

Supplementary Information (ESI) for Soft Matter

Supplementary Information

Continuous fabrication of monodisperse polylactide microspheres by droplet-to-particle technology using microfluidic emulsification and emulsion-solvent diffusion

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Fabrication of microsphere

Poly(D,L-lactide) (PLA, $M_n = 3,200$, $M_w/M_n = 1.12$) or oil-soluble poly(ethylene glycol)-*b*-poly(D,L-lactide) (o-PEG-PLA, $M_n = 14,200$, $M_w/M_n = 1.20$, hydrophile-lipophile balance (HLB) = 5.6) was dissolved in ethyl acetate (EA) which served as an dispersed (organic) phase. The concentration of PLA or blend ratio of PLA to o-PEG-PLA was varied. The concentrations of PLA were 1.0, 2.5 and 5.0 wt%. The o-PEG-PLA/PLA blend ratios (w/w) were 50/0, 50/20 and 50/40. Aqueous solution containing 1 wt% of water-soluble poly(ethylene glycol)-*b*-poly(D,L-lactide) (w-PEG-PLA, $M_n = 4,400$, $M_w/M_n = 18.2$) and saturated with EA was used as a continuous (aqueous) phase. After complete dissolution of polymers in solvents, each solution was placed in a glass microsyringe (1000 series, Hamilton Company, RN). The microsyringes were mounted on syringe pumps (BS-MD1001, ISIS Co., Ltd) and syringe pump controller (BS-MD1020, ISIS Co., Ltd) which can synchronously operate two syringes at various flow rates. The solutions were separately fed into a Y-shaped microfluidic device. The organic phase flow channel (Φ 126 μm wide \times 75 μm depth) meets the aqueous phase flow channel (Φ 136 μm wide \times 75 μm depth) at an angle of 44°. The flow rate of the organic phase (Q_d) was kept constant at 60 $\mu\text{L h}^{-1}$ while that of the aqueous phase (Q_c) was controlled from 300 to 6000 $\mu\text{L h}^{-1}$. Prepared O/W emulsion droplets were directly poured into 100 mL of ultrapure water via Teflon tube ($\Phi = 0.5$ mm, $L = 20$ cm), which was connected to the outlet of the microfluidic device. The end of the tube was immersed in the ultrapure water in a vessel (110 mL). EA was rapidly removed from the droplet (organic phase) by solvent diffusion to the water, resulting in hardened microspheres. The system was run for more than 15 min. after which solidified microspheres were collected in

a 15 mL of centrifuging tube, centrifuged (11,000 rpm, 3 min), and rinsed with ultrapure water three times to remove excess w-PEG-PLA. Then, the microsphere suspension was lyophilized over night.

Prepared O/W emulsion droplets in the Teflon tube were observed using an optical microscope (OLYMPUS BX50). The microspheres after freeze-drying were observed by a scanning electron microscope (SEM, S-4700, Hitachi, Ltd.) at an intensity of 1 kV under various magnifications. Prior to observation, the samples were coated with Pt-Pd using a sputter-coater (E-1030 Ion Sputter, Hitachi, Ltd.). From optical microscopy images and SEM micrographs, the polydispersity of droplets and microspheres was characterized as the coefficient of variation (CV), $CV = \sigma / D$, where σ is the standard deviation of droplet diameter (μm) and D is the mean diameter of the droplets (μm). To obtain D and CV of droplets and microspheres, we measured the dimensions of at least 200 samples at all experimental points on a graph.

Measurement of the interfacial tension

The interfacial tensions between EA and EA-saturated aqueous solutions containing w-PEG-PLA at various concentrations were measured with a Wilhelmy plate interfacial tension meter (K100, Krüss). The aqueous solution (5 mL) containing w-PEG-PLA at various concentrations was poured into a 50 mL vessel, and then EA (20 mL) was gently added onto the aqueous solution layer. The measurements were performed at 15°C. The interfacial tension was accepted as an equilibrium value when it was constant independent of time.

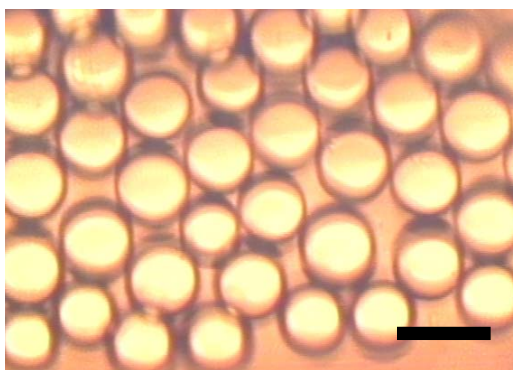


Figure S1 Optical microscopy image of O/W emulsion droplets prepared using an aqueous solution containing 1 wt% of w-PEG-PLA without EA as a continuous phase (The Q_d and Q_c were 60 and 600 $\mu\text{L h}^{-1}$, respectively). Scale bar represents 100 μm .

