Electronic Supplementary Material (ESI) for Polymer Chemistry.

Supporting Information

A 3D Printed Drug Delivery Implant formed from a Dynamic Supramolecular Polyurethane Formulation

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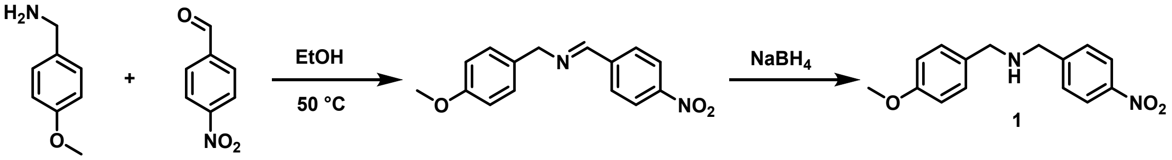
Synthesis of *N*-(4-Methoxybenzyl)-1-(4-nitrophenyl)methanamine 1



N-(4-Methoxybenzyl)-1-(4-nitrophenyl)methanamine **1** was synthesised in accordance to the previously reported procedure.[S1] Briefly; to a stirred solution of 4-nitrobenzaldehyde (4.00 g, 26.45 mmol) in ethanol (50 mL) was added 4-methoxybenzylamine (4.38 g, 31.92 mmol) and resulting mixture stirred at 50 °C for 18 hours. Ethanol was removed *in vacuo* before the crude solid was passed through silica plug using ethyl acetate as the eluant. The resultant imine intermediate was then dissolved in methanol (50 mL) and stirred with sodium borohydride (39. 68 mmol, 1.5 eq., 1.50 g) for 4 hours at room temperature. The solvent was subsequently removed *in vacuo* after which water was added and the product isolated by extraction with ethyl acetate (3 × 50 mL) to yield an orange oil (7.18 g, 84%). IR (ATR) ν/cm^{-1}: 3098, 3024, 3008, 2963, 2932, 2913, 2835, 1676, 1639, 1605, 1600, 1580, 1510, 1443, 1440, 1417, 1378, 1340, 1298, 1295, 1245, 1219, 1179, 1144, 1106; ^{1}H NMR (400 MHz, CDCl3) δ ppm: 8.18 (2H, appt.d, AA'XX', CCHC*H*CNO$_2$), 7.52 (2H, appt.d, AA'XX', CC*H*CHCNO$_2$), 7.24 (2H, appt.d, AA'BB', CC*H*CHCOCH$_3$), 6.89 (2H, appt.d, AA'BB', CCHC*H*COCH*3*), 3.90 (2H, s, NHC*H*$_2$ArNO*2*), 3.81 (3H, s, ArOC*H*$_3$), 3.75 (2H, s, NHCH2ArOCH3), 1.60 (s, br, NH), ^{13}C NMR (100 MHz; CDCl3) δ ppm: 159.1, 158.9, 149.0, 141.7, 130.5, 129.4, 128.9, 123.8, 114.1, 64.6, 55.3.

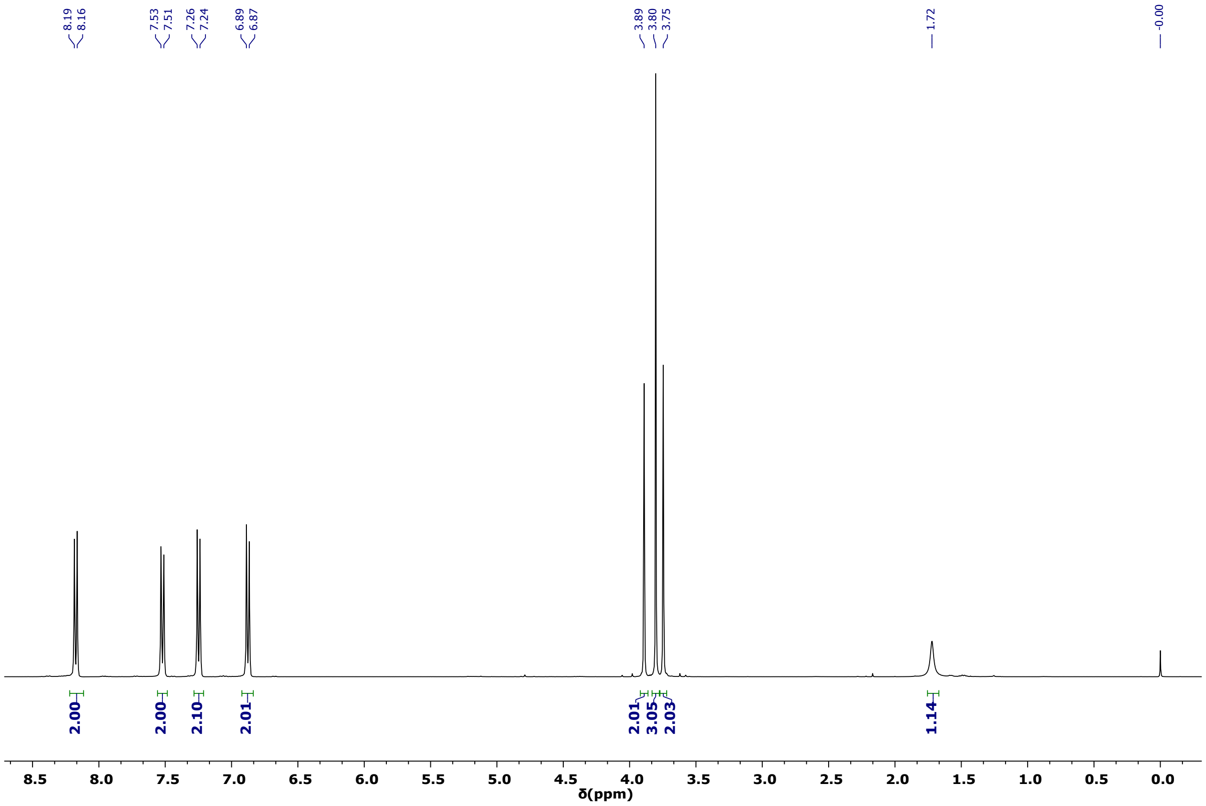


Figure S1: ^{1}H NMR spectrum of *N*-(4-methoxybenzyl)-1-(4-nitrophenyl)methanamine.

