Supplementary Information

Microfluidic synthesis of PLGA nanoparticles enabled by an ultrasonic microreactor

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Contents

1. Blank PLGA nanoparticles

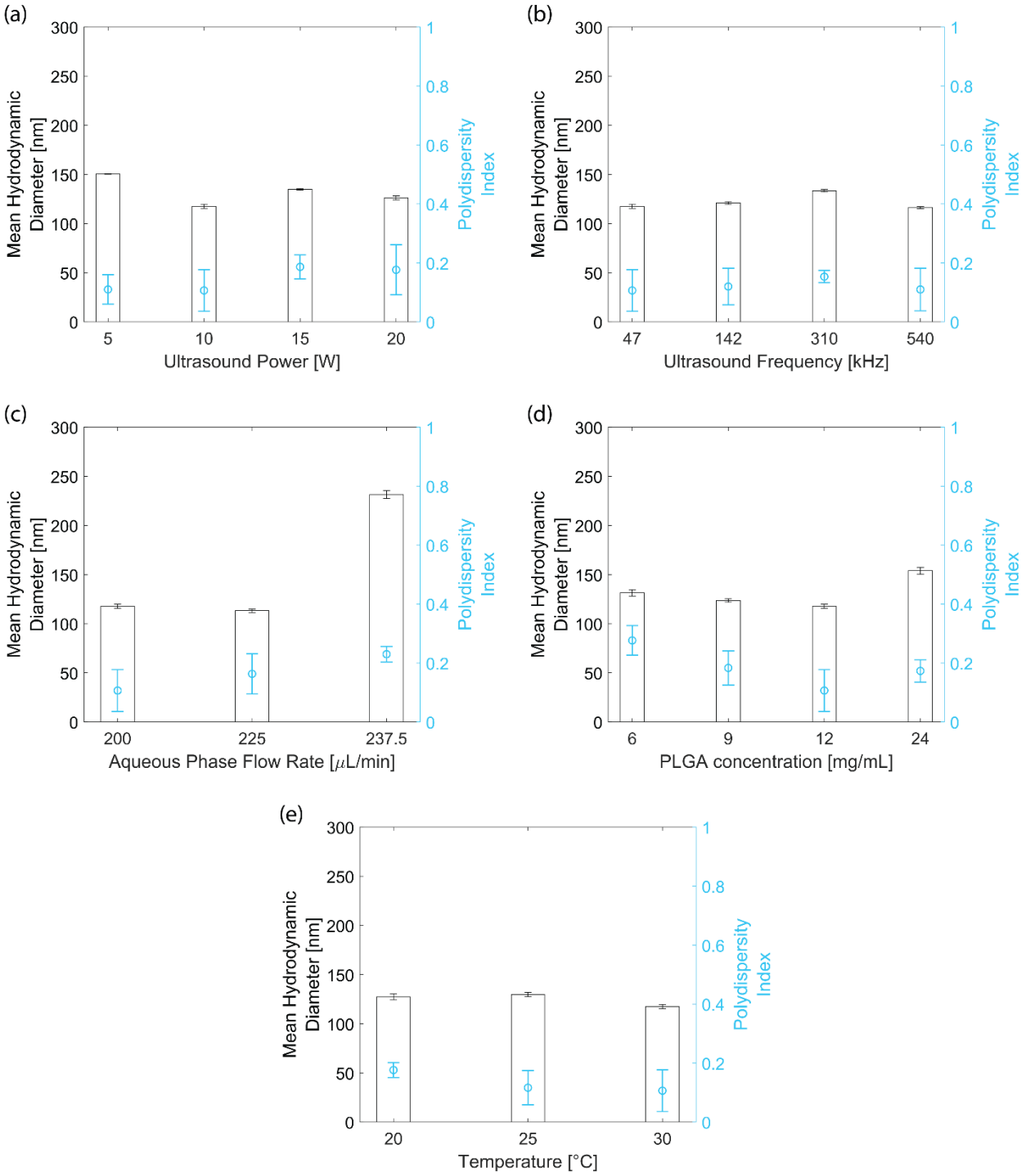

Figure S1. Mean hydrodynamic diameter and polydispersity index of the blank PLGA nanoparticles.

