Supplementary Information

A New Engineering Process of Biodegradable Polymeric Solid Implants for Ultra-Long-Acting Drug Delivery

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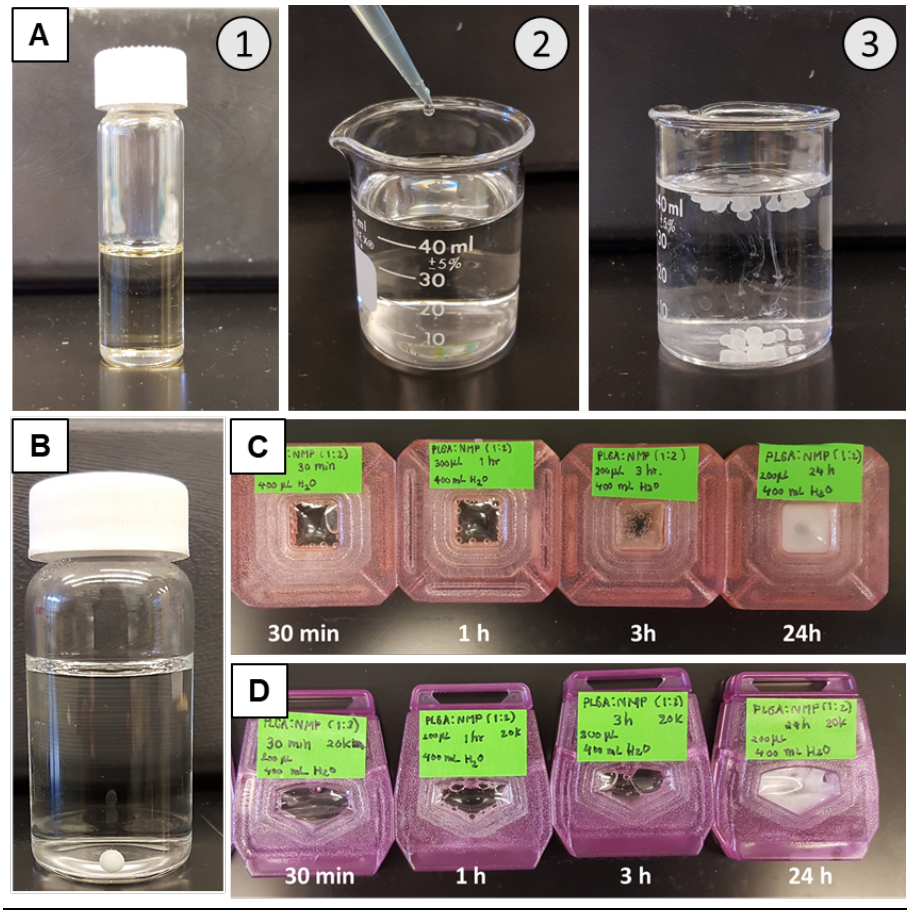
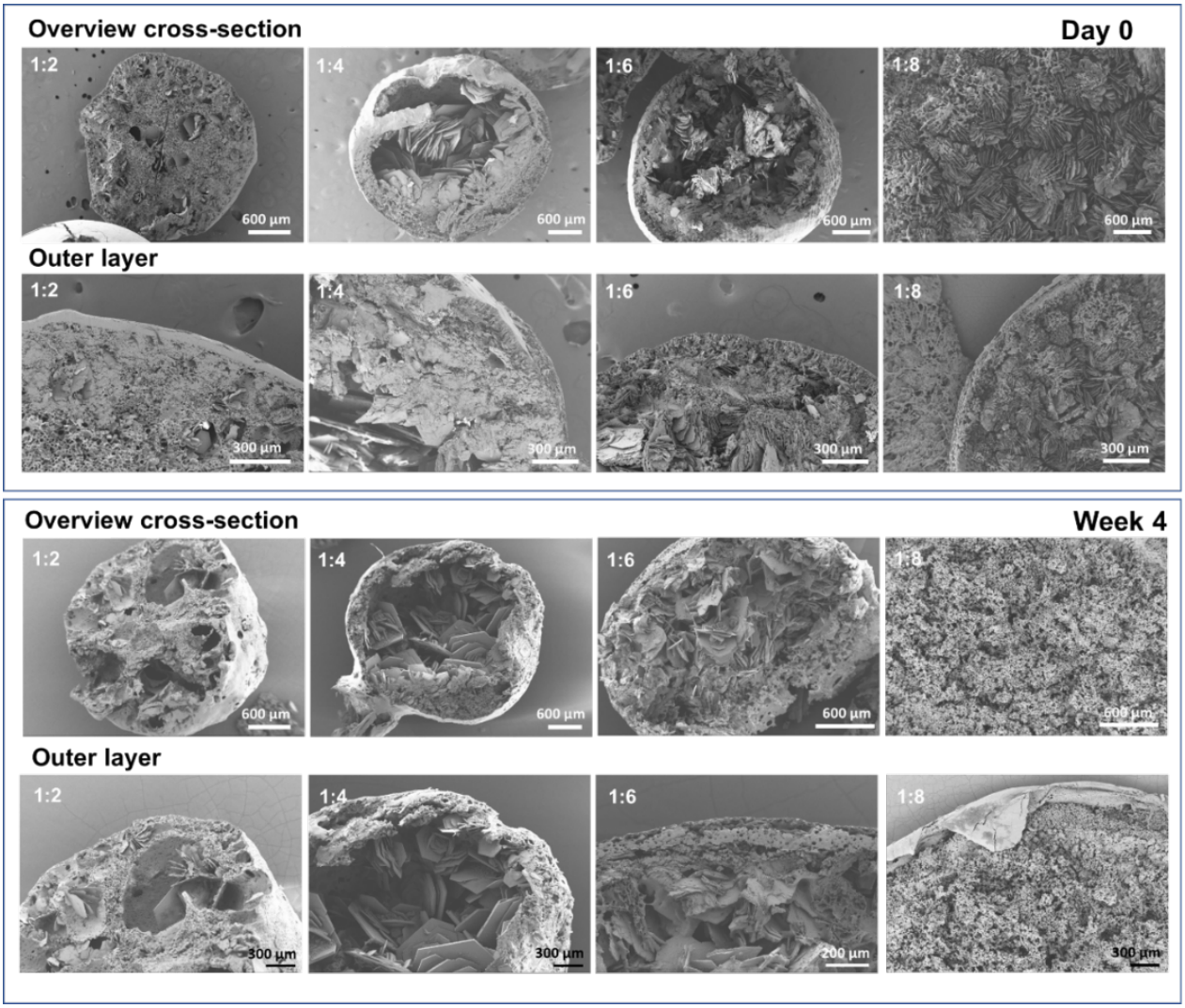
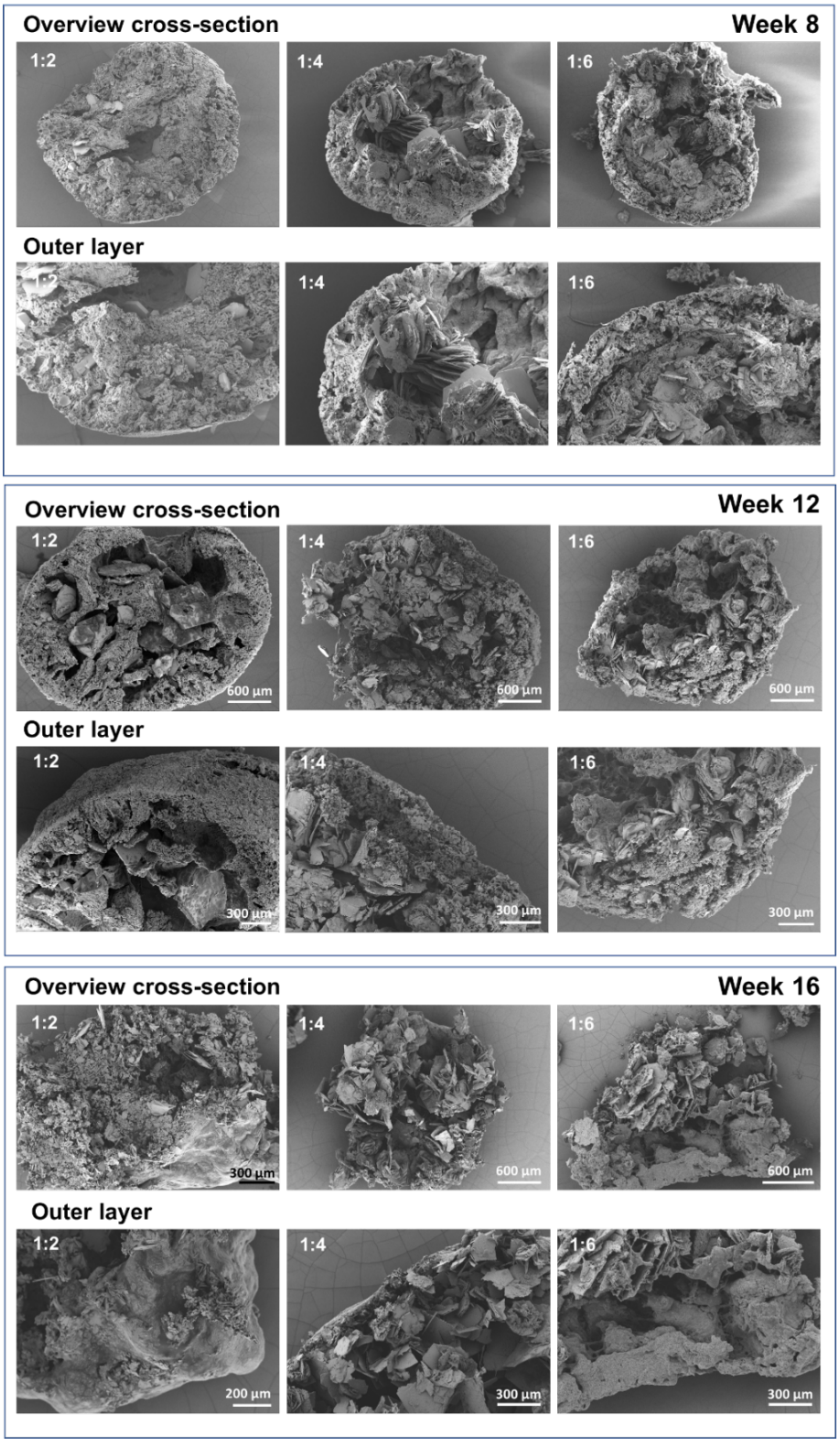