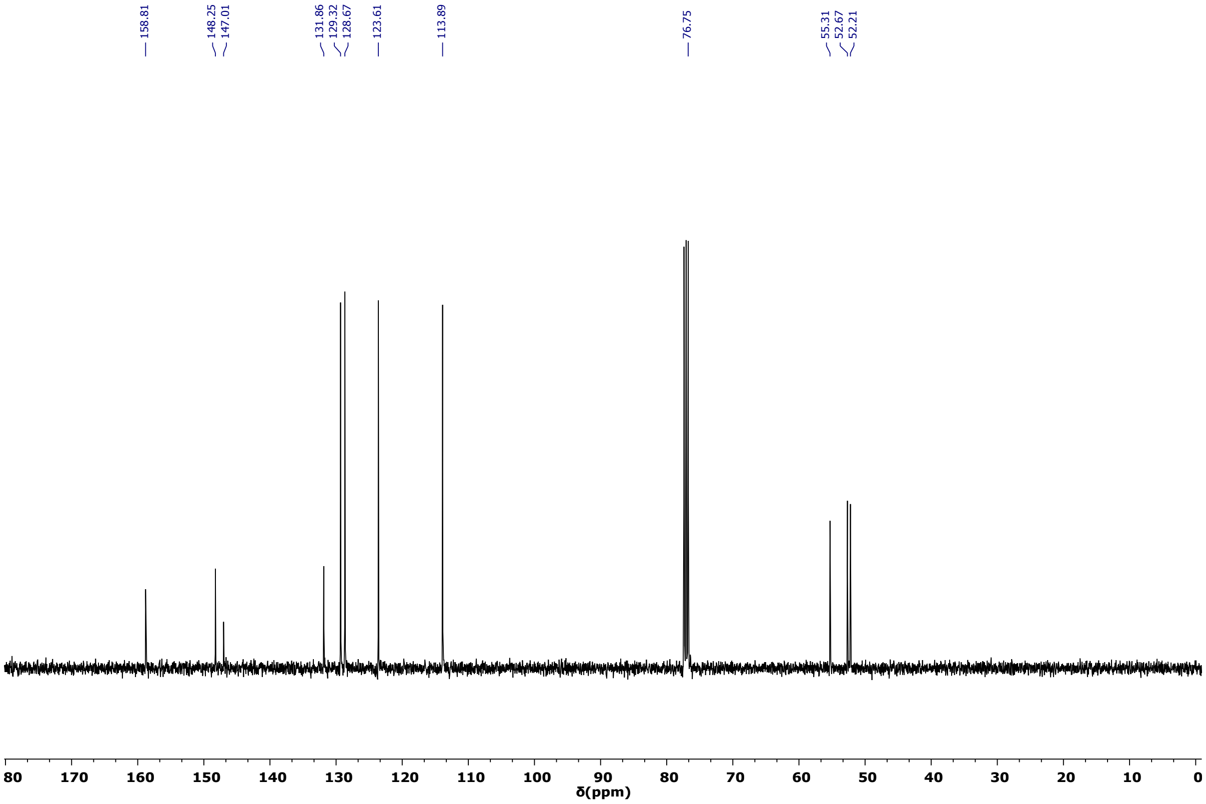


Figure S2: ^{13}C NMR of N-(4-Methoxybenzyl)-1-(4-nitrophenyl)methanamine.

Synthesis of the N-(4-Methoxybenzyl)-1-(4- nitrophenyl)methanamine capped polyurethane (SPU1).[S1]

The polyol was dried in vacuum oven at 120 °C under partial vacuum for 1 hour prior to use. Krasol HLBH-P 2000 **2** (20 g, 9.5 mmol) was mixed with 4,4′-Methylenebis(phenyl isocyanate) **3** (5.02 g, 20.1 mmol) in the bulk for 3 hours at 80 °C under N_2. The resulting mixture was then dissolved in anhydrous THF (150 mL) and cooled to room temperature. To the pre-polymer **4** was added *N*-(4-methoxybenzyl)-1-(4-nitrophenyl)methanamine **1** (5.57 g, 20.46 mmol) and the solution stirred for 2 hours at 50 °C. The solution was concentrated *in vacuo* and the product isolated with repeated precipitations from THF in methanol (3 × 1 L) to yield the product **SPU1** as a light orange coloured solid (22.6 g, 75%). IR (ATR) ν/cm^{-1}: 3331, 2957, 2921, 2851, 1644, 1596, 1512, 1462, 14)12, 1342, 1304, 1241, 1174, 1108, 1031, 972, 813, 777, 735, 700 ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (4H, appt.d, AA'XX', $CCHC\mathit{H}CNO_2$), 7.50 (4H, appt.d, AA'XX', $CC\mathit{H}CHCNO_2$), 7.17 (4H, appt.d, AA'BB', $CC\mathit{H}CHCOCH_3$), 7.14–6.98 (16H, m, Ar), 6.89 (4H, appt.d, AA'BB', $CCHC\mathit{H}COCH_3$), 6.50 (2H, br, N*H*C(O)O), 6.32 (2H, N*H*C(O)N*H*), 4.75 (5H, s, $NC\mathit{H}_2ArNO_2$), 4.47 (5H, s, $NC\mathit{H}_2ArOCH_3$), 4.20 - 4.10 (4H, m, $CH_2C\mathit{H}_2OC(O)NH$), 3.86 (4H, m, $ArC\mathit{H}_2Ar$), 3.81 (6H, s, $ArOC\mathit{H}_3$), 2.03–0.65 (407H, m, $((C\mathit{H}_2)_4)_n$. ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.6, 155.8, 147.4, 145.5, 136.4, 135.9, 129.4, 128.4, 128.1, 127.8, 124.0, 120.2, 114.7, 67.9, 55.4, 50.7, 40.5, 39.3, 37.8, 36.1, 33.8, 32.7, 30.7, 30.2, 29.8, 26.8, 25.7, 10.9; GPC (THF): M_n = 6100 Da, M_w = 12600 Da, $Đ$ = 2.06; DSC: T_g = -47.6 °C, 19.45 °C.

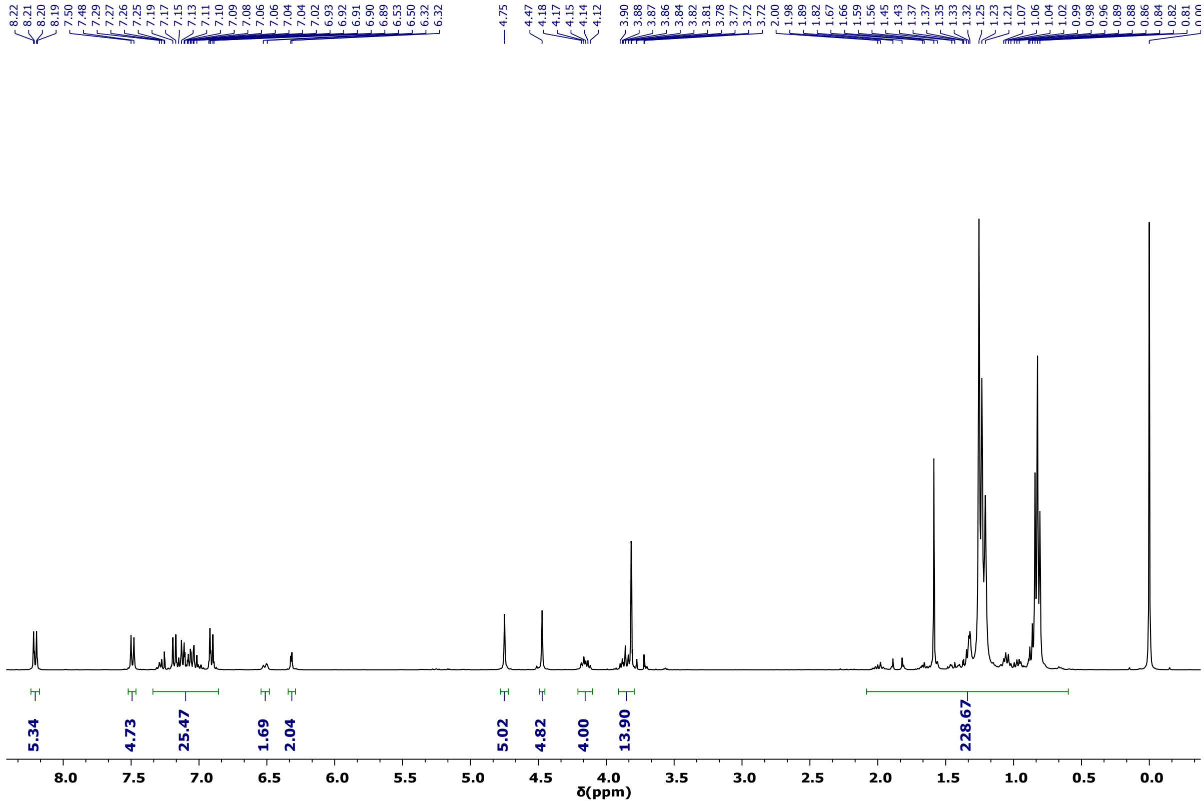


Figure S3: ^{1}H NMR spectrum of the polyurethane **SPU1**.