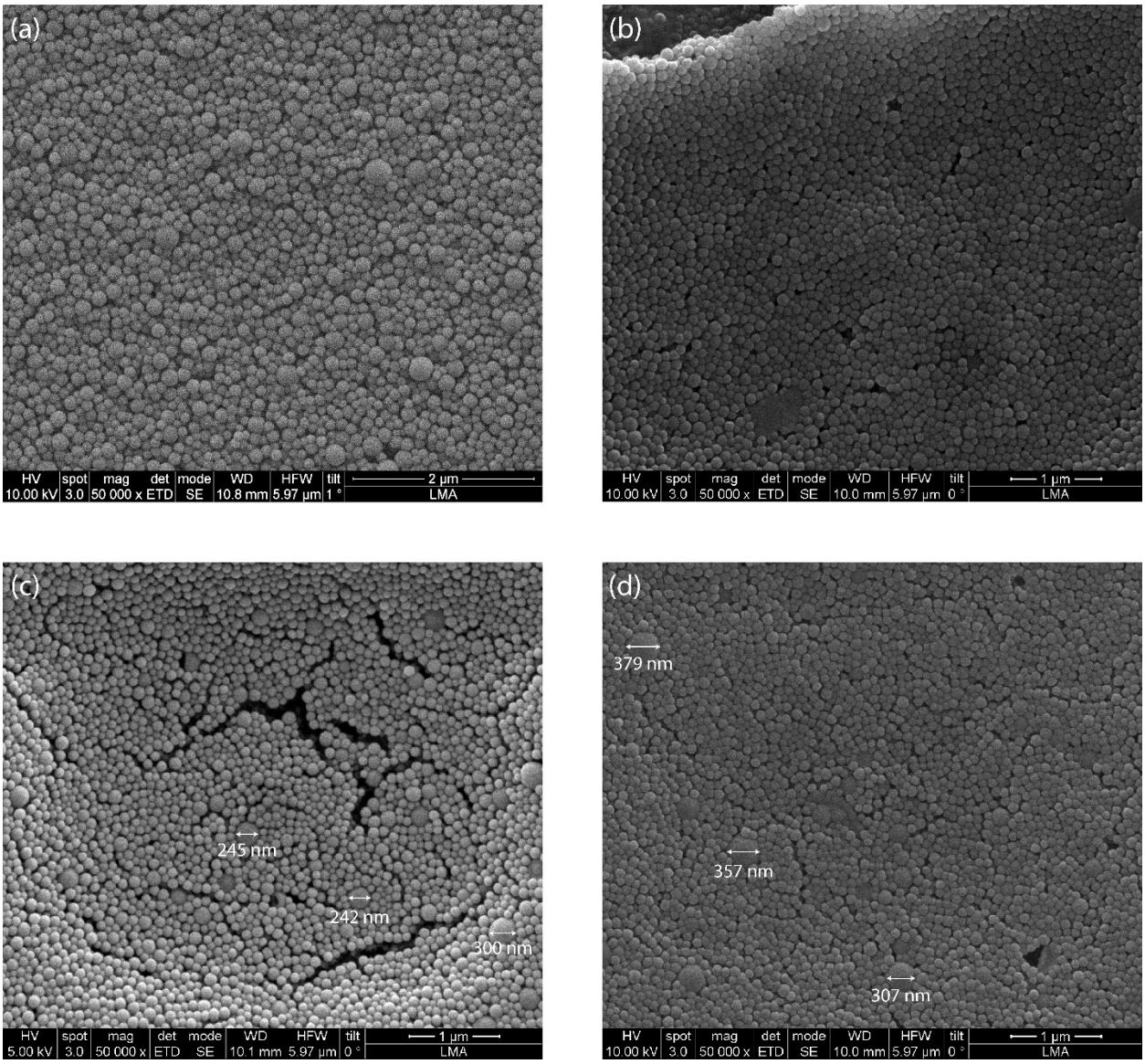

Figure S2. SEM images of the blank PLGA nanoparticles synthesized for the ultrasonic frequency of (a) 48 kHz, (b) 142 kHz, (c) 310 kHz, and (d) 550 kHz. The ultrasonic microreactor was operated at a power of 10 W. The PLGA concentration was 12 mg/mL.

