Electronic Supplementary Material (ESI) for Lab on a Chip.

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Electronic Supplementary Information for

Microfluidic preparation of monodisperse PLGA-PEG/PLGA microspheres with controllable morphology for drug release

*Wenwen Chen,[a] Hao Li,[a] Xinyue Zhang,[a] Yutao Sang *[a] and Zhihong Nie *[a]*

a State Key Laboratory of Molecular Engineering of Polymers, Department of Macromolecular Science, Fudan University, Shanghai 200438, China.

* Corresponding Author E-mail: zhnie@fudan.edu.cn

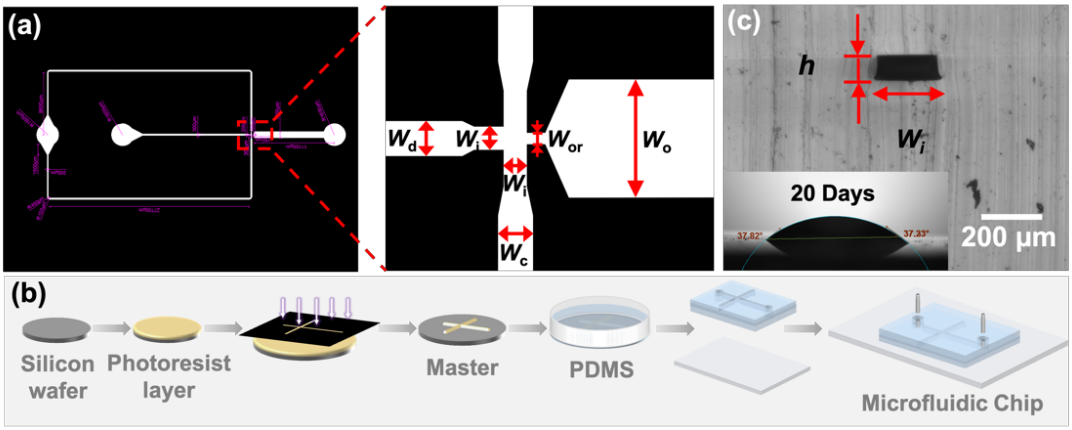

Fig. S1. Schematic diagram of the design (a) and fabrication (b) of microfluidic chips; photo of the chip cross-section (c) in which the inserted is the water contact of hydrophilic-treated PDMS surface.

Tab. S1. Geometric parameters of design and measurement of the microchannel.

	W_d	W_c	W_i	W_{or}	W_o	h
Design (μm)	300	300	200	100	1000	-
Measurement* (μm)	300 ± 8	300 ± 7	200 ± 7	100 ± 3	1000 ± 12	100 ± 8

Measurement*: The measured geometry parameters were average at least three chip samples, observed by optical microscopy, where the height of the microchannel (*h*) was measured from the chip cross-section photos, as shown in Fig. S1c.

Chemicals and Consumables

Acetone, ethanol and isopropyl alcohol (IPA) were purchased from China's Sinopharm Chemical Reagent Co., Ltd.. Silicon wafers (Shunsheng Electronic Technology Co., Ltd.), SU-8 2100 and SU-8 developer (MicroChem, USA), base and curing agent of PDMS (Sylgard 184 Silicone Elastomer, Dow Corning, USA), 1*H*,1*H*,2*H*,2*H*-perfluorooctyl-trichlorosilane (FOTS, 98%, Adamas-beta), other consumables used in microfluidic platform including PTFE tubes, stainless steel needles, etc. (Suzhou Wenhao Chip Technology Co., Ltd.)

Fabrication of microfluidic devices

Briefly, SU-8 photoresist was first spin-coated onto a clean and dry silicon wafer. The spin-coating condition of 500 rpm for 15 s following 2000 rpm for 50 s was determined to obtain a layer with thickness of about 100 μm, thus a channel height of 100 μm, as shown in the chip cross-section in Fig. S1c. Subsequently, the photoresist-coated wafer was pre-baked at 65°C for 10 mins following 95°C for 30 mins on a hotplate; exposed to UV light through a custom-made mask; baked at 95°C for 15 mins; naturally cooled, and then developed to remove the uncured SU-8, resulting in a master with the raised channel pattern. The master was plasma-treated and placed in a vacuum desiccator with PFOCT overnight to reduce its surface energy and avoid sticking during soft lithography processes.