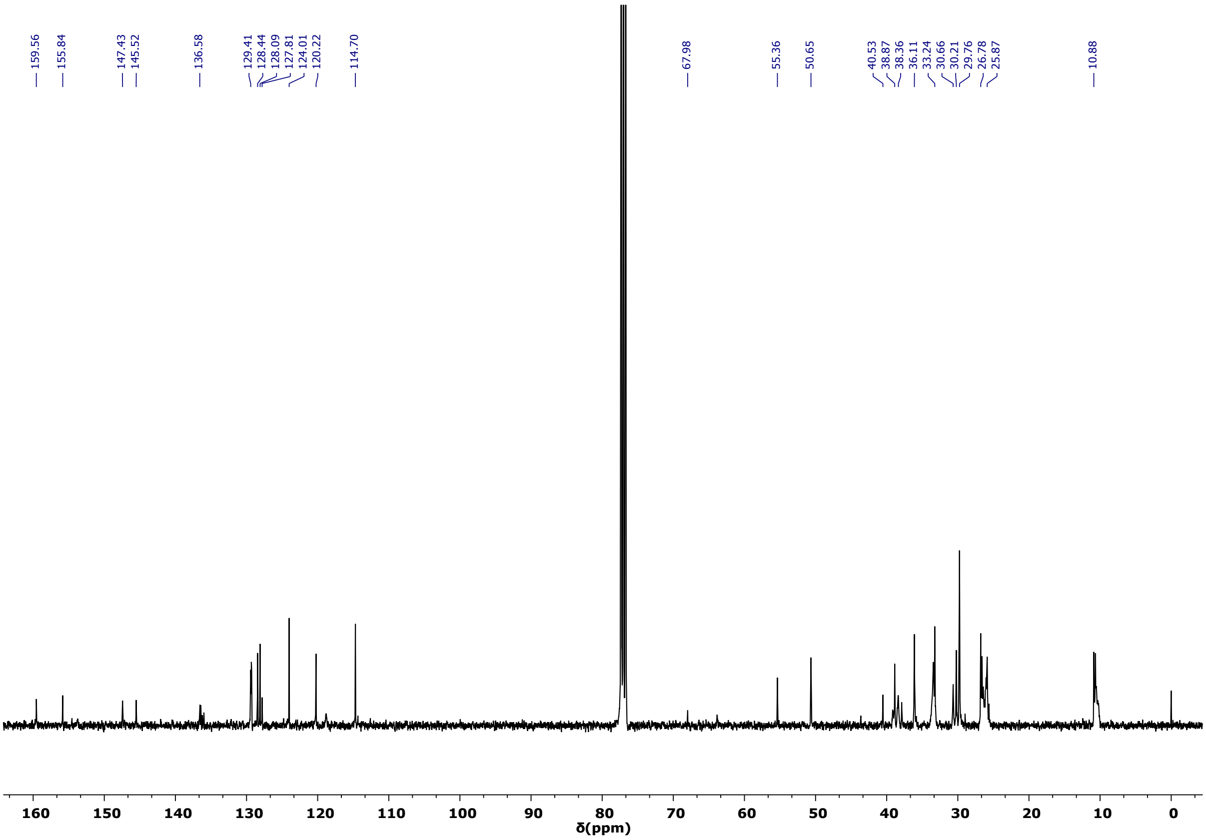


Figure S4: ^{13}C NMR spectrum of the polyurethane **SPU1**.

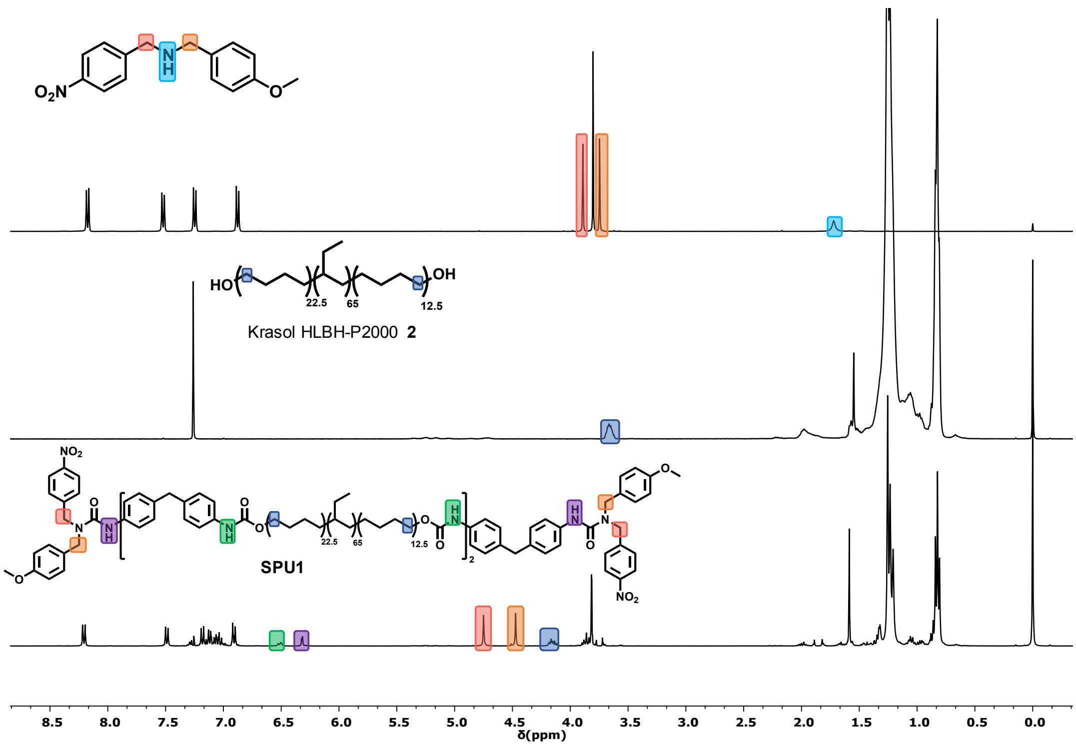


Figure S5: Stacked ^{1}H NMR spectra of the end-group (N-(4-Methoxybenzyl)-1-(4-nitrophenyl)methanamine **1**, polymer **2**, and **SPU1**, confirming the formation of the urethane and urea linkages.

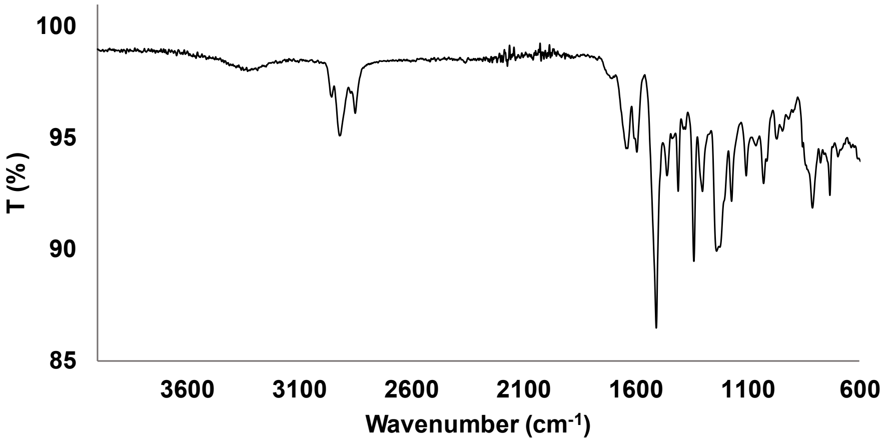


Figure S6: Infrared spectrum of **SPU1**.