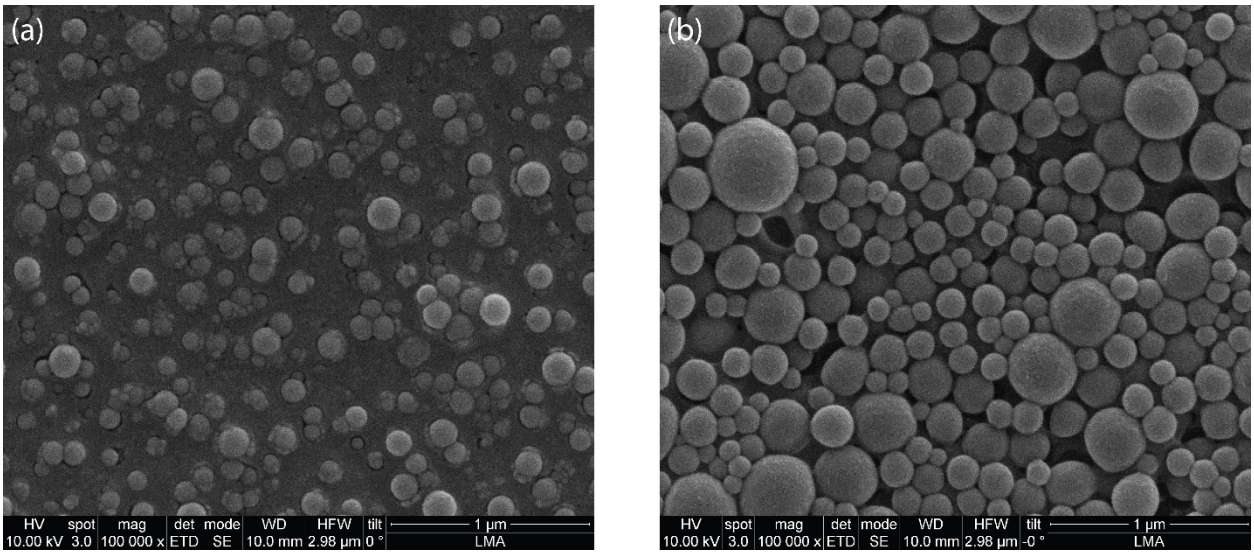

Figure S3. SEM images of the blank PLGA nanoparticles synthesized for the volume fraction of (a) 10% and (b) 5%. The ultrasonic microreactor was operated at a frequency and power of 48 kHz and 10 W respectively. The PLGA concentration was 12 mg/mL.