Supplementary Figure 1. Formation of PSIs via phase inversion. **A**) Placebo ISFI formulation prepared by dissolving PLGA (50:50, 27 kDa) in NMP at 1:2 w/w ratio (**1**); direct injection of a placebo solution in PBS (**2**); PSIs formed after incubation for 24 h at 37ºC (**3**). **B**) PLGA spherical PSI formed by direct injection in PBS and incubation for 24 h at 37ºC. **C** and **D**) PSIs formed overtime at 37ºC after injection into dialysis membranes.



Supplementary Figure 2. SEM images showing cross-sections of DTG PSIs at day 0 and 28 post-incubation in release media (PBS, pH 7.4 with 2% Solutol) at 37ºC. DTG PSIs were prepared using 1:2, 1:4, 1:6 and 1:8 w/w PLGA/NMP ISFI formulations loaded with DTG at near saturated concentration (110, 170, 200 and 220 mg/g DTG respectively). DTG could not be detected in PSIs prepared with 1:8 w/w PLGA/NMP ISFI formulation post-incubation for 4 weeks in PBS at 37ºC.



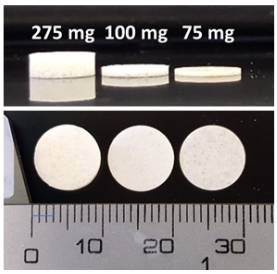
Supplementary Figure 3. SEM images showing cross-section of DTG PSIs at 8-, 12-and 16-weeks post-incubation in release media (PBS, pH 7.4 with 2% Solutol) at 37ºC. DTG PSIs were

prepared with 1:2, 1:4, 1:6, 1:8 w/w PLGA/NMP ISFI formulations loaded with DTG at near saturated concentration (110, 170, 200, 220 mg/g DTG respectively). PLGA degradation and change in DTG PSIs microstructure was clearly observed overtime with presence of larger pores and lower PLGA content in weeks 12 and 16 compared to week 8.

A

PSI prepared with 1 mL 1:6 PLGA/(NMP/DMSO) ISFI via injection in a dialysis membrane and phase inversion

B

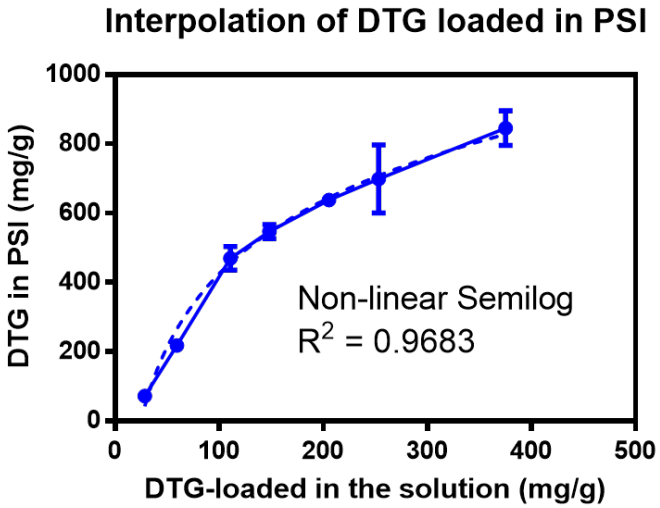


PSIs prepared with 1, 0.35 or 0.25 g of DTG-PLGA solid powder (65 wt%) by compression