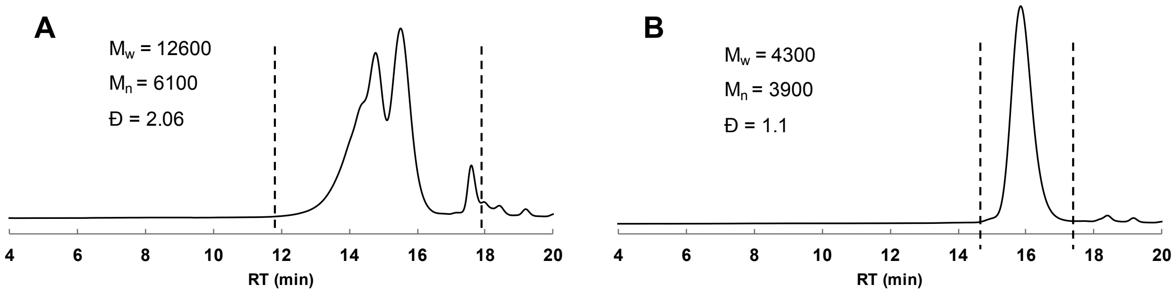
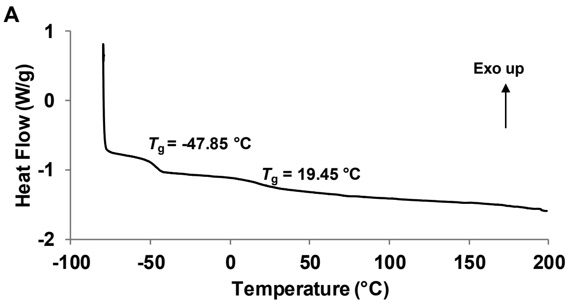


Figure S7: GPC eluograms of A) **SPU1** and B) Krasol HLBH-P2000. The regions used for molecular weights calculations are shown between the hashed lines. Analysis was carried out in THF against PS standards. The small peaks above 18 min are system peaks.[S2]



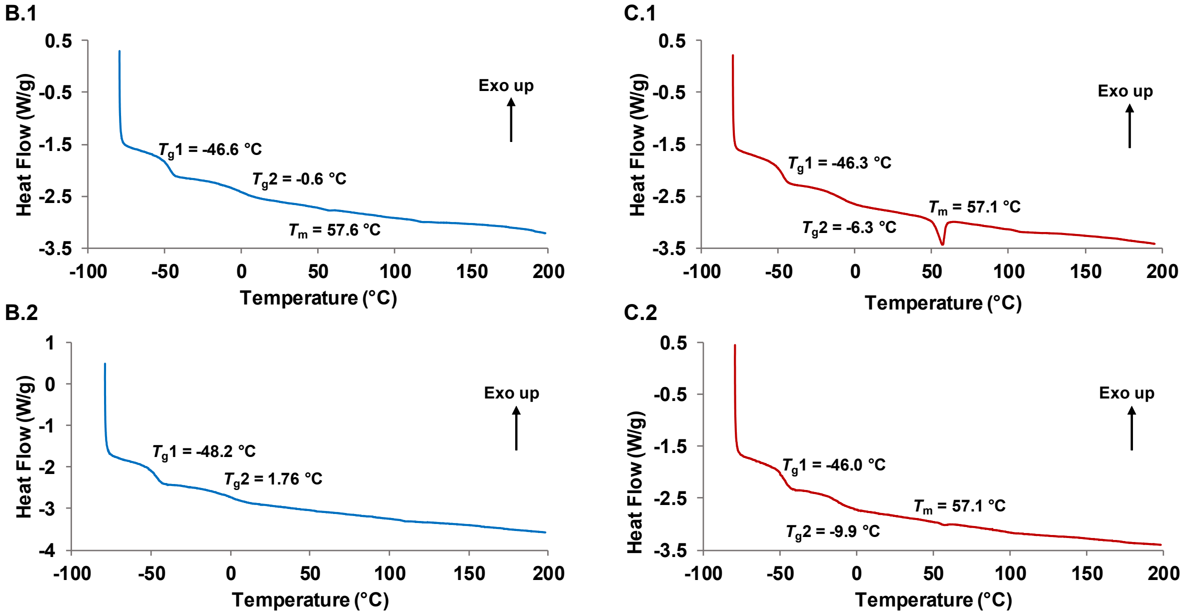


Figure S8: Differential Scanning Calorimetry of A) **SPU1**, B) **F1** 1: cast and 2: printed, C) **F2** 1: cast and 2: printed showing all thermal transitions. Shown in the graphs are the second cycle of the 3 cycles experiment.

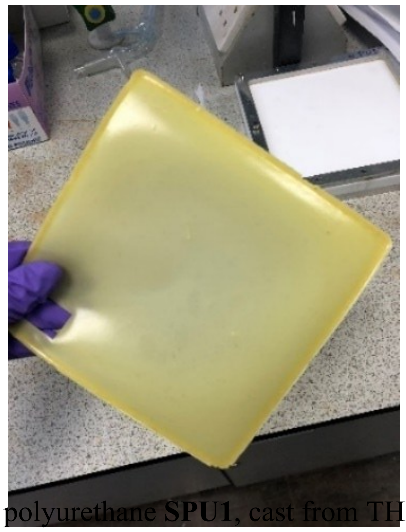


Figure S9: Image of a film of the polyurethane **SPU1**, cast from THF.