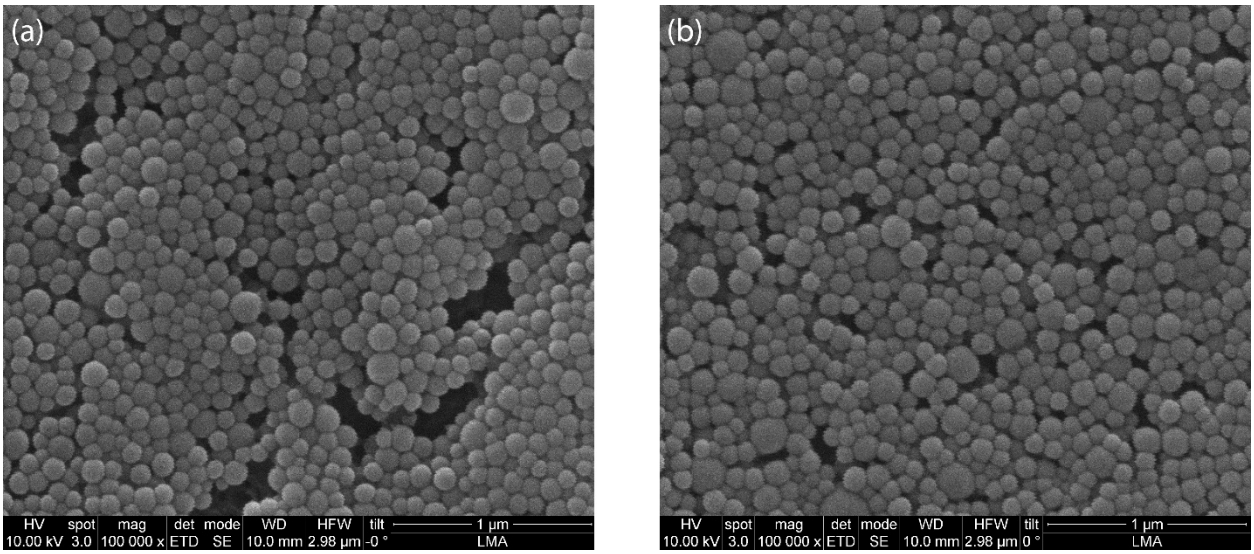

Figure S4. SEM images of the blank PLGA nanoparticles synthesized for the outlet temperature of (a) 20 °C and (b) 25 °C. The ultrasonic microreactor was operated at a frequency and power of 48 kHz and 10 W respectively. The PLGA concentration was 12 mg/mL.