C

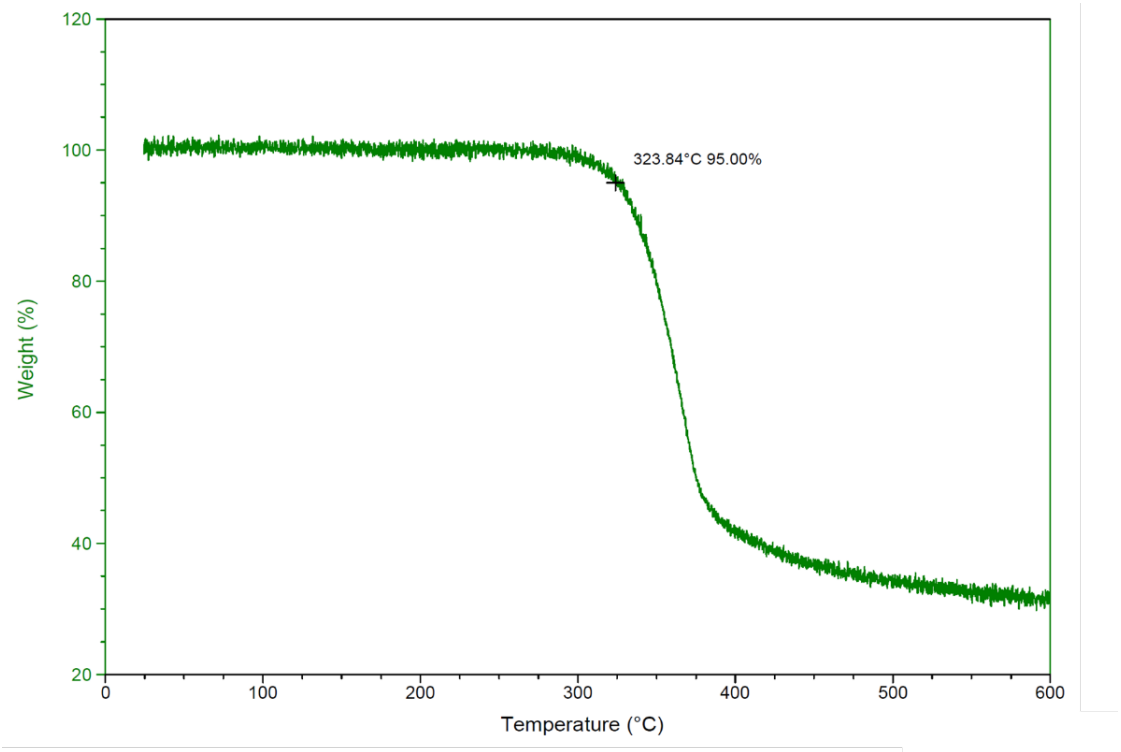
DTG in 1:6 PLGA/(NMP/DMSO) solution		DTG in PSIs	
w/w (mg/g)	%	w/w (mg/g)	%
225.52 ± 13.47	22.5	643.10 ± 28.40	64.3

D



Supplementary Figure 5. Characterization of PSIs fabricated by phase inversion and direct compression. **A)** Image of PSI prepared by injection of 1 mL 1:6 PLGA:(NMP/DMSO 9/1) solution in a dialysis tube and phase inversion after incubation in PBS at 37ºC for 24 h. The

resulting PSI had a 10 mm OD and 25 mm length and a mass of 275 mg. **B)** Images of PSIs prepared with 275 mg, 100 mg, and 75 mg of micronized DTG-PLGA solid powder (650 mg/g DTG) by compression. The micronized DTG-PLGA solid powder was prepared by direct injection of 1:6 PLGA:(NMP/DMSO 9/1) solution containing 250 mg/g DTG and phase inversion. The resulting 275-mg PSI, 100-mg PSI and 75-mg PSI had 10 mm OD/2.5 mm thickness, 10 mm OD/1 mm thickness, and 10 mm OD/0.7 mm thickness, respectively. The PSI prepared by this combination technique is more compact compared to the same-weighted PSI prepared in **A**. **C)** Comparison of the analytical concentration of DTG in an initial ISFI formulation (1:6 PLGA:(NMP/DMSO 9:1)) and the final DTG concentration in the corresponding PSI prepared by phase inversion and compression (n=4). **D)** Interpolation of analytical DTG concentration in PSIs and in the 1:6 PLGA:(NMP/DMSO 9:1) ISFI precursor formulation quantified by HPLC (n=4).



