was comprised of parallel filaments with an average width of 413 µm, equivalent to the internal diameter (ID) of a 22 G nozzle (Figure 1 (c)).

Table 1: HPMC based ink formulations

	Polymer (%w/v)	API (%w/v)	Additives (%w/v)	
Ink name	**HPMC**	**PAC**	**PVP**	**SiO_2**
15 HPMC	15			
20 HPMC	20			
20 PVP			20	
HPMC+PVP	15		20	
HPMC+PVP+PAC	15	5	20	
HPMC+PVP+PAC+SiO_2	15	5	20	8

Rheological measurements were conducted at 21ºC using a rheometer (Discovery HR30, TA Instruments, New Castle, Delaware, USA) with a cone-plate geometry. Continuous flow ramps were performed by varying the shear rate from 0.1 to 100 s^{-1}. Three replicates were taken for each ink. The width and pore area of the printed structures were measured in ImageJ software (Version 1.8.0, Bethesda, Maryland, USA). The measurements were repeated at 5 different sites on the sample. The data were plotted using Origin software (Version 2018, Northampton, Massachusetts, USA). Error bars represent the mean ± standard deviation.

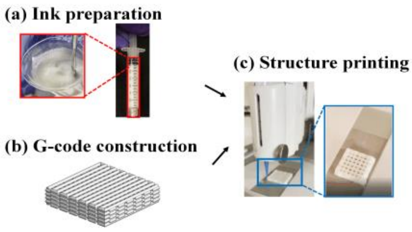

Fig. 1: Schematic of printing 3D construct using the semisolid 3D printing technique.

DOI: 10.18416/AMMM.2021.2109541

III. Results and discussion

III.I Ink rheological behaviour

The viscosity of the HPMC-based inks was evaluated through steady-state shear viscosity measurements (Fig. 2). It was noted that the ink extrudability and printability were highly dependent on the viscosity profile. For instance, 20HPMC was failed to extrude due to high viscosity while 15PVP was not printable in filaments due to its low viscosity. After adding 5%w/v PAC in the HPMC+PVP ink, the ink viscosity was significantly dropped ($p \leq 0.05$), while after adding SiO_2, ink viscosity increased. In our study, the printable ink (i.e., HPMC+PVP and HPMC+PVP+PAC+SiO_2) was observed within the viscosity range of 700-1000 Pa s.

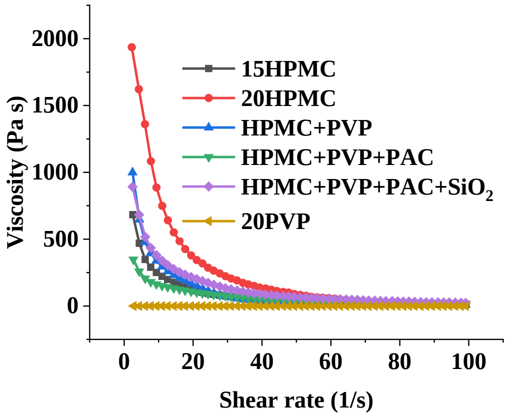

Fig. 2: The shear rate-viscosity flow curves.

III.II Shape fidelity analysis

First layer 3D printing

The printing process parameters (i.e., extrusion rate and printing speed) directly influence the shape fidelity of the first layer filament deposition. The extrusion rate and printing speed were varied to ensure the width of the printed filament was similar to the nozzle diameter (Fig. 3). All inks showed minor filament width shrinkage up to 20 mins and remained constant from 20 mins onwards. The printing speed for all inks was set at 10 mm/s; while the extrusion rate was at 4.3, 2 and 4.1 µL/s for inks of HPMC+PVP, HPMC+PVP+PAC and HPMC+PVP+PAC+SiO_2, respectively. It was noted that there is a correlation between extrusion rate and ink rheology behaviour. A higher extrusion rate was required when the ink exhibits a higher viscosity at rest.

Multiple layers 3D printing

With the optimised extrusion rate and printing speed conditions based on first layer 3D printing, the 3D constructs were built in a layer-by-layer manner. Fig. 4 shows the changes in pore area with time for 3D constructs made up of 14 layers. It was noted that incorporation of PAC results in merging after 20 mins drying at room temperature. The thickness of the 3D printed construct significantly decreased ($p \leq 0.05$) as a result of the merging issue. The addition of SiO_2 into the blend significantly improved ($p \leq 0.05$) the outcome where the formed pore areas were observed to be similar to the theoretical value.

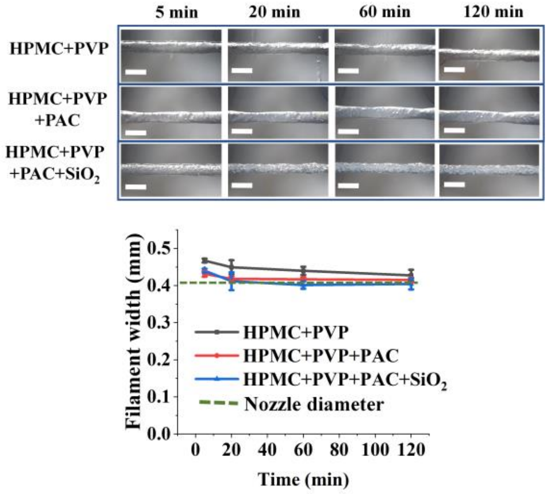

Fig. 3: The width of first layer printed filament in comparison with the nozzle diameter (ID = 413 µm) (scale bar=0.9 mm).

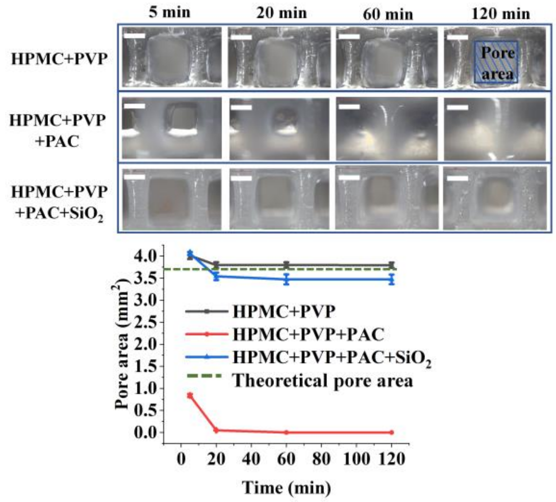

Fig. 4: The pore area of multiple layer 3D construct in comparison with the theoretical value (3.7mm^2)(scale bar=0.9 mm).

IV. Conclusions

A PAC-loaded HPMC-based semisolid ink was optimised for tablet fabrication. A clear relationship between the viscosity at the rest of the ink and filament printability was observed. The introduction of drugs into the ink blend showed a significant merging issue which reduces the quality of printing. Addition of SiO_2 relieved the merging issue and improved the printing shape fidelity.

Acknowledgments

Redistributed Manufacturing in Healthcare Network (RiHN). The RiHN was awarded a grant from the UK Engineering and Physical Sciences Research Council (EPSRC) (Ref. EP/T014970/1).

Author's statement

Conflict of interest: Authors state no conflict of interest.

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