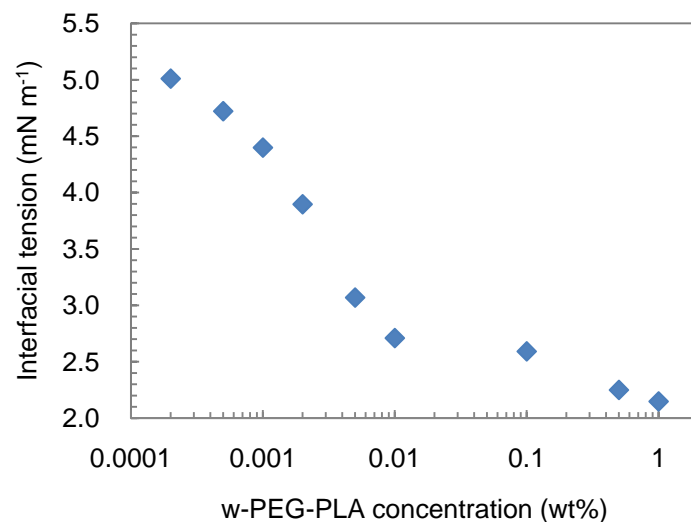


Figure S2 Effect of w-PEG-PLA concentration on the interfacial tension between EA and EA-saturated aqueous solution.

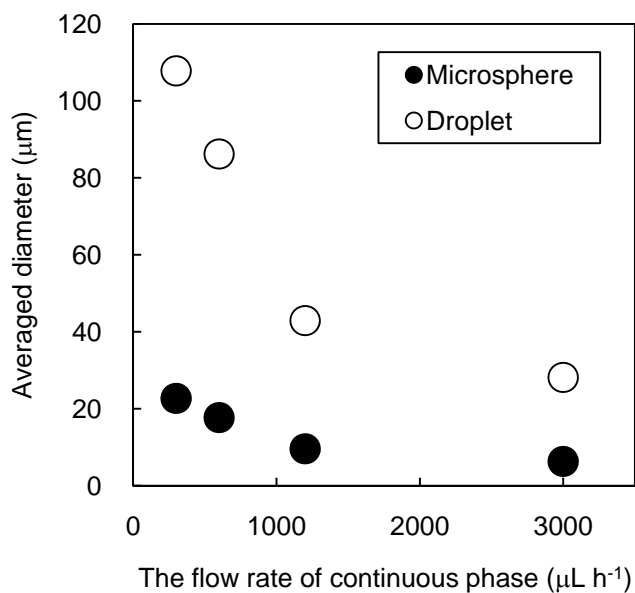


Figure S3 Effect of continuous flow rate on the diameter of droplet and PLA microspheres. The flow rate of dispersed phase and the PLA concentration were fixed at 60 μL h⁻¹ and 1 wt%, respectively. The w-PEG-PLA concentration in the continuous phase was kept constant at 1 wt%.