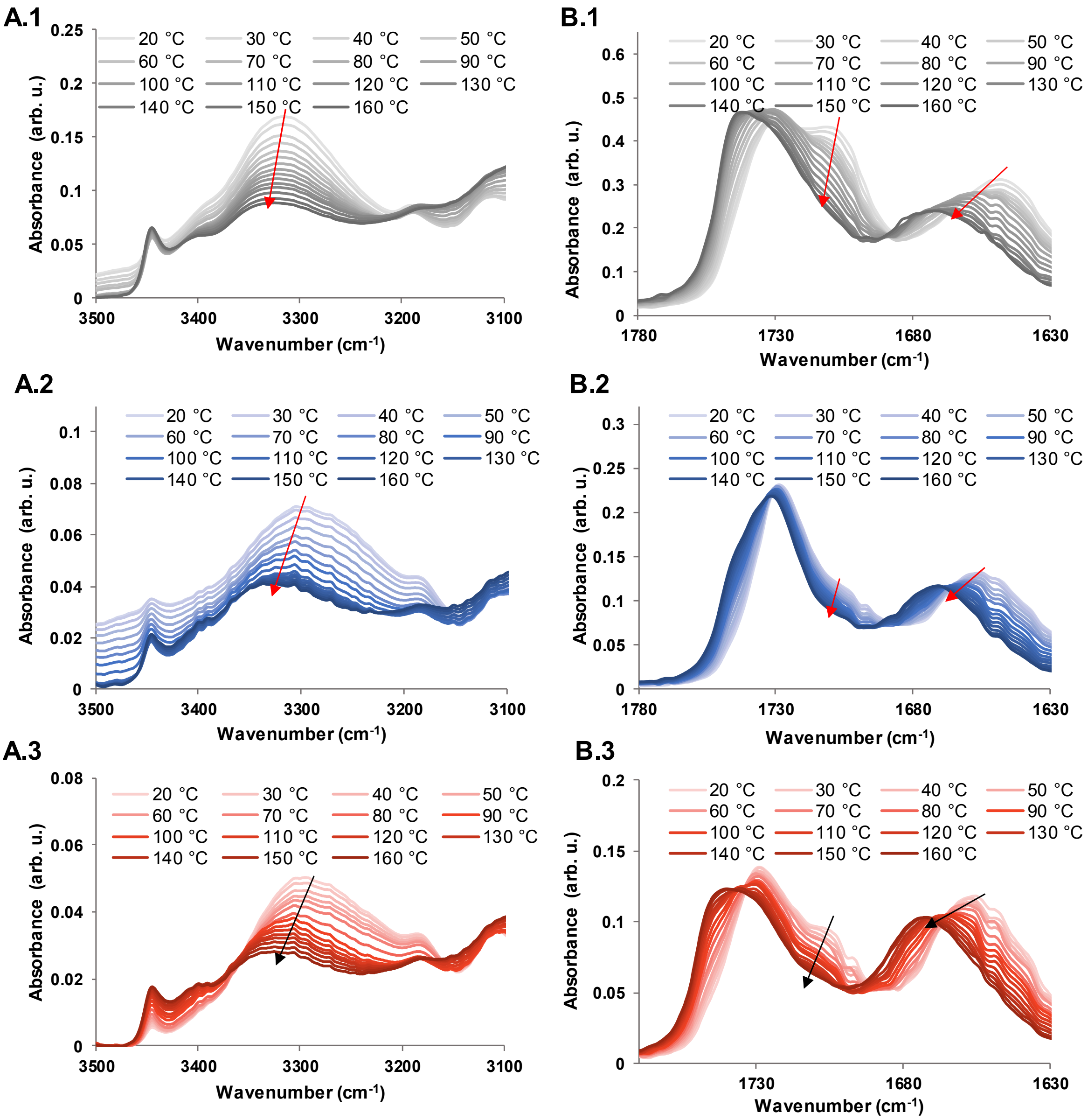


Figure S10: VT-FTIR spectra on heating (20 °C – 160 °C) of 1) **SPU1,** 2) **F1** and 3) **F2**. Shown are A) NH stretching region and B) carbonyl stretching region. Arrows show the shift from hydrogen bonding towards free species.[S3]

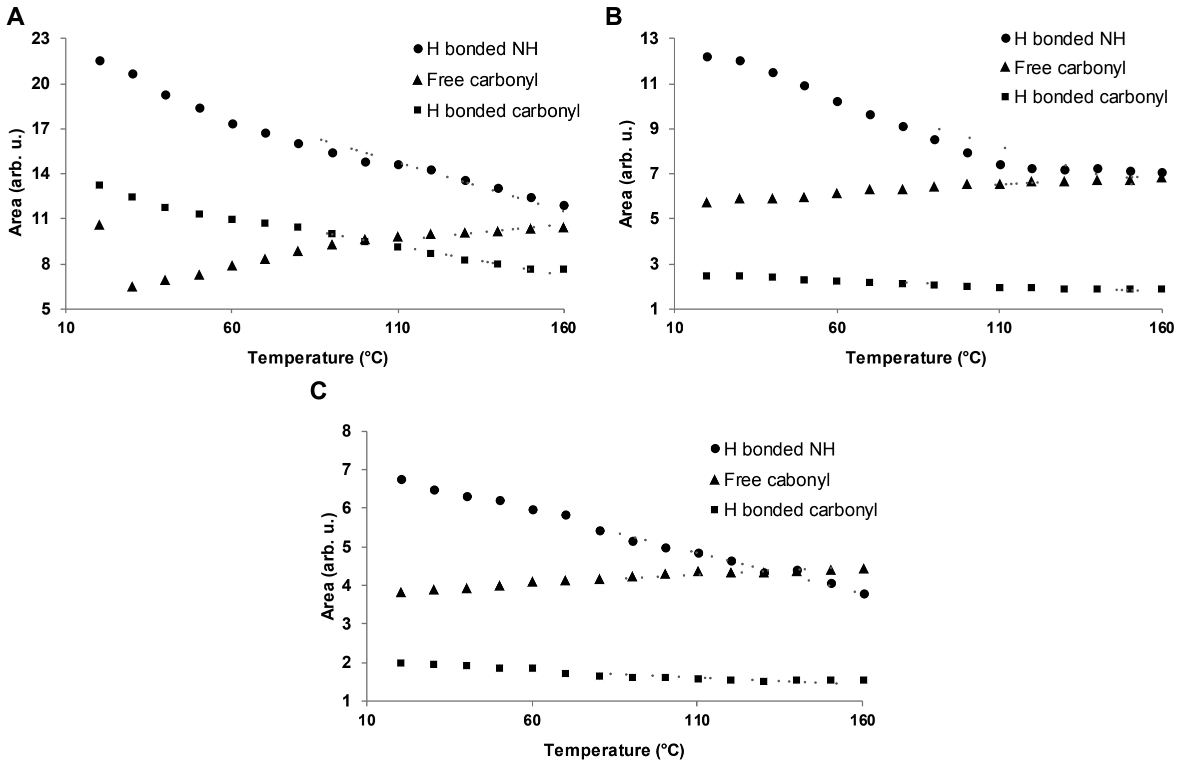


Figure S11: Plots of the absorbance peak areas corresponding to hydrogen bonding NHs, in addition to free and hydrogen bonded carbonyls for A) **SPU1**, B) **F1** and C) **F2** from IR spectroscopy**.** Areas were calculated by fitting Gaussian distributions to IR absorbances in order to deconvolute the signals.

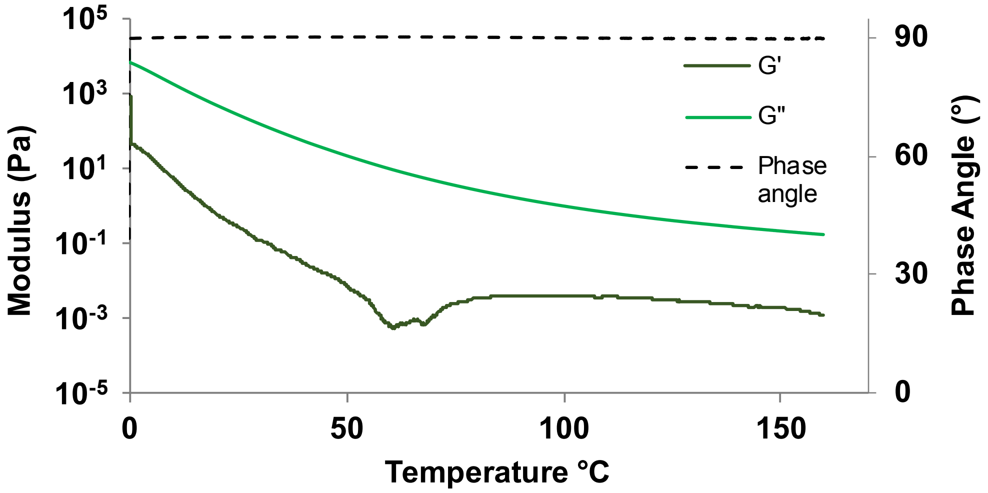


Figure S12 : Rheological behaviour of the viscous liquid, hydrogenated polybutadiene (Krasol HLBH-P2000) **2** used as the starting material in the synthesis of **SPU1**.

