

Journal of Materials Chemistry B

Materials for biology and medicine

Accepted Manuscript

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An investigation into the effects of ink formulations of semi-solid extrusion 3D printing on the performance of the printed solid dosage forms

Bin Zhang^{a,b,†}, Peter Belton^c, Xin Yi Teoh^{a,d}, Andrew Gleadall^e, Richard Bibb^f, and Sheng Qi^a †

^aSchool of Pharmacy, University of East Anglia, Norwich, UK

^bDepartment of Mechanical and Aerospace Engineering, Brunel University London, London, UK

^cSchool of Chemistry, University of East Anglia, Norwich, UK

^dSchool of Pharmacy, University College London, London, UK

^eWolfson School of Mechanical, Electrical and Manufacturing Engineering, Loughborough University, Loughborough, UK

^f Nottingham School of Art & Design, Nottingham Trent University, UK

† Corresponding author. E-mail: sheng.qi@uea.ac.uk ; bin.zhang@brunel.ac.uk



Abstract

View Article Online
DOI: 10.1039/D3TB01868G

Semi-solid extrusion (SSE) 3D printing has recently attracted increased attention for its pharmaceutical application as a potential method for small-batch manufacturing of personalised solid dosage forms. It has the advantage of allowing ambient temperature printing, which is especially beneficial for the 3D printing of thermosensitive drugs. In this study, the effects of polymeric compositions (single hydroxypropyl methylcellulose (HPMC) system and binary HPMC+ Polyvinylpyrrolidone (PVP) system), disintegrant (silicon oxide (SiO_2)), and active pharmaceutical ingredients (tranexamic acid (TXA) and paracetamol (PAC)) on the printability of semisolid inks and the qualities of SSE printed drug-loaded tablets were investigated. Printability is defined by the suitability of the material for the process in terms of its physical properties during extrusions and post-extrusion, including rheology, solidification time, avoiding slumping, etc. The rheological properties of the inks were investigated as a function of polymeric compositions and drug concentrations and further correlated with the printability of the inks. The SSE 3D printed tablets were subjected to a series of physicochemical properties characterisations and *in vitro* drug release performance evaluations. The results indicated that an addition of SiO_2 would improve 3D printing shape fidelity (e.g., pore area and porosity) by altering the ink rheology. The pores of HPMC+PVP+5PAC prints completely disappeared after 12 hours of drying (pore area = 0 mm^2). An addition of SiO_2 significantly improved the pore area of the prints which are $3.5 \pm 0.1 \text{ mm}^2$. It was noted that the drug release profile of PAC significantly increased ($p < 0.05$) when additive SiO_2 was incorporated in the formulation. This could be due to a significantly higher porosity of HPMC+PVP+ SiO_2 +PAC ($70.3 \pm 0.2\%$) compared to HPMC+PVP+PAC ($47.6 \pm 2.1\%$). It was also likely that SiO_2 acted as a



disintegrant and speeding up the drug release process. Besides, the incorporation of APIs with different aqueous solubilities, as well as levels of interaction with the polymeric system showed significant impacts on the structural fidelity and subsequently the drug release performance of 3D printed tablets.

Keywords: Semi-solid extrusion 3D printing, drug delivery, personalised medicine, disintegrant, ink rheology, printability, shape fidelity, *in vitro* drug release.

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1 **1 Introduction**

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2 3D printing is attracting increasing attention in the pharmaceutical science community
3 due to its flexibility and customizability potential for personalised medicine when
4 compared to traditional pharmaceutical mass manufacturing techniques (1, 2). In recent
5 years, several 3D printing techniques have been investigated for their potential
6 pharmaceutical applications, including stereolithography (3, 4), selective laser sintering
7 (5), inkjet printing (6, 7), and material-extrusion 3D printing (8-11). Among these,
8 thermal-based 3D printing processes, including fused deposition modelling (FDM),
9 direct powder extrusion and droplet deposition-based 3D printing (12-16), are widely
10 researched. However, thermal-based 3D printing requires the active pharmaceutical
11 ingredient (API) to go through at least one (and two for FDM) thermal processes
12 (heating above melting point to create the material filament by extrusion and
13 subsequent reheating during printing), which could cause drug thermal degradation and
14 is not suitable for thermosensitive drugs. Several modifications have been attempted to
15 reduce the thermal stress associated with thermal-based 3D printing methods, such as
16 adding plasticisers to the formula to lower the melting/glass transition temperature of
17 the bulk polymers, thus lowering the printing temperature required to process the
18 material (8, 17-21), but none of these can completely eliminate the effects of heat during
19 printing.

20

21 Semi-solid extrusion (SSE) 3D printing is a 3D printing technology which extrudes
22 semi-solid materials such as pastes and gels through a defined size nozzle to create a
23 new structure after solidification (e.g., tablets). Compared to thermal-based 3D printing
24 methods, SSE 3D printing can operate under a heat-free condition as the printing solely



25 relies on the extrusion of viscoelastic semi-solid inks through a nozzle with a
26 displacement-controlled driving mechanism (22-25). The rheological and mechanical
27 properties of the ink formulas are critical for successful SSE 3D printing (26-28). The
28 formulated ink is technically a slurry (with solid contents) or a gel (soluble ingredients
29 with hydrated polymer network) (23, 29-32). It is commonly recognised in the literature
30 that in order to achieve high geometrical fidelity using SSE 3D printing, meaning
31 accurately reproducing the original CAD design, certain characteristics are required.
32 These are that the ink needs to exhibit non-Newtonian properties and shear-thinning
33 behaviour (i.e. reduction in viscosity with applied shear stress) to generate continuous
34 flow during extrusion (24, 33, 34). If the ink viscosity is too low, discontinuous droplets
35 or overflowing and deformation of filaments would occur, while nozzle clogging
36 happens, if the ink viscosity is too high (35-37). Thickening additives often have to be
37 used to adjust the ink viscosity (38-40).

38
39 A wide range of pharmaceutical applications of SSE 3D printing have been
40 demonstrated in the literature, including chewable and fast-disintegrating dosage forms
41 as well as polypills (41, 42), which have been developed for paediatric patients, patients
42 with dysphagia and patients with high pill burdens. These published works highlighted
43 the potential of SSE as a manufacturing method to produce personalised medicines for
44 targeted patient groups. Whilst SSE 3D printing has advantages, it still remains in the
45 research and development stage, and there are presently the limitations of (1) suitable
46 ink formulation for 3D printing, (2) lack of understanding of the influences of
47 ingredients in the ink formula on drug release. Thus, in order to translate the technology

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48 to clinical practice, a fundamental understanding of the key principles of optimising the
49 printability of SSE inks is needed to guide new product development (22, 27, 43).

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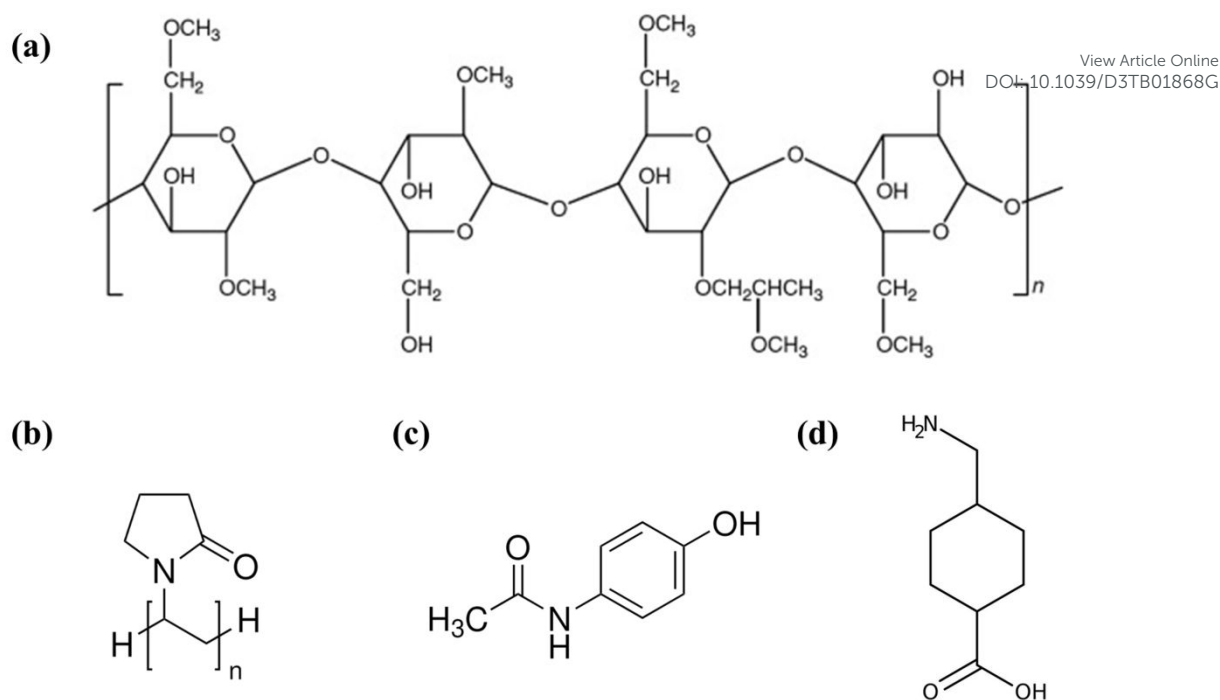
50
51 Commonly used excipient/additive of pharmaceutical products i.e. HPMC, PVP and
52 SiO₂ (44-46) were selected in this study. As a ramification of our previous study where
53 HPMC-PVP was identified as an ideal excipient combination in semisolid extrusion-
54 based 3D printing (22), therefore, this study aims to investigate the effect of additive
55 and APIs incorporation on the printability and drug release performance of 3D printed
56 tablets. In this study, additive SiO₂ as the disintegrant and two APIs with different levels
57 of water solubilities (i.e., tranexamic acid (TXA) and paracetamol (PAC)) were
58 incorporated into the ink to observe the changes in ink properties. Subsequently, an
59 attempt to establish the relationship between ink properties, shape fidelity of printed
60 tablets and *in vitro* drug release behaviours was conducted.