The mixture of PDMS base and curing agent at a mass ratio of 10:1 was cast on the master and cured in a 90°C oven for 2 hrs. Once cured, a PDMS sheet with the chip pattern was cut and separated from the mold by a scalpel. Holes were drilled at the entrances and exits for tube connection. The patterned sheet was plasma-treated with a smooth and flat PDMS sheet for 30 s. Carefully aligned, pressed together, the two sheets were bond and form the closed channel. Finally, a microfluidic chip was obtained, as shown in Fig. 1b. It is worth mentioning that we optimized the method of hydrophilic modification of the PDMS channel surface to obtain long-term stable strong hydrophilicity (Fig. S1c inserted photo). The specific method is as follows: immediately after bonding, 5% (w/v) PVA/H_2O was introduced into the channel. After standing at room temperature for 15 mins, the chip was placed in an oven at 90°C for 15 mins. It was used after returning to room temperature, and the channel remained filled with water.

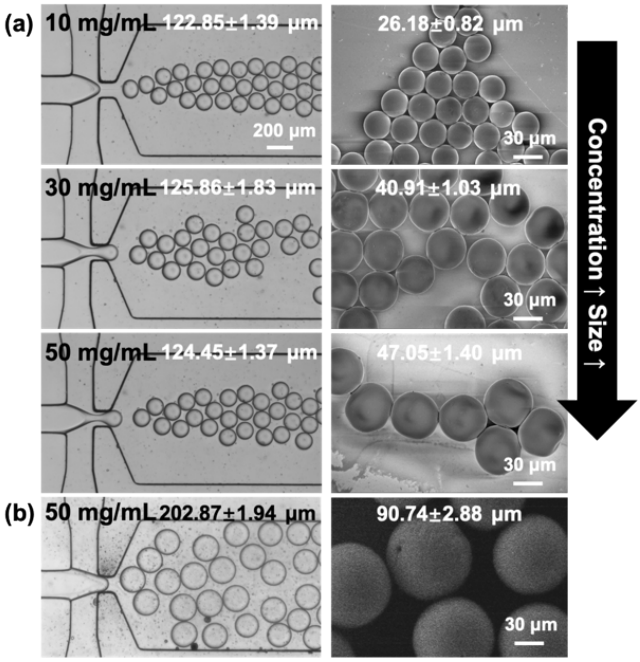

Fig. S2. Optical microscopy images of droplets and SEM images of microspheres (the scale bars are 30 μm). (a) microspheres from droplets of the same size but with different c_{PLGA}: 10 mg/mL, 30 mg/mL, 50 mg/mL, and the sizes of microspheres are 26.18 ± 0.82, 40.91 ± 1.03 μm, 47.05 ± 1.40 μm; (b) microspheres from droplets of large size and high c_{PLGA}, and the size of microspheres is 90.74 ± 2.88 μm.