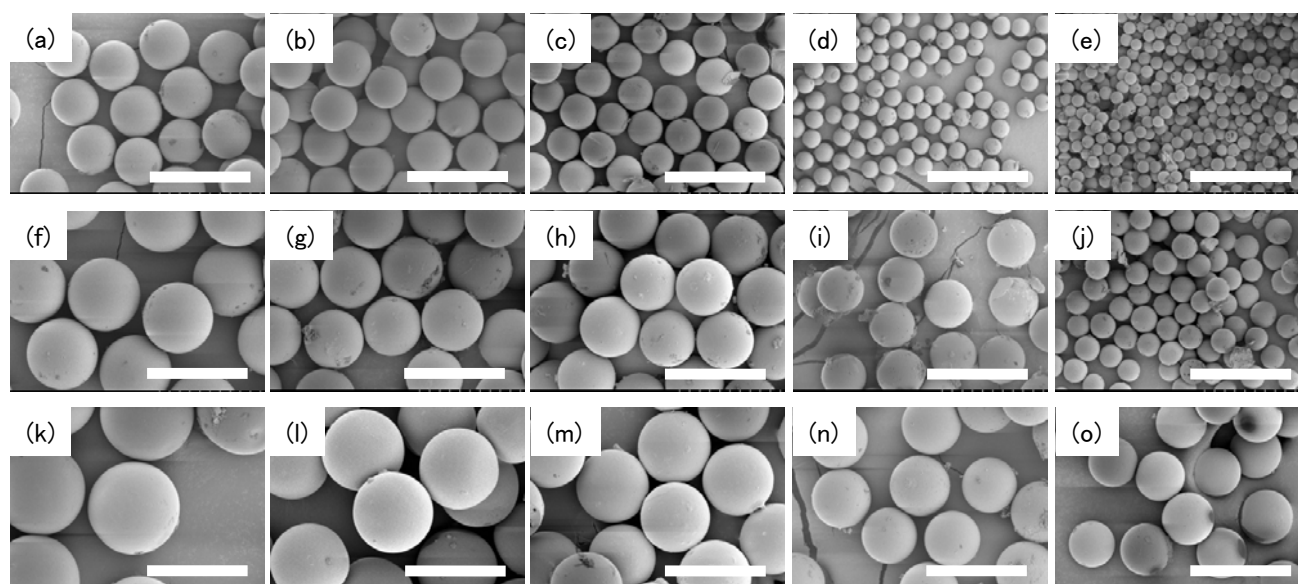


Figure S4 SEM images of PLA microspheres prepared by varying the flow rate of the continuous phase and the PLA concentration. The flow rates of the continuous phase were fixed at 300 (a, f, k), 600 (b, g, l), 1,200 (c, h, m), 3,000 (d, i, n), and 6,000 $\mu\text{L h}^{-1}$ (e, j, o). The PLA concentrations in the dispersed phase were 1.0 (a, b, c, d, e), 2.5 (f, g, h, i, j), and 5.0 wt% (k, l, m, n, o). The flow rate of the dispersed phase and the w-PEG-PLA concentration in the continuous phase were kept constant at 60 $\mu\text{L h}^{-1}$ and 1 wt%, respectively. Scale bars represent 50 μm .

Table S1 Summary of the diameter and CV value of PLA microspheres

Q_c ($\mu\text{L h}^{-1}$)	PLA 1wt%		PLA 2.5 wt%		PLA 5 wt%	
	d (μm)	CV (%)	d (μm)	CV (%)	d (μm)	CV (%)
300	24.9	4.2	36.8	4.7	46.6	3.7
600	22.7	4.2	31.3	3.8	40.0	3.8
1,200	17.7	5.4	28.8	4.1	35.9	5.2
3,000	9.6	4.9	23.8	5.3	29.8	5.5
6,000	6.3	5.3	12.6	6.8	25.3	5.9

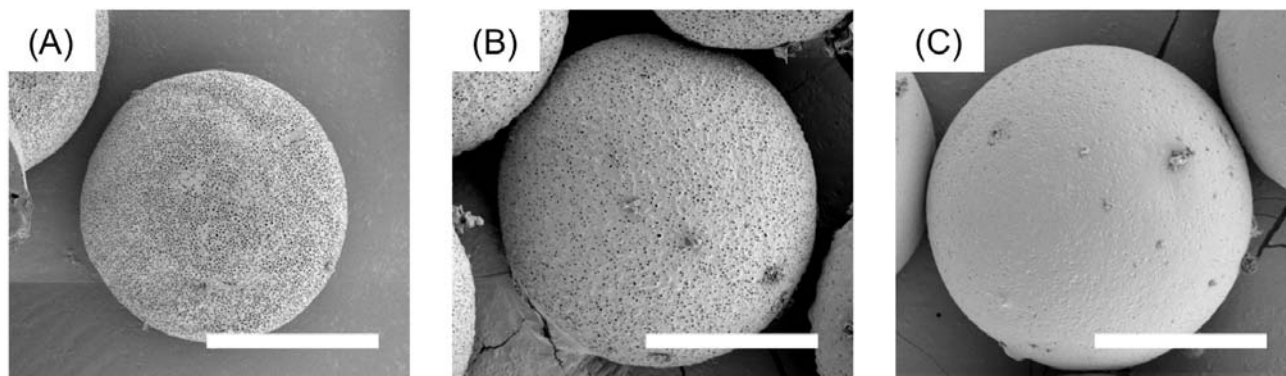


Figure S5 SEM images of magnified view of o-PEG-PLA/PLA microspheres prepared by changing the blend ratios of PLA to o-PEG-PLA in the dispersed phase. The blend ratios were (A) 50/0, (B) 50/20, and (C) 50/40 (w/w). Scale bars represent 50 μm .