61 **2 Materials and methods**

62 **2.1 Materials**

63 Hydroxypropyl methylcellulose (HPMC) (METOLOSE® SR 90SH-4000, Mw 270,000
64 g/mol) was donated by Shin-Etsu Chemical Co. Ltd. (Tokyo, Japan).
65 Polyvinylpyrrolidone (PVP, Mw 50,000 g/mol) and silicon oxide (SiO₂, 50 µm) were
66 received as generous gifts from BASF (Ludwigshafen, Germany) and Evonik
67 (Darmstadt, Germany) respectively. Tranexamic acid (TXA, Mw 157.21 g/mol) and
68 paracetamol (PAC, Mw 151 g/mol) were purchased from Molekula (Darlington, UK).
69 Salicylaldehyde (SA), used as an agent for UV detection of the TXA, was purchased
70 from Sigma-Aldrich (St. Louis, Missouri, United States). The chemical structures of
71 polymers and drugs are shown in **Figure 1**.





72

73 Figure 1. Chemical structures of polymers and drugs (a) HPMC, (b) PVP, (c) PAC and
74 (d) TXA.

75

75 2.2 Ink formulation

76 Both TXA- and PAC-loaded inks were prepared by dissolving the drug (at drug
77 concentrations of TXA 5-30% w/w, and 5% w/w PAC) in 20g deionised water at
78 ambient temperature (circa 21 °C). Subsequently, HPMC and PVP were respectively
79 added at 15-20% w/w to be dispersed to form a homogenous semi-solid mass under
80 mechanical stirring. SiO₂ powder (with a mean particle size of 50 μm) was added to the
81 HPMC/PVP drug-loaded inks as a disintegrant additive. The ink preparation protocol
82 is described in **Figure S1**, and the compositions of the ink formulated are listed in **Table**
83 **1**.

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Table 1. List of investigated inks and their corresponding ingredients*

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Ink name	Polymer	Additive		API	
	HPMC (%w/w)	PVP (%w/w)	SiO ₂ (%w/w)	TXA (%w/w)	PAC (%w/w)
Influence of additive/excipient					
15HPMC	15	-	-	-	-
30HPMC	30	-	-	-	-
35HPMC	35	-	-	-	-
PVP	-	20	-	-	-
HPMC+PVP	15	20	-	-	-
HPMC+PVP+SiO ₂	15	20	8	-	-
Influence of API					
HPMC+15TXA	15	-	-	15	-
HPMC+PVP+15TXA	15	20	-	15	-
HPMC+PVP+SiO ₂ +15TXA	15	20	8	15	-
HPMC+5PAC	15	-	-	-	5
HPMC+PVP+5PAC	15	20	-	-	5
HPMC+PVP+SiO ₂ +5PAC	15	20	8	-	5
Influence of API concentration					
HPMC+PVP	15	20	-	-	-
HPMC+PVP+5TXA	15	20	-	5	-
HPMC+PVP+15TXA	15	20	-	15	-
HPMC+PVP+30TXA	15	20	-	30	-

88

*All % w/w is calculated by the weight of each ingredient to the weight of deionised water.

8



89 **2.3 Design 3D constructs**View Article Online
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90 3D constructs of the drug-loaded prints with different layer thicknesses and infill were
 91 designed to examine the geometry effect on drug release. The detailed design
 92 parameters of the constructs are summarised in **Table 2**. The designs can be divided
 93 into two approaches: (1) 3D tablet lattice with two options for the number of layers (4
 94 and 14) whilst the pore width and filament width were kept constant; (2) 3D constructs
 95 with a fixed number of layers (14) but with various infill densities by varying the pore
 96 width at 1 mm or 2 mm.

97 **Table 2.** The CAD parameters of the 3D constructs designs of drug-loaded prints.

	Tablet width (mm)	Tablet length (mm)	Tablet thickness (mm)	Filament width (mm)	Pore width (mm)
Influence of layer number					
HPMC+PVP+5TXA_4layer	20	20	1	0.4	2
HPMC+PVP+15TXA_4layer	20	20	1	0.4	2
HPMC+PVP+5TXA_14layer	20	20	3	0.4	2
HPMC+PVP+15TXA_14layer	20	20	3	0.4	2
Influence of infill (%)					
HPMC+PVP+5TXA_25%infill	20	20	3	0.4	2
HPMC+PVP+15TXA_25%infill	20	20	3	0.4	2
HPMC+PVP+5TXA_50%infill	20	20	3	0.4	1
HPMC+PVP+15TXA_50%infill	20	20	3	0.4	1

98

99



100 **2.4 SSE 3D printing**

101 An SSE 3D printer (BioX, Cellink Life Sciences, Gothenburg, Sweden) was used to
102 fabricate the drug-free and drug-loaded 3D constructs. The G-code of the design was
103 generated in accordance with the predesigned CAD model. All prints were performed
104 at ambient temperature (circa 21 °C), and the printing nozzle and printing platform were
105 not heated. The ink materials were extruded from a 22 Gauge nozzle, which is
106 equivalent to an internal diameter (ID) of 413 µm. The extrusion rate (1–5 µL/s) and
107 printing speed (5–20 mm/s) were optimised to obtain a filament diameter close to the
108 nozzle diameter upon printing. Each layer was comprised of parallel filaments with an
109 average width of circa 413 µm.

110 **2.5 Rheological measurements**

111 Rheological measurements of the inks were conducted at ambient temperature using a
112 rheometer (Discovery HR30, TA Instruments, New Castle, Delaware, USA) with a
113 cone-plate geometry. Continuous flow ramps were performed by varying the shear rate
114 from 0.1 to 100 s⁻¹. Three replicates were measured for each ink formula.

115 **2.6 Shape fidelity and surface morphology analysis of the prints**

116 A FDSC196 polarised light microscope (PLM) (Linkam Scientific, Surrey, UK) was
117 used to detect drug crystals through birefringent observation as an indication of the
118 changes in drug solubility limit in the inks after the addition of HPMC and PVP (as the
119 addition of HPMC and PVP may affect the aqueous solubility of the drug).

120 The microscope was used to inspect the printed constructs. The pore areas of the printed
121 structures were measured using Image J software (Version 1.8.0, Bethesda, Maryland,
122 USA). The measurements were repeated at three different prints and three pores were
123 measured for each print. The dimensional data were plotted using Origin software



124 (Version 2018, Northampton, Massachusetts, USA). Error bars represent the mean \pm
 125 standard deviation. The pore area of 3D printed tablets was later compared with the
 126 theoretical value. A theoretical value of pore area at 4 mm² was identified as expressed
 127 as the square of pore width. Thus, the pore area under-sizing (%) is calculated in Eq.
 128 (1).

$$129 \quad \text{Pore area under – sizing (\%)} = \frac{A_{\text{theory}} - A_{\text{printing}}}{A_{\text{theory}}} \quad (1)$$

130 where A_{theory} is theoretical pore area, A_{printing} is the pore area at n^{th} mins after printing.
 131 Assuming SSE 3D printed samples are dried, experimental solid volume (V_{exp}) of the
 132 printed constructs was calculated based on their actual weight (M_{exp}) divided by their
 133 density (ρ_{exp}), as shown in Eq. (2).

$$134 \quad V_{\text{exp}} = \frac{M_{\text{exp}}}{\rho_{\text{exp}}} \quad (2)$$

135
 136 Considering the samples were printed with HPMC, PVP and SiO₂ mixed with API (i.e.,
 137 TXA or PAC), the density of SSE 3D printed samples was calculated using Eq. (3).

$$138 \quad \rho_{\text{exp}} = \rho_1 * R_1 + \rho_2 * R_2 + \rho_3 * R_3 + \rho_4 * R_4 \quad (3)$$

139 where ρ are HPMC, PVP, SiO₂ and APIs density. The density of HPMC, PVP, SiO₂,
 140 TXA and PAC are 1.39, 1.20, 2.65, 1.10 and 1.26 g/cm³, respectively (47-51). R is the
 141 weight fractions of HPMC, PVP, SiO₂ and APIs within the SSE 3D printed samples.
 142 ρ_{exp} is the density of the printed constructs. The porosity was calculated from the
 143 percentage of the experimental solid volume (V_{exp}) of the total volume (V_{total}) of the
 144 printed construct using Eqs. (4) and (5). W , L and T are the length, width, and thickness
 145 of the 3D constructs which were measured at the outermost edges using a vernier
 146 calliper.



$$V_{total} = W * L * T \quad (4)$$

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$$Porosity = \left(1 - \frac{V_{exp}}{V_{total}}\right) \quad (5)$$

The surface morphology of the printed samples was evaluated using scanning electron microscopy (SEM) technique with a Zeiss Gemini 300 (Carl Zeiss AG, Oberkochen, Germany). The samples were sputter-coated with gold prior to scanning. The images were taken at magnifications from 25 to 200 × with an acceleration voltage of 10 kV.