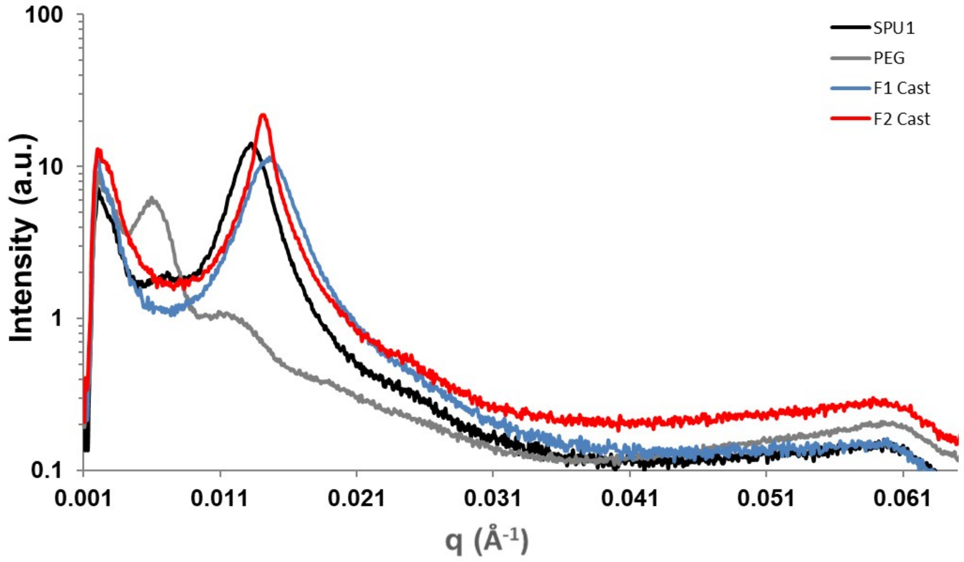


Figure S13: SAXS patterns of cast films of the **SPU1**, PEG (20 kDa), **F1** and **F2**.

Table S1: The dimensions and calculated percentage deviations of each print. Deviation = 100 × (individual print value-mean value) / (mean value)

Formulation F1						
Sample Number	Length (mm)	Width (mm)	Thickness (mm)	Length deviation	width deviation	Thicknes deviatio
1	29.63	3.20	2.55	0.16%	2.79%	0.43%
2	29.87	3.20	2.52	0.97%	2.79%	-0.75%
3	29.64	3.10	2.57	0.20%	-0.42%	1.22%
4	29.68	3.05	2.53	0.33%	-2.02%	-0.35%
5	29.68	3.15	2.55	0.33%	1.19%	0.43%
6	29.20	2.99	2.55	-1.29%	-3.95%	0.43%
7	29.50	3.10	2.51	-0.28%	-0.42%	-1.14%
8	29.40	3.09	2.54	-0.62%	-0.74%	0.04%
9	29.80	3.10	2.52	0.74%	-0.42%	-0.75%
10	29.42	3.15	2.55	-0.55%	1.19%	0.43%
STD	**0.19**	**0.06**	**0.02**			
Mean	**29.58**	**3.11**	**2.54**			

Table S2: The masses and calculated percent deviation from the mean for each print. Percent deviation = 100 × (implant mass − mean implant mass) / (mean implant mass)

Formulation F1

Sample Number	Mass (g)	Mass Deviation
1	0.2252	0.51%
2	0.2272	1.38%
3	0.2261	0.93%
4	0.2294	2.39%
5	0.2283	1.89%
6	0.2187	-2.41%
7	0.2190	-2.27%
8	0.2222	-0.85%
9	0.2223	-0.81%
10	0.2224	-0.76%
Mean	**0.224**	

Formulation F2

Sample Number	Mass (g)	Mass Deviation
1	0.2316	9.47%
2	0.218	3.04%
3	0.2002	-5.38%
4	0.2125	0.44%
5	0.2104	-0.55%
6	0.2222	5.02%
7	0.1990	-5.94%
8	0.1941	-8.28%
9	0.2136	0.98%
10	0.2141	1.21%
Mean	**0.212**	

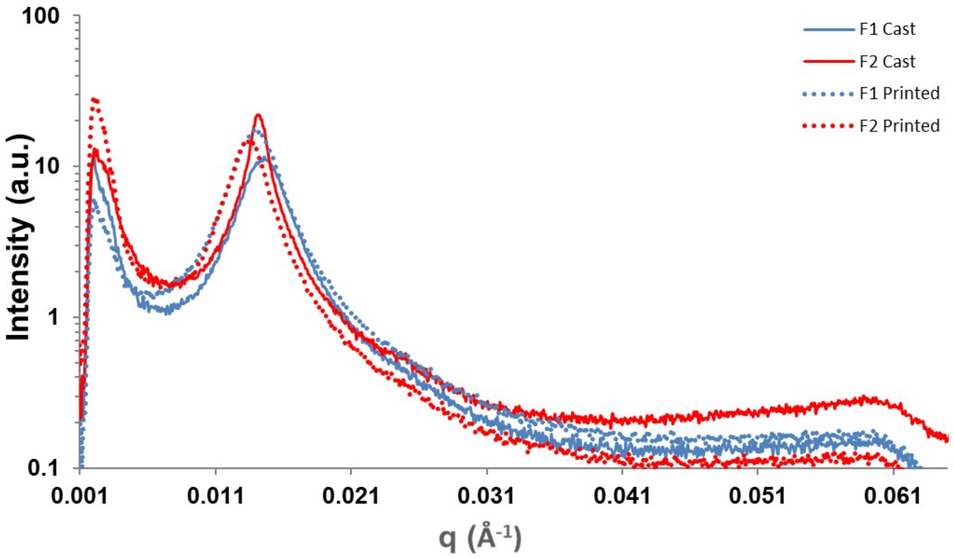
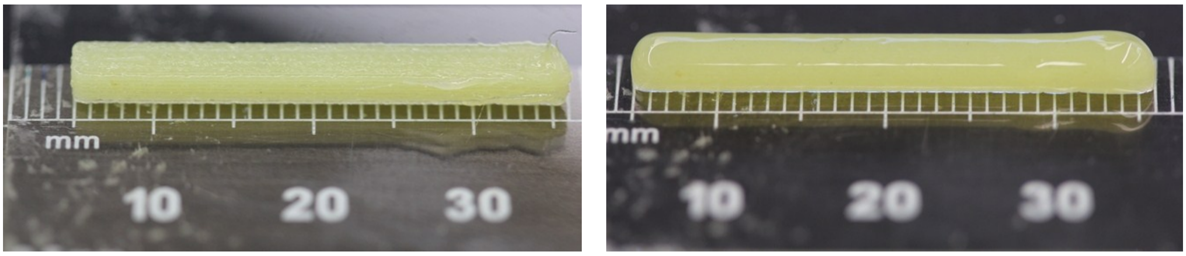


Figure S14: A comparison of SAXS patterns from cast and 3D printed formulations **F1** and **F2**.



Printed bar day 0

Printed bar day 7

Figure S15: Images of the printed formulation **F1** showing creep over 7 days.