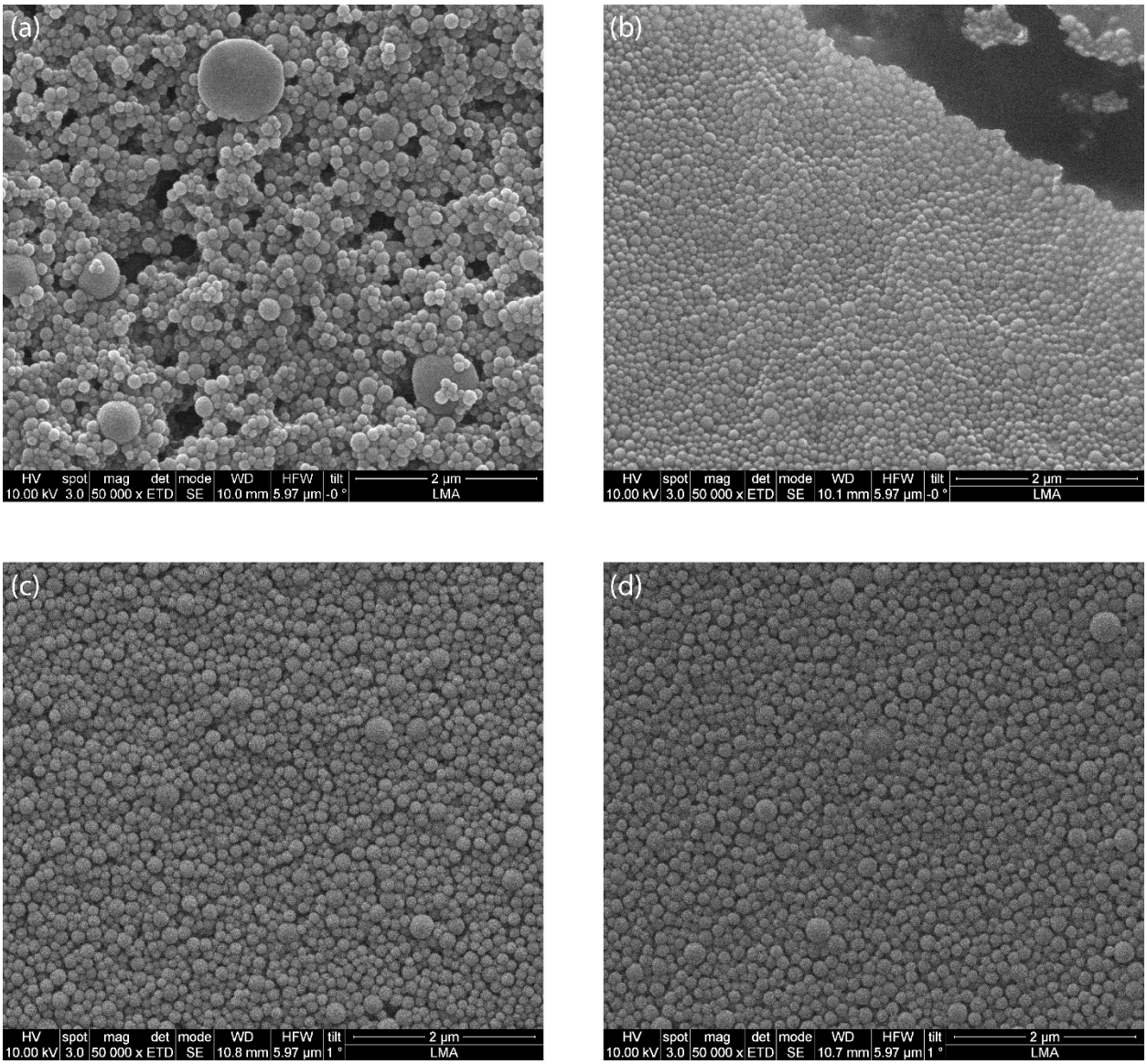

Figure S5. SEM images of the blank PLGA nanoparticles synthesized for the PLGA concentration of (a) 6 mg/mL, (b) 9 mg/mL, (c) 12 mg/mL, and (d) 24 mg/mL. The ultrasonic microreactor was operated at a frequency and power of 48 kHz and 10 W respectively.

2. Nile Red-loaded PLGA nanoparticles

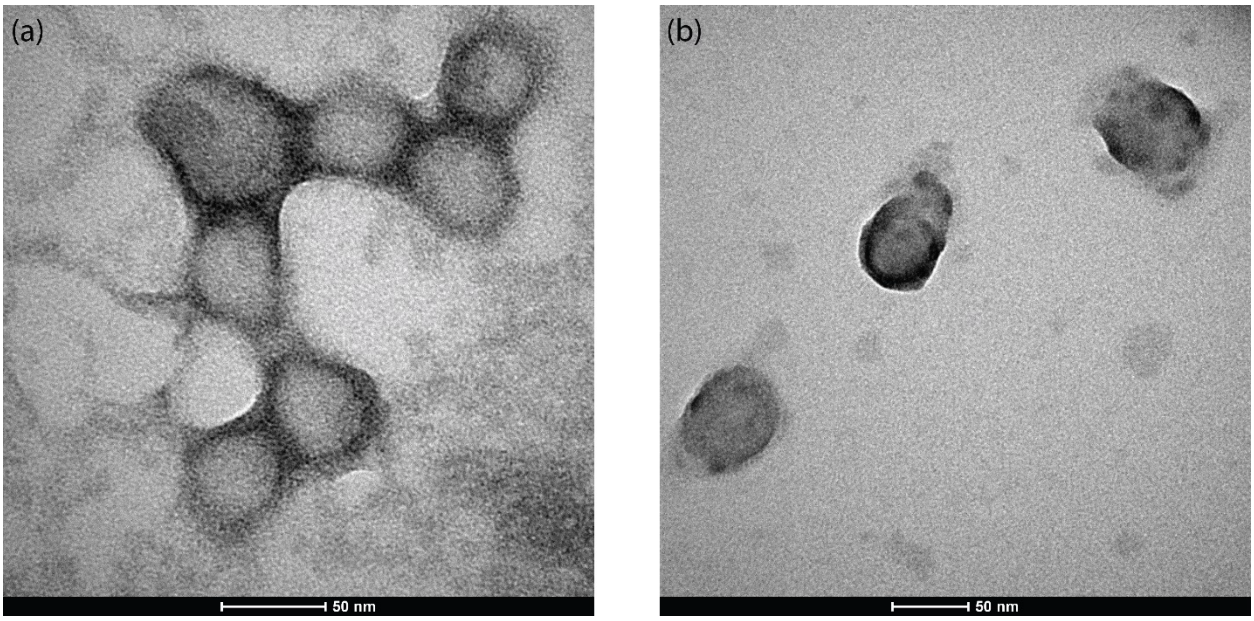

Figure S6. TEM image of Nile Red-loaded PLGA nanoparticles synthesized at (a) 5 W and (b) 15 W and ultrasonic frequency of 48 kHz.