2.7 Physicochemical properties characterisation

A Fourier transform infrared (FTIR) spectrophotometer (VERTEX 70, Bruker Optics, Ettlingen, Germany), equipped with a Golden Gate, Attenuated Total Reflectance (ATR) accessory (Specac Ltd., Orpington, United Kingdom) fitted with a diamond internal reflection element, was used to examine the raw materials, physical mixtures and printed tablets. The spectra were collected over a wavenumber range of 600–4500 cm⁻¹ with a resolution of 2 cm⁻¹ at ambient temperature. As the SSE 3D printed samples were dried at ambient temperature (21 °C) for 72 h, thermogravimetric analysis (TGA) was conducted using TGA 5500 discovery series (TA Instruments, Newcastle, USA) to identify the moisture content of the dried 3D printed samples. 5–7 mg of sample was loaded into the instrument and subjected to a temperature program of 10 °C/min from 25 °C to 700 °C under a nitrogen atmosphere (20 mL/min). Trios (TA Instruments, Newcastle, USA) software was used to analyse the acquired results. All measurements were performed in triplicate on three different tablets.

2.8 Mechanical strength analysis

To evaluate the mechanical strength of the prints, puncture tests were performed on the printed tablets with a TA-XT Plus Texture analyser (Stable Micro Systems), using a



170 spherical probe (diameter 5 mm). The puncture tests were performed on the centre of
171 the fully dried 3D printed samples ($20 \times 20 \times 3$ mm cuboid). Force and displacement
172 data were recorded using Texture Expert from Stable Micro Systems Ltd. software. The
173 speed of the probe was set at 1.0 mm/s during compression. Triplicate measurements
174 on three different tablets were performed.

175 **2.9 *In vitro* drug release study**

176 The *in vitro* drug release behaviours of the drug-loaded constructs were tested in 25 mL
177 of pH 7.4 phosphate-buffered saline (PBS) with 100 rpm agitation at 37 °C in a shaking
178 incubator (IKA, Staufen, Germany). A sink condition was maintained throughout the
179 drug release period. Three millilitres samples were extracted and replenished with an
180 equal volume of fresh medium at predetermined time intervals. Salicylaldehyde (SA)
181 was used as the reagent for the UV spectrophotometry detection of TXA (52). One
182 millilitre of TXA drug solution was added to 1 mL of 1% w/v SA solution. The
183 complete reaction was attained after 12 hours. The UV detection was carried out at 422
184 nm for TXA and 243 nm for PAC. TXA and PAC samples were placed in a 96-well
185 quartz microplate for UV detection using a CLARIO star microplate reader (BMG
186 Labtech, Ortenberg, Germany). The drug release experiments were performed in
187 triplicate for each construct design.

188 **2.10 Statistical analysis**

189 Numerical data were expressed as the mean \pm standard deviation and analysed via
190 Student's t-test to determine the differences among the groups. Statistical significance
191 is indicated when $p \leq 0.05$, while no significance when $p > 0.05$.

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193 **3 Results and discussion**

194 **3.1 Ink development**

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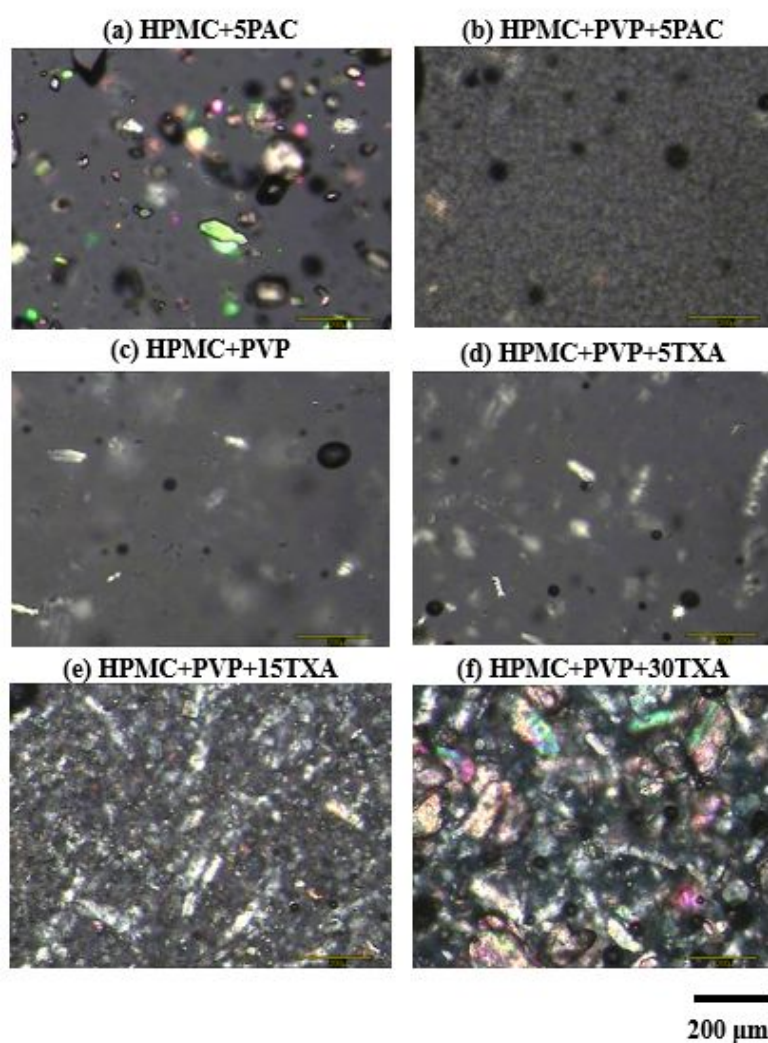
195 **3.1.1 Effect of additive and API**

196 The visual inspection of the initial physical appearance of the inks (formulas shown in
197 **Table 1**) after manually stirring for 5 minutes at ambient temperature (21 °C) is
198 presented in the Supplementary Material (**Figure S1a-d**). HPMC at 15 and 30 % w/w
199 did not mix well in water to form a homogenous ink. 20% w/w PVP in water forms an
200 ink solution with low viscosity. An addition of 20% w/w PVP to 15% w/w HPMC
201 transformed the ink into a viscous and homogeneous paste which is ideal for SSE 3D
202 printing.

203 The effect of the incorporation of API on the inks was studied using TXA and PAC.
204 TXA is a low molecular weight (157.21 g/mol) zwitterionic compound with an aqueous
205 solubility of 167 mg/mL (53) while PAC has an aqueous solubility of 14 mg/mL (54).
206 Owing to the limit of aqueous solubility, only 5% and 15% w/w TXA were fully
207 dissolved in the water, whereas 5% w/w PAC and 30% w/w TXA formed a suspension
208 and crystalline PAC and TXA can be seen by PLM. PAC particulates in the 5% w/w
209 PAC suspension remained observed upon the addition of 15% w/w HPMC dry powders.
210 However, the amount of PAC particulates decreased after the addition of 20% PVP as
211 evident in **Figure 2a-b**. On the other hand, an addition of 15% w/w HPMC and 20%
212 w/w PVP dry powders to the TXA solutions (5 and 15% w/w) and TXA suspension
213 (30% w/w) revealed particulates birefringence in all PLM captures (**Figure 2c-f**). The
214 PLM images of HPMC+PVP with 5% w/w TXA and the blank were noted as extremely
215 similar, as shown in **Figure 2c-d**, proving that some particulates may be the presence
216 of undissolved polymers. No birefringence associated with crystalline TXA particles



217 was observed, indicating a full dissolution of 5% w/w TXA in HPMC+PVP ink.
 218 Unexpectedly, the addition of HPMC and PVP to 15% w/w TXA solution resulted in
 219 the recrystallisation of TXA particles, where birefringence of TXA was observed as
 220 shown in **Figure 2e**. This observation shows the addition of HPMC and PVP has
 221 reduced the aqueous solubility of the TXA drug. As TXA content increased, more
 222 crystalline TXA was observed in the PLM images of HPMC+PVP+30TXA ink (**Figure**
 223 **2f**).