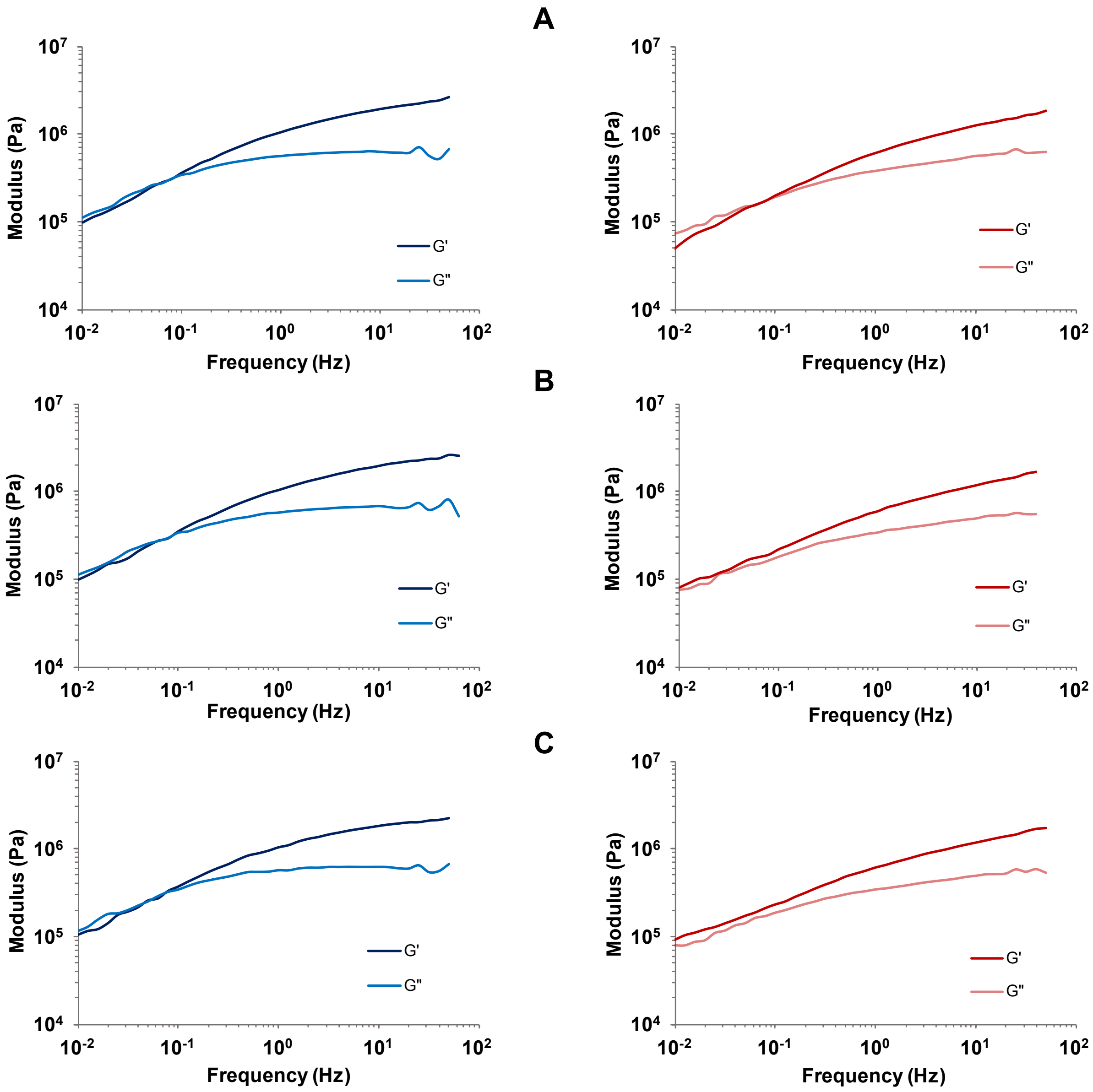


Figure S16: Variation of moduli with frequency for **F1** (left) and **F2** (right) over A) 0, B) 3 and C) 7 days aging period at ambient condition.

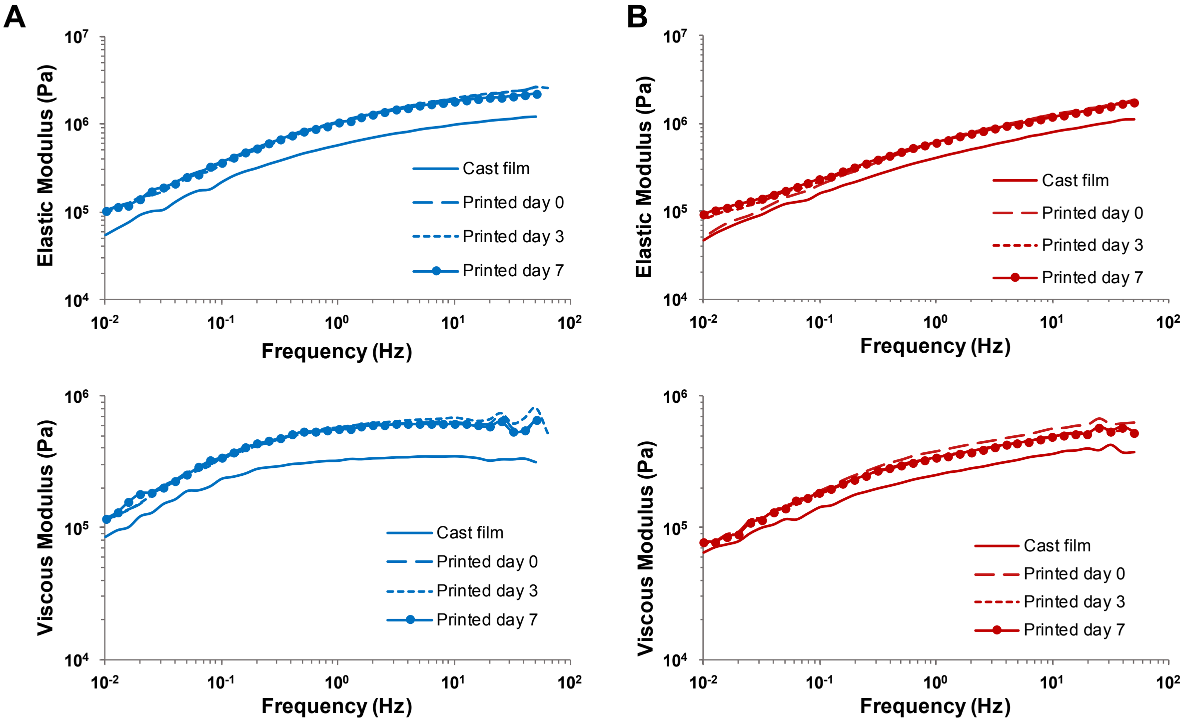


Figure S17: Variation of elastic and viscous modulus *vs*. frequency at 25 °C for drop cast and 3D printed disks in A) **F1** and B) **F2**.