3. PLGA-ethyl acetate viscosity

Table S1. The viscosity of the organic phase for the concentration range of 6-24 mg/mL of PLGA in ethyl acetate at 30 °C. The viscosity was measured with an Ubbelohde viscometer.

PLGA concentration [mg/mL]	**Viscosity at 30 °C [mPa.s]**
6	0.49
9	0.54
12	0.59
24	0.85

4. PLGA degradation: GPC analysis

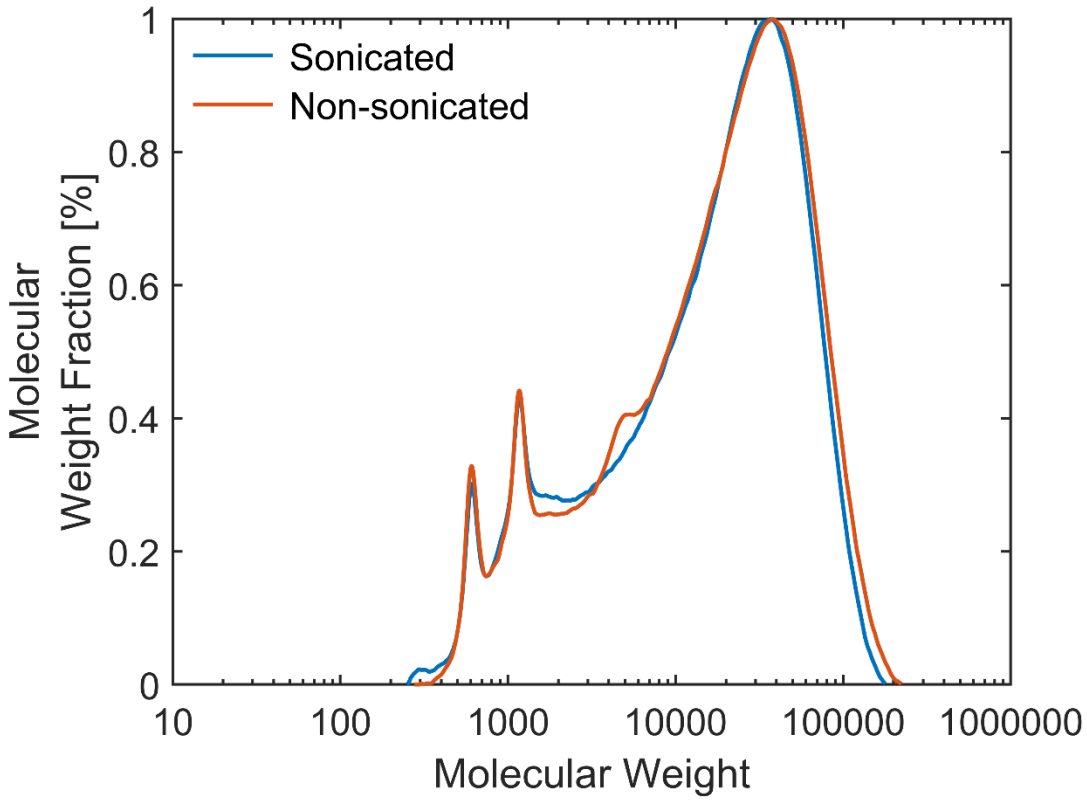

Figure S7. Molecular weight distribution of PLGA. 12 mg/mL PLGA in ethyl acetate sonicated in the reactor at the ultrasound frequency and power of 48 kHz and 10 W respectively. The flow rate of the organic phase was 50 µL/min (residence time 20 min, outlet temperature 30 °C). 1 mL of the sonicated sample was collected after 1 reactor residence time.

The molecular weight of the PLGA was determined for sonicated and non-sonicated conditions to determine if sonication has any influence on the degradation of the polymer and reduction in molecular weight. PLGA in ethyl acetate (12 mg/mL) solution was supplied to the reactor at 50 µL/min (residence time 20 min) and 1 mL sample was collected in a vial. The solution was sonicated at 48 kHz and 10 W. The sample was air-dried overnight to remove ethyl acetate and weighed to determine the mass of PLGA. THF was added to the vial to make a PLGA in THF solution (10 mg/mL) for gas permeation chromatography. Molecular weights and distributions were measured by gel permeation chromatography (GPC, SHIMADZU LC40) equipped with a differential refractive index detector (RID) and with THF eluent at 30°C, 1.0 mL/min flow rate. Two PSS SDV linear analytical 5µm 300×8mm columns were used and calibrated using 10 polystyrene (PS) standards (M_n = 682-55200 g/mol).