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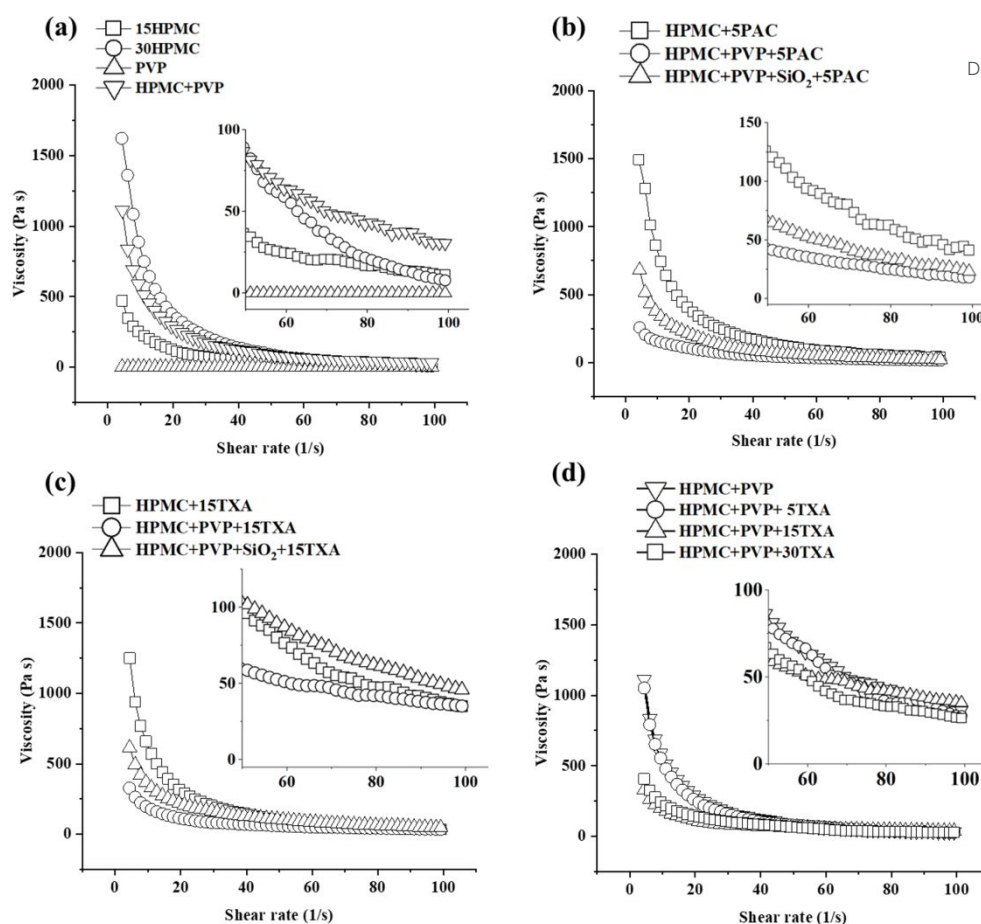
Figure 2. The polarized light microscopy images of the inks with (a) HPMC+5PAC, (b) HPMC+PVP+5PAC, (c) HPMC+PVP, (d) HPMC+PVP+5TXA, (e) HPMC+PVP+15TXA and (f) HPMC+PVP+30TXA.



228 The rheological properties of all formulated inks were evaluated at steady-state shear
229 viscosity measurements. PVP solution behaves as a Newtonian fluid and shows the
230 lowest viscosity that does not change with shear rate increment (**Figure 3a**). In contrast,
231 HPMC-based inks exhibited non-Newtonian fluid shear thinning behaviour (i.e., the
232 viscosity decreases when the shear rate increases). The low-shear viscosities of inks
233 increased with increasing HPMC concentrations. The addition of PVP to 15HPMC ink
234 did not change the shear-thinning behaviour of the ink. Interestingly, the addition of
235 20PVP to 15HPMC showed a significant decrease ($p \leq 0.05$) in the low-shear viscosity
236 of the ink (HPMC+PVP) as compared to 30HPMC despite containing a higher
237 percentage weight of solute. This could be due to a possible plasticizing effect by PVP
238 due to hydrogen bond formation (55). Additional PVP also significantly decreases ($p \leq$
239 0.05) the low-shear viscosity of both PAC and TXA-loaded HPMC-based inks, as
240 shown in **Figure 3b-c**. On the other hand, SiO₂ significantly increased ($p \leq 0.05$) the
241 low-shear viscosity of both PAC and TXA-loaded HPMC+PVP-based inks. Suspension
242 of silica particles in polymer solutions is thixotropic, displaying a gradual increase in
243 their low-shear viscosity. This has been attributed to the formation of a network
244 between polymer chains and the contiguous silica particles (56).

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245
246 **Figure 3.** Viscosity shear rate flow curves of the inks. The influences of (a) additive, (b) incorporation
247 of PAC and (c) TXA, and (d) TXA concentration on the ink viscosities. (Detailed ink formulation
248 compositions are presented in **Table 1**.)

249 The influence of TXA concentration on the rheological properties of the inks is shown
250 in **Figure 3d**. The addition of 5% w/w TXA showed no effect on the low-shear
251 viscosity of HPMC+PVP ink. A decrease in low-shear viscosity of inks was noted
252 when TXA concentration increased from 5% to 15% w/w, but no difference was
253 observed from 15% to 30% w/w TXA. This is because TXA has fully dissolved in
254 HPMC+PVP ink at 5% w/w, as described in the PLM images in **Figure 2c-d** but not at
255 15% and 30% w/w.

256



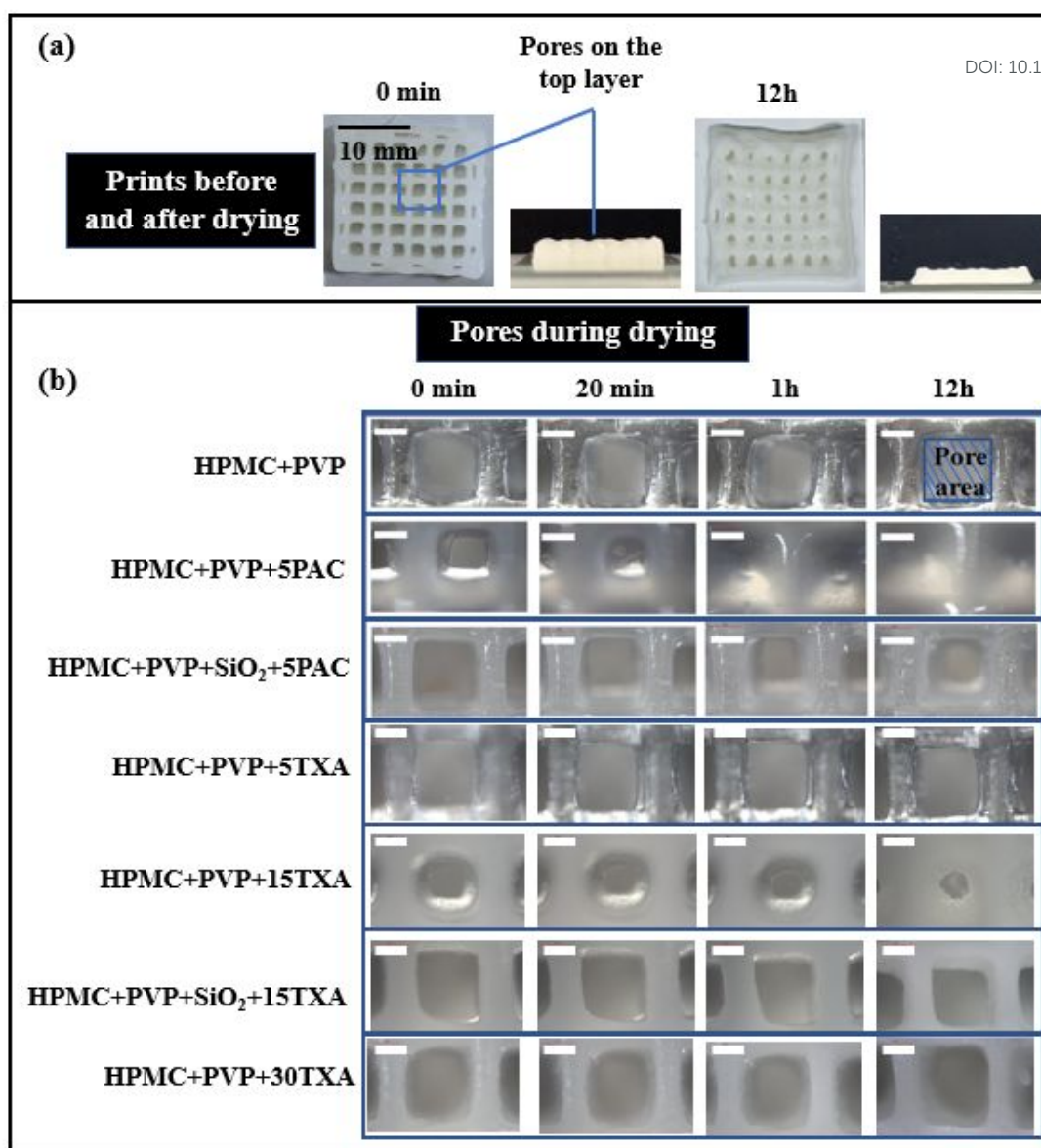
257 Correlation of ink properties and printed shape fidelity

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258 As ink contains a large amount of solvent (water for this study), solvent evaporation
259 during drying often leads to the shrinkage of the 3D printed constructs and subsequently
260 poor shape fidelity. **Figure 4** shows the physical appearances of 3D printed tablets of
261 HPMC+PVP+15TXA (15% w/w drug loading) and HPMC+PVP+5PAC (5% w/w drug
262 loading) immediately upon complete deposition of all designed layers and 12 hours
263 post-drying at ambient temperature. A thermogravimetric analysis (TGA) on dried
264 HPMC+PVP+15TXA and HPMC+PVP+5PAC samples showed a loss of weight up to
265 100 °C (i.e., water content evaporation) by $1.45\pm 0.10\%$ and $0.94\pm 0.31\%$ respectively
266 as presented in the Supplementary Material (Figure S2).