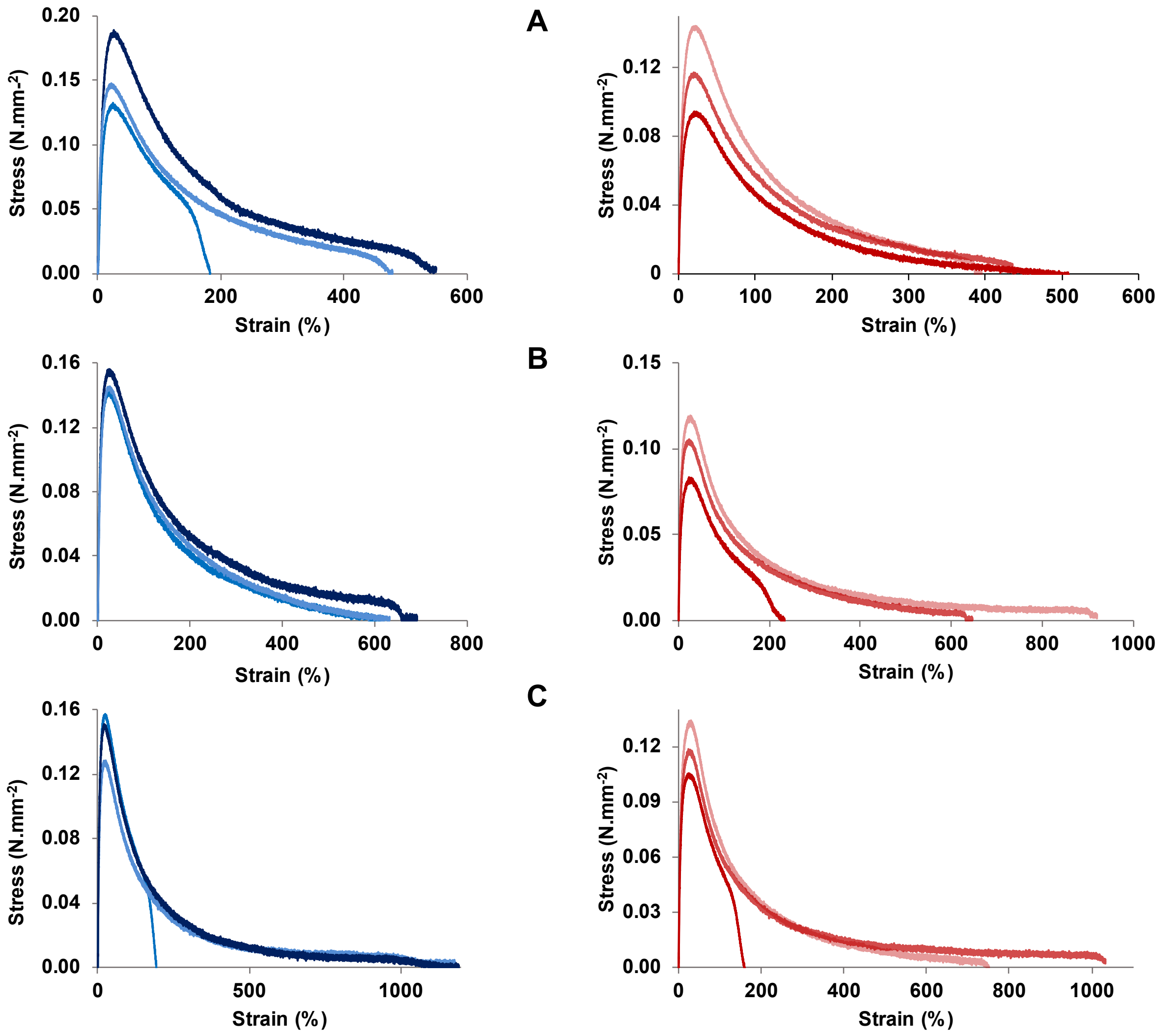


Figure S18: Stress-strain curves of the Printed **F1** (left) and **F2** (right) upon aging at ambient condition for A) 0, B) 3 and C) 7 days. Each graph shows three replications.

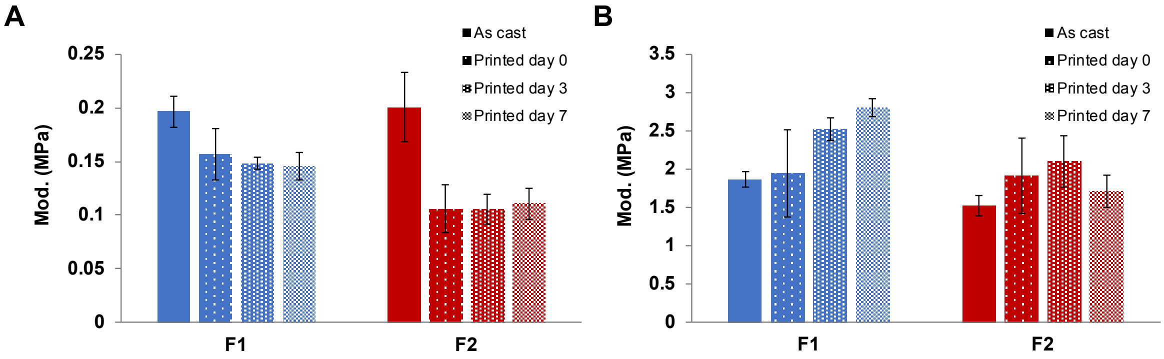


Figure S19: Bar charts comparing the A) ultimate tensile strength and B) Young's modulus of printed formulations **F1** and **F2** over 7 days.

Table S3: Summary of tensile testing comparing cast formulations (**F1** and **F2**) and creep printed bars.

	F1				**F2**			
	Cast	**Day 0**	**Day 3**	**Day 7**	**Cast**	**Day 0**	**Day 3**	**Day 7**
Young's Modulus (MPa)	1.87 ± 0.10	1.95 ± 0.57	2.52 ± 0.15	2.80 ± 0.11	1.52 ± 0.13	1.91 ± 0.50	2.09 ± 0.34	1.71 ± 0.22
Ultimate Tensile Strength (MPa)	0.20 ± 0.01	0.16 ± 0.02	0.15 ± 0.01	0.14 ± 0.01	0.20 ± 0.03	0.11 ± 0.02	0.10 ± 0.01	0.11 ± 0.01

Table S4: The predicted paracetamol release behaviour from the implants based on fitting the dissolution data to Zero order, First order and Korsmeyer-Peppas release models.

	F1				**F2**			
Model	**Predicted time to 100% release (month)**	**R^2**	**Slope**	**y-intercept**	**Predicted time to 100% release (month)**	**R^2**	**Slope**	**y-intercept**
Zero Order	3.99E+01	0.9285	3.46E-03	1.84E+00	6.54E+01	0.9975	2.11E-03	1.58E+00
First Order	**8.48E+00**	0.9062	7.02E-04	2.68E-01	**4.91E+00**	0.999	1.18E-03	4.64E-01
Korsmeyer-Peppas	1.33E+12	0.9901	1.31E-01	8.82E-02	2.88E+18	0.9604	9.00E-02	1.87E-01

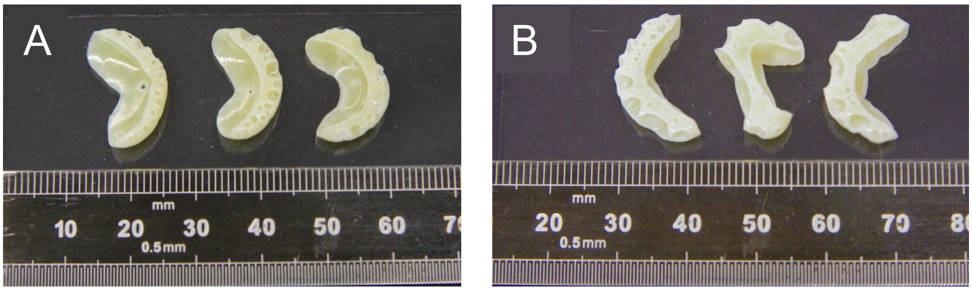


Figure S20: Images of the printed paracetamol bars, **F1 (A)** and **F2 (B)**, after dissolution testing (7 days) at 37 °C.

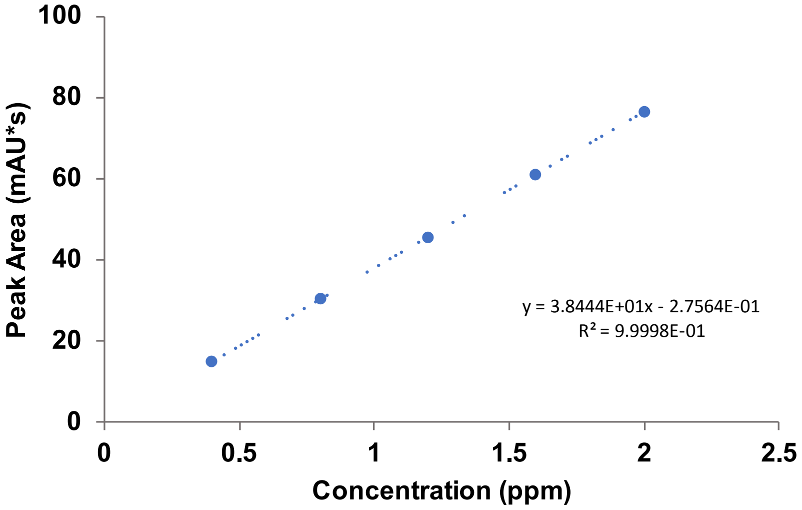


Figure S21: HPLC calibration curve for paracetamol in 0.05 M phosphate buffer (pH 6.8).

References

S1 A. Feula, A. Pethybridge, I. Giannakopoulos, X. Tang, A. Chippindale, C. R. Siviour, C. P. Buckley, I. W. Hamley and W. Hayes, *Macromolecules*, 2015, **48**, 6132–6141.

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