M_W (sonicated) = 37941.19

M_W (non-sonicated) = 38581.41

5. NR-PLGA encapsulation efficiency and dye loading

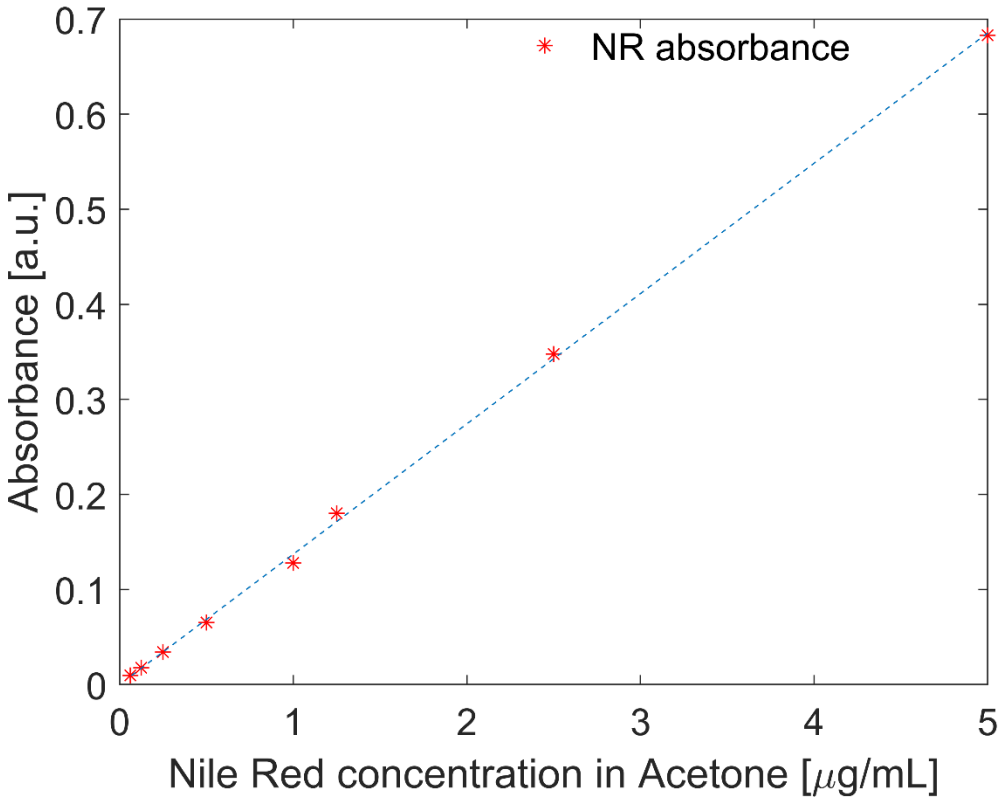

Figure S8. Calibration curve of the absorbance of Nile Red in acetone.