267 As shown in **Figure 4a**, a great shrinkage in the thickness of all 3D printed tablets was
268 identified. This shrinkage is due to the water loss of SSE 3D printed tablets during the
269 drying process. Pore area changes (defined as the empty void between filaments, as
270 shown in **Figure 4b**) of the top layer of the prints were monitored for 12 hours during
271 drying.



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273 **Figure 4.** (a) 3D printed HPMC+PVP+15TXA tablet immediately after printing (0 min) and 12 h post-

274 drying at ambient temperature (21 °C); (b) The top pore area changes were observed at the time

275 intervals (0 min, 20 min, 1h and 12 h) for HPMC+PVP, HPMC+PVP+5PAC,

276 HPMC+PVP+SiO₂+5PAC, HPMC+PVP+5TXA, and HPMC+PVP+15TXA,277 HPMC+PVP+SiO₂+15TXA, and HPMC+PVP+30TXA (scale bar in (b) represents 900 μm).

278 To evaluate the effect of API concentration on shape fidelity, a range of inks with

279 different TXA concentrations (5, 15 and 30% w/w) were studied. As shown in **Figure**280 **4**, the shape fidelities of drug-loaded prints were compared to the blank ink base by

19



281 utilising the pore structures as the key indicator. TXA was fully dissolved in ink when
282 5% w/w was loaded but partially dissolved at 15% and 30% w/w. This indicates that
283 HPMC+PVP and HPMC+PVP+5TXA inks initially had no solid contents. In contrast,
284 HPMC+PVP+15TXA ink contains an amount of solid crystalline drug particles and
285 worse in HPMC+PVP+30TXA.

286 As depicted in **Figure 4b**, HPMC+PVP, HPMC+PVP+5TXA and
287 HPMC+PVP+30TXA prints showed small change in pore areas during drying, whereas
288 HPMC+PVP+15TXA print showed nearly $50.5 \pm 1.1\%$ pore area under-sizing during
289 the 12 hours drying. This seems to contradict the observation in PAC where solid
290 content increment would improve shape fidelity. The viscosity data shown in **Figure**
291 **3d** revealed nearly identical viscosities of HPMC+PVP and HPMC+PVP+5TXA inks,
292 which are significantly higher than the viscosities of the inks with 15% and 30% w/w
293 drug loading. It is clear at this point that the fully dissolved 5% w/w TXA showed no
294 impact on the viscosity of the HPMC-PVP solution. This may explain the good shape
295 fidelities of the HPMC+PVP and HPMC+PVP+5TXA inks after printing and drying.

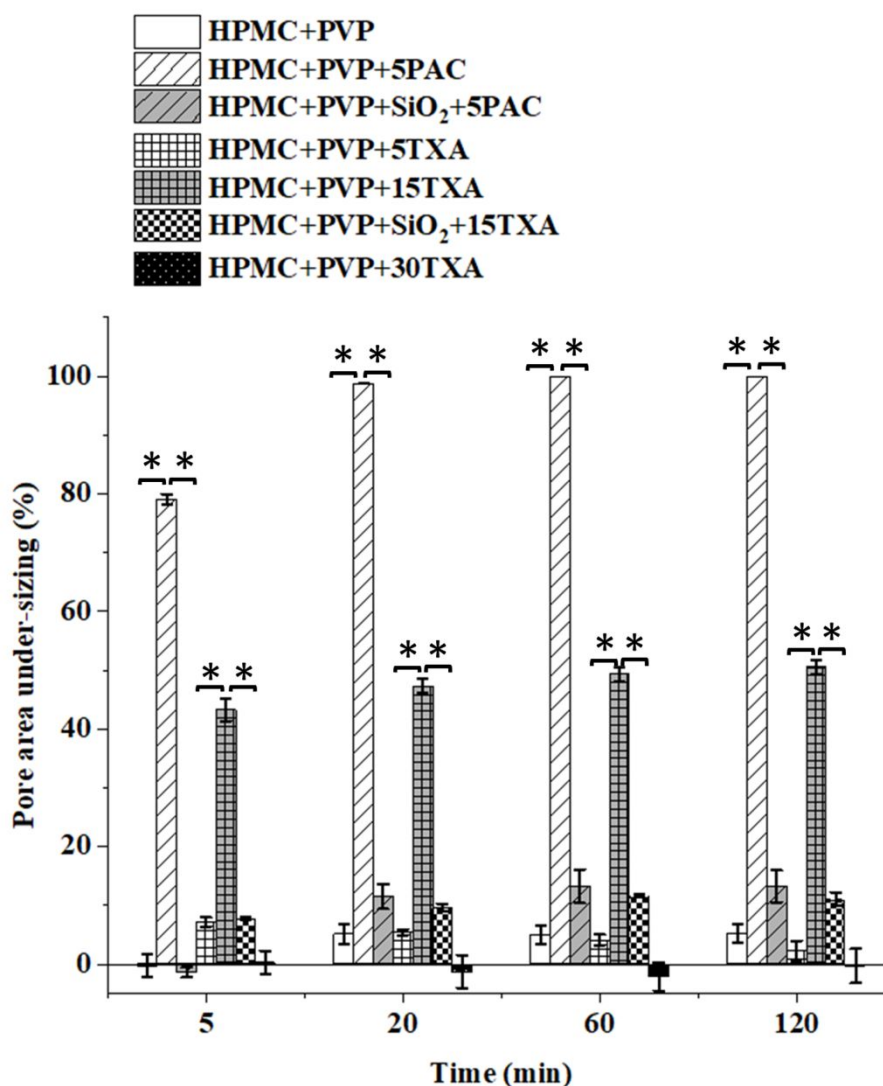
296
297 In 30% w/w TXA drug-loaded ink, consistent nozzle blockage was observed during 3D
298 printing which hurdle the replication of sample printing. This could be reasoned due to
299 the accumulation of undissolved TXA with unknown particle size and subsequently
300 lead to nozzle blockage (diameter of $413 \mu\text{m}$) during the extrusion process of 3D
301 printing. Therefore, only HPMC+PVP+5TXA and HPMC+PVP+15TXA 3D printed
302 tablets were subjected to further investigate the effect of drug concentration on drug
303 release. As the concentration of TXA increased, it was noted that the low-shear
304 viscosity of HPMC+PVP+15TXA and HPMC+PVP+30TXA inks significantly



305 reduced ($p \leq 0.05$). Based on the observation of the rheological behaviour of 5% w/w
306 drug-loaded ink against the blank, dissolved TXA within the ink did not affect the low-
307 shear viscosity ($p \geq 0.05$). This indicates the undissolved TXA particles have led to a
308 viscosity reduction, particularly when high drug concentrations were loaded. For
309 HPMC+PVP+30TXA ink, the high amount of particulate contents could pack together
310 during drying and subsequently inhibit the ink flow which resulted in the observed lack
311 of pore area changes (26).

312
313 The corresponding pore area under-sizing percentage with the time is shown in **Figure**
314 **5**. The pores of HPMC+PVP+5PAC prints were completely closed and disappeared
315 after 12 hours of drying. HPMC+PVP+15TXA showed a significant under-sizing in
316 pore areas ($p \leq 0.05$), but not a complete pore closure. The pore area of
317 HPMC+PVP+15TXA decreased by $50.5 \pm 1.1\%$ after 12 hours. The addition of SiO_2
318 (which is an insoluble and structuring additive for both ink formulations) significantly
319 improved ($p \leq 0.05$) the shape fidelities of the prints after drying and avoided pore
320 closures. HPMC+PVP+ SiO_2 +15TXA ink maintained the shape fidelity much better
321 than HPMC+PVP+15TXA during drying. This could be attributed to the high solid
322 contents in the HPMC+PVP + SiO_2 +15TXA ink formula.





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325 HPMC+PVP+5PAC, HPMC+PVP+SiO₂+5PAC, HPMC+PVP+5TXA, and HPMC+PVP+15TXA,326 HPMC+PVP+SiO₂+15TXA and HPMC+PVP+30TXA (* indicating $p \leq 0.05$).

327 The physical appearances and SEM images of post-drying 3D printed HPMC+PVP inks

328 loaded with TXA and PAC are shown in **Figure 6**. A greater pore area reduction329 occurred in the tablets printed using inks without SiO₂, and the pores were completely

330 sealed in the samples printed using the PAC-loaded ink. This is likely to be due to the