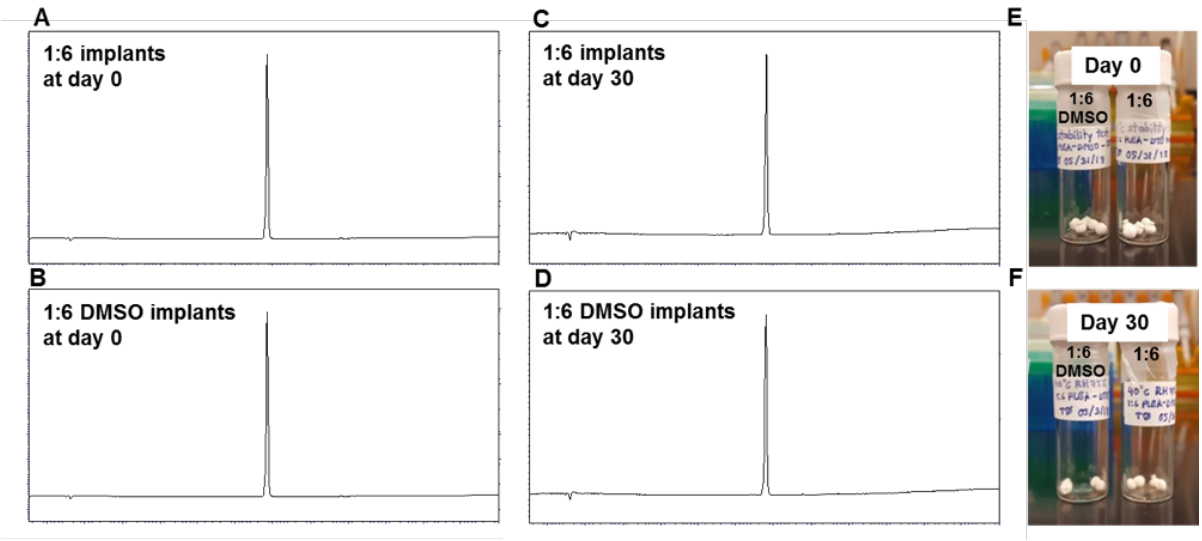
Supplementary Figure 6. Thermogravimetric analysis of pure DTG. The DTG sample was heated from 0-600°C at a ramp rate of 10°C/min under nitrogen at a flow rate of 20 mL/min. Decomposition temperature of DTG was ~325°C.

S1. Accelerated stability studies

Prior to investigating stability of DTG PSIs prepared by a combination of phase inversion and compression, the stability of DTG PSIs prepared by phase inversion only was investigated under accelerated storage conditions. The results showed that DTG PSIs prepared by 1:6 PLGA/NMP and 1:6 PLGA/(NMP:DMSO) were chemically and physically stable for 30 days at 40°C/75% RH (**Supplementary Table 1**). No degradation products were detected by HPLC analysis (**Supplementary Figure 7A-D**). The physical appearance (color, size) of the solid implants remained unchanged over 30 days of storage at 40°C/75% RH (**Supplementary Figure 7E-F**).

Table S1. DTG concentration in PSIs prepared with 1:6 w/w PLGA/NMP (PSI I), and 1:6 w/w PLGA/(NMP:DMSO 9:1) (PSI II) after storage at 40°C/75% RH for 30 days.

Storage time (days)	DTG concentration (mg/g)	
	PSI I	PSI II
0	583.22 ± 3.29	600.12 ± 10.59
7	539.45 ± 13.51	600.38 ± 13.91
14	586.48 ± 10.72	612.02 ± 14.28
30	594.00 ± 8.77	632.33 ± 6.57



Supplementary Figure 7. HPLC chromatograms of DTG in PSIs prepared by phase inversion of 1:6 w/w PLGA/NMP and 1:6 w/w PLGA/(NMP:DMSO) before (**A-B**), and after storage at 40ºC and 75% RH for 30 days (**C-D**). Physical appearances of the dried spherical PSIs fabricated with 1:6 w/w PLGA/NMP, and 1:6 w/w PLGA/(NMP:DMSO) before (**E**) and after storage at 40ºC and 75% RH for 30 days (**F**).