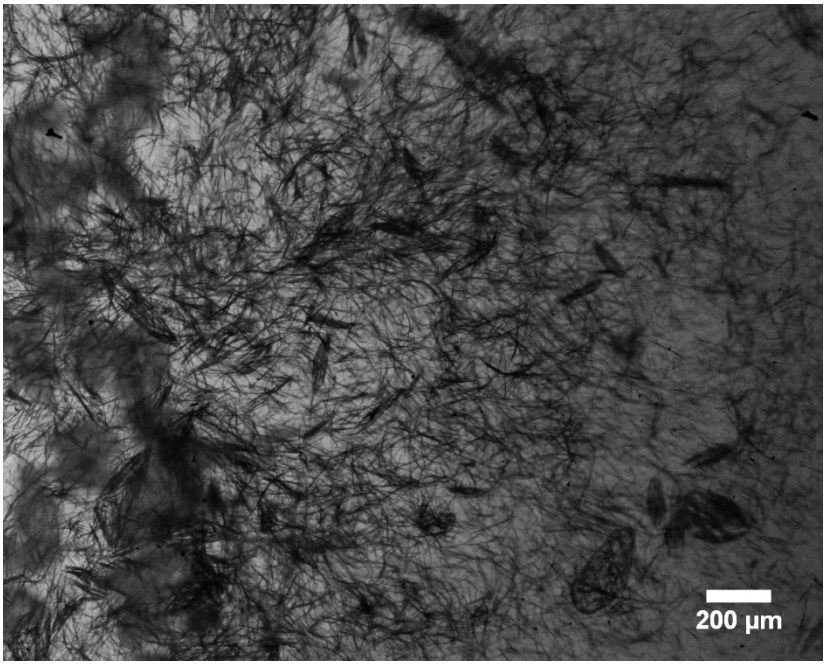

Figure S9. Precipitated needle-shaped Nile Red crystals in the NR-PLGA nanoparticle suspension after ethyl acetate evaporation.

6. NR-PLGA *in-vitro* release

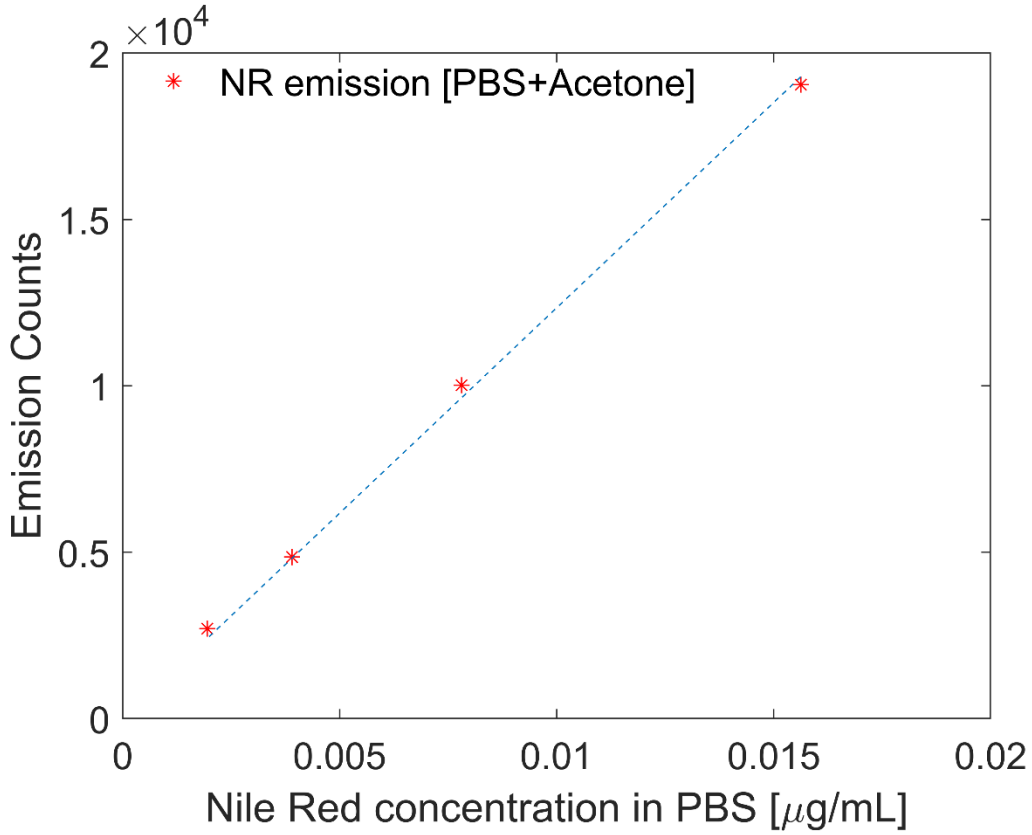

Figure S10. Calibration curve for the Nile Red emission count vs concentration in PBS + acetone (1:2 volume ratio).