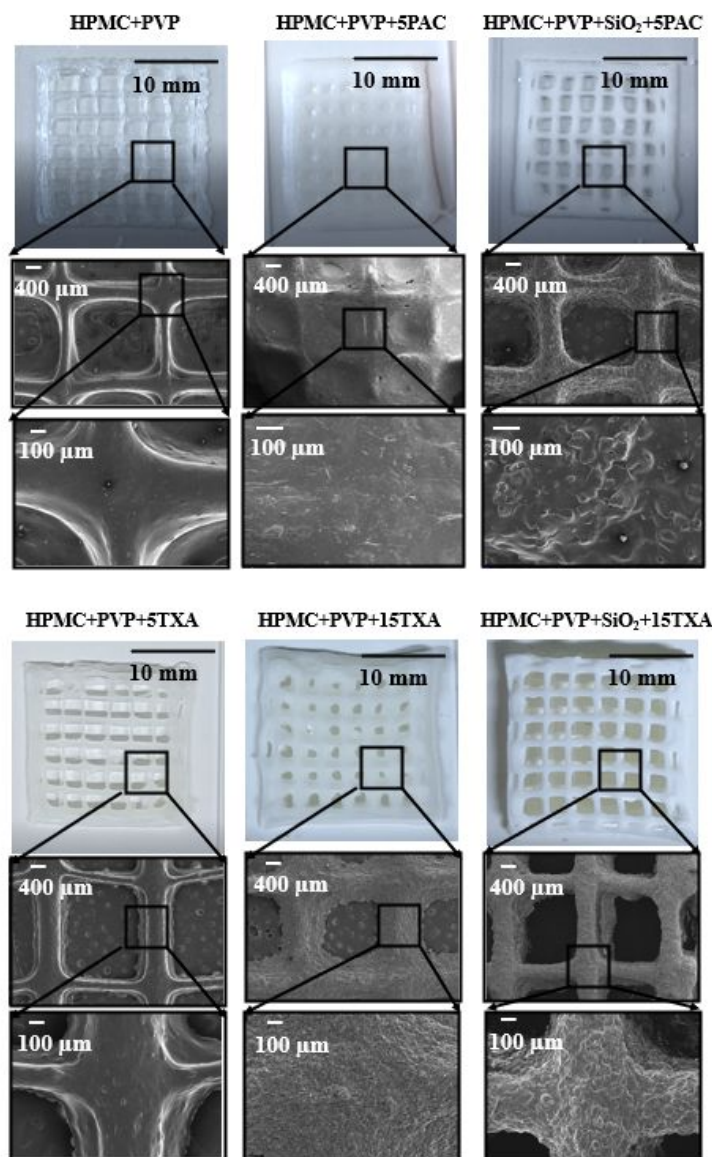
331 decrease in the low-shear viscosity of ink (as shown in **Figure 3d**). The addition of332 SiO₂ to the inks increased the solid content of the inks. This led to a significant increase

22



333 in the low-shear viscosities of inks ($p \leq 0.05$) with both drugs in comparison to the inks
 334 without SiO₂. The higher solid content translated into a lower solvent content and in
 335 turn shortened the drying. The higher viscosity led to weaker spreading and flow of the
 336 ink during drying. The combination of both high solid content and high viscosity led to
 337 the improvement in shape fidelity.

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338
 339 **Figure 6.** Physical appearances and SEM images of dried 3D printed tablets of HPMC+PVP,
 340 HPMC+PVP+5PAC, HPMC+PVP+SiO₂+5PAC, HPMC+PVP+5TXA, and HPMC+PVP+15TXA,
 341 HPMC+PVP+SiO₂+15TXA.

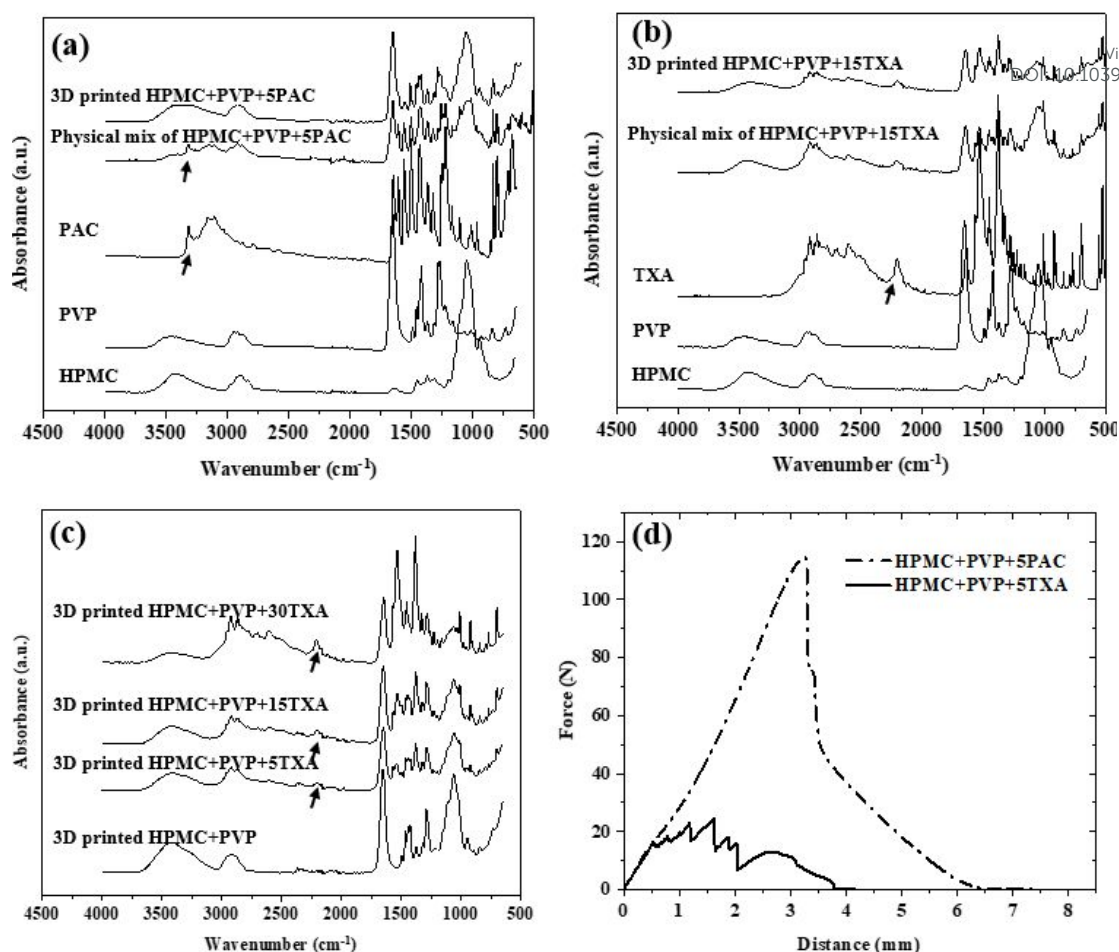


342 ATR-FTIR was carried out to investigate any possible molecular interactions between
343 the polymer, additive, and API. The ATR-FTIR spectra of HPMC, PVP, PAC, TXA,
344 physical mixture and dried SSE 3D printed tablets are shown in **Figure 7a-b**. The
345 spectrum of HPMC shows an absorption band at 3445 cm^{-1} assigned to the stretching
346 frequency of the hydroxyl (-OH) group. Other stretching vibration bands related to C-
347 H and C-O were observed at 2929 cm^{-1} and 1056 cm^{-1} , respectively. The peaks of pure
348 HPMC were similar to the literature (57). The FTIR spectrum of PVP displays a peak
349 at 3424 cm^{-1} , assigned to O-H stretching. The peaks at 2950 cm^{-1} and 1652 cm^{-1} were
350 assigned to asymmetric stretching of CH_2 and stretching of C-O, respectively (58). As
351 seen in **Figure 7a**, the spectrum of PAC shows a characteristic vibrational peak for NH
352 stretching at 3326 cm^{-1} due to the presence of crystalline material (59, 60).

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Figure 7. FTIR results of PAC-loaded HPMC+PVP 3D printed tablet (a), TXA-loaded HPMC+PVP 3D printed tablet (b), HPMC+PVP+TXA tablets with various TXA concentrations (c), and the mechanical properties of HPMC+PVP+5PAC and HPMC+PVP+5TXA tablets obtained from puncture tests. The curves displayed for the puncture test were plotted with average values from three replicates.

In contrast to the pure PAC and physical mixture HPMC+PVP+PAC, the sharp peak of N-H stretching at 3326 cm^{-1} (as the arrow indicated in **Figure 7a**) has disappeared in 3D printed HPMC+PVP+PAC. This is likely due to PVP interacting with PAC *via* hydrogen bonding and potentially reducing the crystallinity of PAC. This is also supported by the preliminary DSC data as shown in Figure S3. The thermogram depicted a melting peak of PAC ($159.50\pm 2.15^\circ\text{C}$) in the physical mixture HPMC+PVP+PAC, but an absence in the dried SSE printed HPMC+PVP+PAC.

25



366 As seen in **Figure 7b**, the spectrum of TXA shows a strong cluster of peaks in the
367 region 3000 to 2500 cm^{-1} , representing both NH^{3+} and CH vibrational modes of TXA.
368 (22). There was no significant shift or new peak formation/disappearance in comparison
369 to the physical mixture HPMC+PVP+TXA and 3D printed HPMC+PVP+TXA. FTIR
370 spectra of HPMC+PVP+TXA tablets with various TXA concentrations as shown in
371 **Figure 7c** reported as the concentration increased from 5% to 30% w/w, the intensity
372 of the characteristic peak in 2250 cm^{-1} increased as expected.

373

374 3.1.2 Effect of structural design

375 **Table 3** shows the dimensions of the 3D printed tablets resulting from the influence of
376 additive, drug concentration, layer quantity (4 or 14 layers), and infill percentage (25
377 or 50% infill). There was no significant difference ($p = 0.51$) in terms of outer
378 dimensional measures (width and length) of the printed tablets HPMC+15TXA,
379 HPMC+PVP+15TXA and HPMC+PVP+SiO₂+15TXA. However, a significant
380 difference in tablet thickness and weight was observed. This is due to the substantial
381 increase in solute concentrations (**Table 1**). As the TXA concentration increased from
382 0% to 15% w/w, the tablet thickness and weight of HPMC+PVP, HPMC+PVP+5TXA
383 and HPMC+PVP+15TXA increased significantly ($p < 0.05$).

384 As expected, the layer number affects tablet thickness and weight. For instance, the
385 tablet thickness and weight for HPMC+PVP+5TXA_14 layer are roughly 3 times of
386 HPMC+PVP+5TXA_4 layer. No significant difference in width, length and thickness
387 among the 3D printed tablets with different drug loadings and infills
388 (HPMC+PVP+5TXA_25%infill, HPMC+PVP+15TXA_25%infill,



389 HPMC+PVP+5TXA_50%infill and HPMC+PVP+15TXA_50%infill) were noted, but
 390 a significant difference regarding the tablet weight were expected.

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391 **Table 3.** Dimension, porosity, and weight of the SSE 3D printed tablet.

	Width (mm)	Length (mm)	Thickness (mm)	Pore area (mm ²)	Tablet weight (mg)	Porosity (%)
Influence of additive & API						
HPMC+PVP	19.9±0.1	19.9±0.1	1.3±0.1	3.8±0.1	203.8±21.8	69.8±1.9
HPMC+PVP+5TXA	19.6±0.4	19.4±0.4	1.8±0.1	3.9±0.1	252.7±16.3	72.0±1.0
HPMC+15TXA	18.5±0.0	18.5±0.1	1.8±0.2	3.9±0.1	144.2±4.2	82.9±1.3
HPMC+PVP+15TXA	18.9±0.1	18.7±0.2	20.0±0.0	2.0±0.0	286.2±1.3	67.7±1.0
HPMC+PVP+SiO₂+15TXA	17.7±0.4	17.9±0.3	2.4±0.1	3.6±0.1	312.7±4.9	69.1±2.6
HPMC+PAC	19.9±0.2	20.0±0.1	0.6±0.0	1.8±0.2	73.7±11.1	76.4±2.3
HPMC+PVP+5PAC	19.6±0.4	19.8±0.2	0.9±0.0	0*	223.4±3.3	47.6±2.1
HPMC+PVP+SiO₂+5PAC	19.8±0.3	19.8±0.3	1.5±0.0	3.5±0.1	231.4±6.1	70.3±0.2
Influence of structural design						
HPMC+PVP+5TXA_4layer	19.7±0.1	19.6±0.9	0.6±0.1	3.9±0.1	84.6±11.3	70.6±0.7
HPMC+PVP+15TXA_4layer	19.7±0.1	19.6±0.1	0.5±0.0	2.5±0.8	81.2±0.6	67.9±0.8
HPMC+PVP+5TXA_14layer	19.6±0.4	19.4±0.4	1.8±0.1	3.9±0.1	252.7±16.3	72.0±1.0
HPMC+PVP+15TXA_14layer	18.9±0.1	18.7±0.2	2.0±0.0	2.0±0.0	286.2±1.3	67.7±1.0
HPMC+PVP+5TXA_25%infill	19.6±0.4	19.4±0.4	1.8±0.1	3.9±0.1	252.7±16.3	72.0±1.0
HPMC+PVP+15TXA_25%infill	18.9±0.1	18.7±0.2	2.0±0.0	2.0±0.0	286.2±1.3	67.7±1.0
HPMC+PVP+5TXA_50%infill	18.3±0.1	18.6±0.0	1.9±0.1	0.4±0.1	357.7±14.8	57.1 ±1.0
HPMC+PVP+15TXA_50%infill	18.7±0.2	18.5±0.0	2.1±0.1	0*	463.3±1.8	48.5±2.8

392 *The pores were fully merged during drying.



393 3.2 Drug release of 3D printed tablet

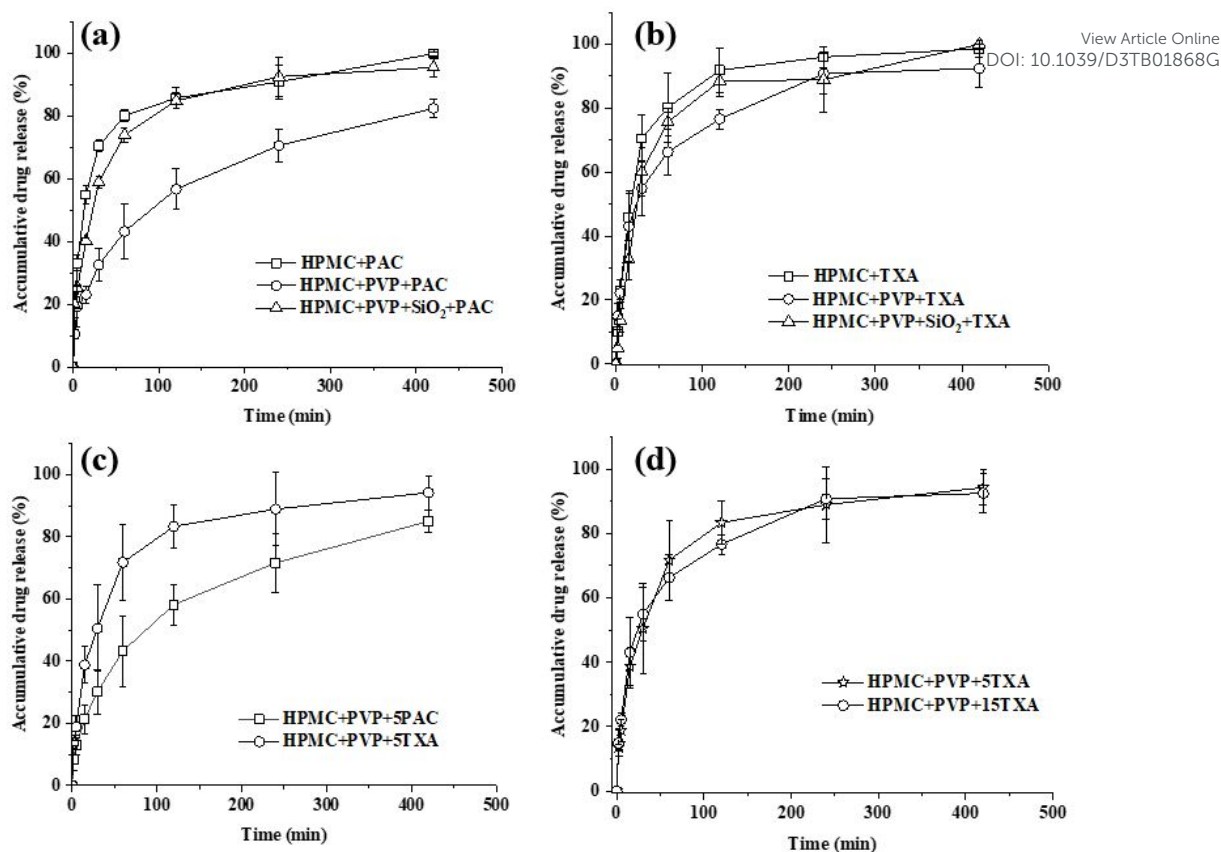
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394 3.2.1 Effect of additive and API

395 The influence of the additive on the drug release of PAC-loaded tablets was investigated
396 (as shown in **Figure 8a**). The addition of PVP without SiO₂ showed a significant
397 decrease in the drug release rate of PAC ($p < 0.05$). This may be due to the porosity of
398 HPMC+PVP+PAC ($\approx 48\%$) being significantly lower than tablets without PVP or with
399 both PVP and SiO₂ ($\approx 70-76\%$). The addition of SiO₂ to HPMC+PVP+PAC ink
400 significantly increased the drug release rate ($p < 0.05$) and reached a similar rate as
401 HPMC+PAC without PVP. The increased drug release of HPMC+PVP+SiO₂+PAC in
402 comparison to HPMC+PVP+PAC is likely to be due to SiO₂ acting as a disintegrant
403 and speeding up the dissolution process, as discussed in other studies (61, 62).

404 The influence of the additive on the *in vitro* drug release of the TXA-loaded 3D printed
405 tablet is shown in **Figure 8b**. The addition of PVP and SiO₂ showed no significant
406 impacts on the drug release rate of HPMC+15TXA, HPMC+PVP+15TXA and
407 HPMC+PVP+SiO₂+15TXA tablets. As shown in **Table 3**, the pore area of
408 HPMC+15TXA, HPMC+PVP+15TXA and HPMC+PVP+SiO₂+15TXA are 3.9 ± 0.1 ,
409 2.0 ± 0.0 and 3.6 ± 0.1 mm². Despite having the smallest pore area ($67.7 \pm 1.0\%$) within
410 the dried prints, the porosity of HPMC+PVP+15TXA is not significantly lower than
411 HPMC+PVP+SiO₂+15TXA ($69.1 \pm 2.6\%$). Thus, the drug release of
412 HPMC+PVP+15TXA was not significantly slower than the other two (i.e.,
413 HPMC+15TXA and HPMC+PVP+SiO₂+15TXA).





414

415 **Figure 8.** *In vitro* drug release data of SSE 3D printed tablets of (a) PAC-loaded tablets, (b) TXA-

416 loaded tablets, (c) the influence of API type, and (d) the influence of API concentration.

417 The influence of API type on the drug release rate is shown in **Figure 8c**. The drug

418 release of PAC-loaded tablets was significantly lower than the one loaded with TXA,

419 despite both having the same (5% w/w) drug loading in the ink. This is possibly due to

420 the porosity of HPMC+PVP+5TXA being significantly higher than

421 HPMC+PVP+5PAC, which are $72.0 \pm 1.0\%$ and $47.6 \pm 2.1\%$, respectively. Another

422 possible reason is TXA-based tablets can easily disintegrate during drug dissolution,

423 which was proved by the puncture mechanical test where TXA tablets require much

424 less force to puncture than PAC tablets. The influence of TXA concentration on drug

425 release has been investigated and illustrated in **Figure 8d**. There was no significant

426 difference between 5% and 15% w/w TXA drug loadings. Although the pore area of

29



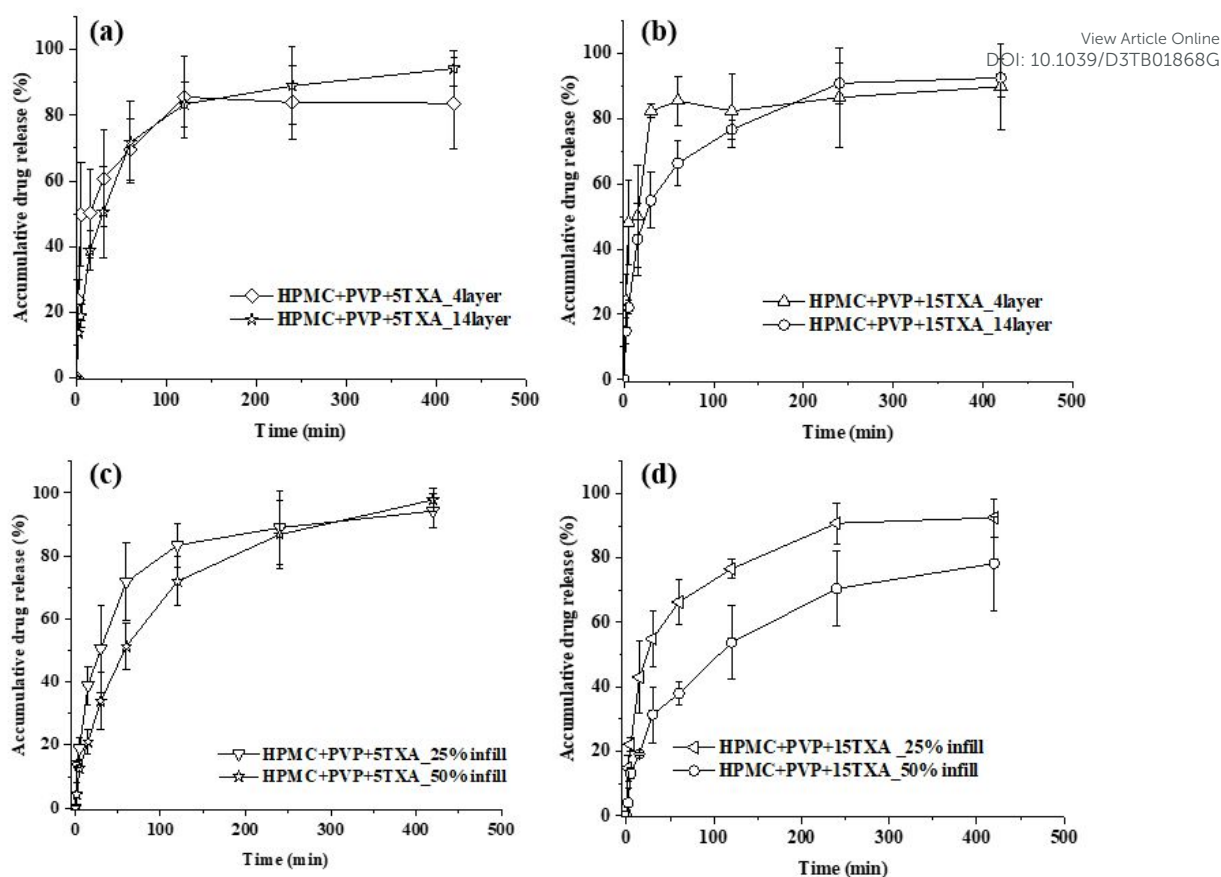
427 HPMC+PVP+5TXA is higher than HPMC+PVP+15TXA, yet, no significant
428 difference ($p > 0.05$) was identified. This could be due to the limitation of measuring
429 pore area by 2D-microscopy images, but porosity existed in three dimensions. Due to
430 the advantage of 3D printing technique, it is possible to have voids in between the 3D
431 printed HPMC+PVP+15TXA_14layer despite a fully merged (pore area = 0 mm²) of
432 the 2D pore area was observed.

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433 3.2.2 Effect of structural design

434 The influence of the number of layers on the drug release rates of the tablets is shown
435 in **Figure 9a-b**. As TXA is a highly water-soluble drug and the drug was fully dissolved
436 in the printed tablets at a drug loading of 5% w/w, theoretically, the release rate limiting
437 factor would be the dissolution of the polymeric matrices. 14- and 4-layer prints have
438 a 3-fold thickness difference, which should be translated into a difference in dissolution
439 rate. However, there was no difference in the drug release rate of the 14- and 4-layers
440 tablets with 5% w/w TXA (**Figure 9a**). This is possibly due to the insignificant
441 difference in pore area and porosity between 14- and 4-layers prints and the ease of
442 tablet disintegration. Both tablets were similar in terms of pore area (3.9 ± 0.1 mm²) and
443 porosity ($71.5 \pm 1.6\%$).





444

445 **Figure 9.** *In vitro* drug release profiles of (a) 5%TXA-loaded tablets and (b) 15%TXA-loaded tablets

446 affected by layer number factor, and (c) 5%TXA-loaded tablets and (d) 15%TXA-loaded tablets

447 affected by infill percentage.

448 As shown in **Figure 9b**, when the loaded drug was increased to 15% w/w, where a

449 significant amount of undissolved drug was present in the prints, the 4-layers drug

450 release rate was significantly higher than the 14-layers between 60-120 minutes. This

451 is possibly due to the higher pore area of 4-layers ($2.0 \pm 0.0 \text{ mm}^2$) compared to 14-layer452 ($2.5 \pm 0.8 \text{ mm}^2$).

453 The infill showed no effect on the drug release rate of the prints loaded with 5% w/w

454 TXA (**Figure 9c**) but significantly affected the prints loaded with 15% w/w TXA455 (**Figure 9d**). This could be due to the significantly lower viscosity of 15% w/w TXA

456 ink than the 5% w/w TXA ink and that resulted in an almost entirely merged of pores
457 within the 3D printed HPMC+PVP+15TXA tablets with 50% infill. The porosity of
458 HPMC+PVP+15TXA_50%infill and HPMC+PVP+15TXA_25%infill were reported
459 at $48.5\pm 2.8\%$ and $57.1\pm 1.0\%$, respectively. In summary, the drug release rates of all
460 TXA drug-loaded 3D printed tablets were lower than the pure TXA powder.

461

462 **4 Conclusion**

463 This study developed an understanding of the influence of additive and API on the
464 prints of SSE 3D printing and their drug release performance. HPMC and binary
465 polymeric system HPMC-PVP-based semisolid inks have been developed for SSE 3D
466 tablet printing. The influence of additive (i.e., SiO₂) and API (i.e., PAC and TXA) on
467 ink rheology behaviour, 3D printing shape fidelity and drug release performance have
468 been investigated and demonstrated. It was shown that the use of additive, API
469 candidate selection and concentration could significantly affect the ink rheology
470 behaviour and further change the shape fidelity of SSE 3D printed tablets. A clear
471 relationship between the low shear viscosity of the semisolid ink and their printability
472 was observed. The API (i.e., PAC and TXA) loaded inks for 3D printing showed more
473 significant pore merging issues than the blank HPMC-PVP based inks. The addition of
474 SiO₂ proved to relieve the pore merging issue. This could be observed from the pore
475 area improvement of HPMC+PVP+SiO₂+5PAC prints at 3.5 ± 0.1 mm² compared to the
476 completely closed (0 mm²) HPMC+PVP+5PAC prints after 12 hours of drying.
477 HPMC+PVP+15TXA formulation showed a significant under-sizing in pore areas ($p \leq$
478 0.05) at $50.5\pm 1.1\%$ after 12 hours of drying. The addition of SiO₂ significantly
479 improved the pore area of the prints to $41.0\pm 2.2\%$. The drug release study showed the



480 drug release rate was affected by the selection of polymeric system and API. PVP
481 showed a significant delay ($p \leq 0.05$) in the drug release of PAC-loaded tablets, possibly
482 due to the poor porosity. Besides, it was noted that the structural properties of 3D
483 printed tablets also affected drug release. Investigation into the layer numbers and infill
484 density showed the layer number had little effect but the infill percentage of TXA
485 tablets significantly influenced drug release, probably due to the effects of pore
486 merging. The insights reported in this study could serve as practical guidance for ink
487 development in fabricating a controlled performance SSE 3D printed porous
488 formulation for personalised pharmaceuticals.

489

490 **Acknowledgement**

491 This research was funded by the Redistributed Manufacturing in Healthcare Network
492 (RiHN). RiHN was awarded a grant from the UK Engineering and Physical Sciences
493 Research Council (EPSRC) (Ref. EP/T014970/1). The authors thank Thomas
494 McDonagh for his help with the mechanical testing.



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DOI: 10.1039/D3TB01868G

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