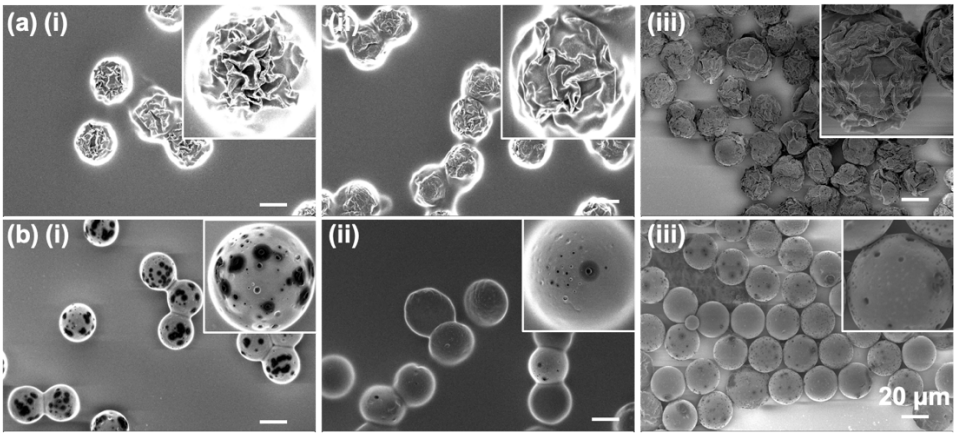

Fig. S3. SEM images of microspheres processed by different methods. (a) PLGA-PEG/PLGAe7576 6:4, DMC/DCM, 4% PVA; (b) PLGAe7576, DMC/DCM, 4% PVA. (i) evaporated by standing, before washing; (ii) evaporated with magnetic stirring, before washing; (iii) evaporated with stirring, after water-washing by centrifugation. The scale bars are 20 μm.

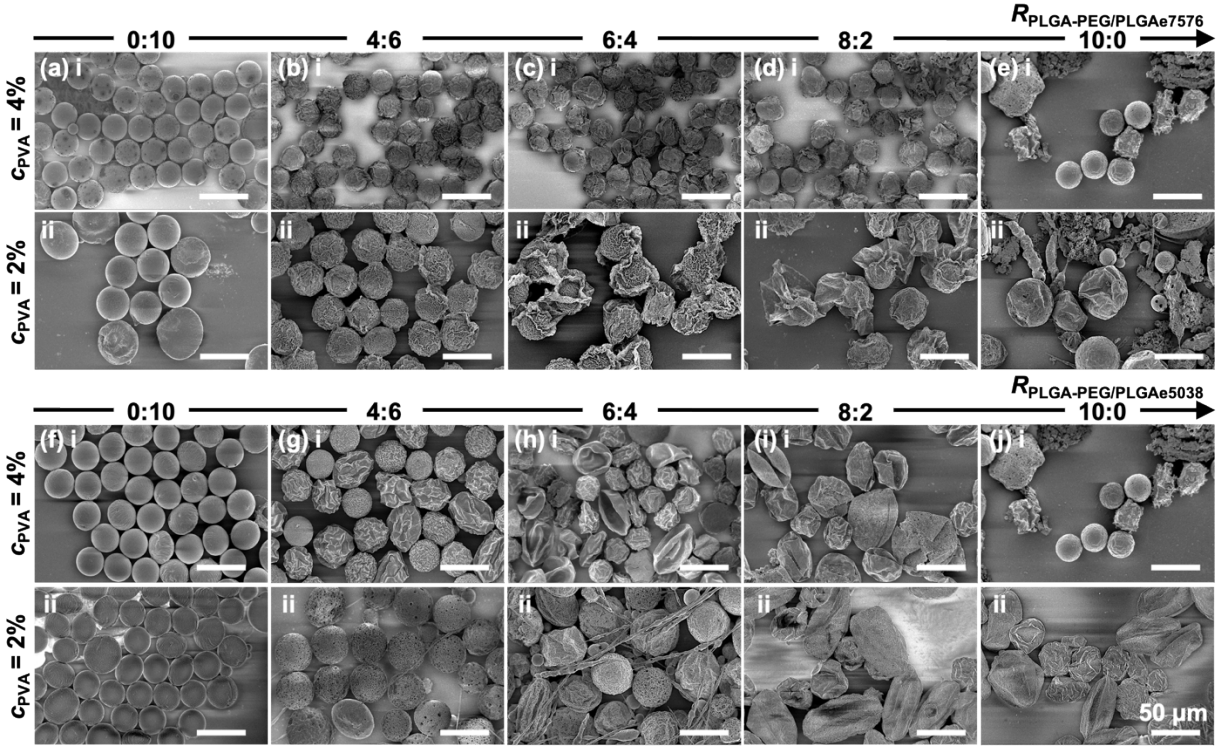

Fig. S4. SEM images of microspheres with different $R_{PLGA-PEG/PLGAe7576}$ (a-e) and $R_{PLGA-PEG/PLGAe5038}$ (f-j) in 4% PVA (i) and 2% PVA (ii). The scale bars are 50 µm.

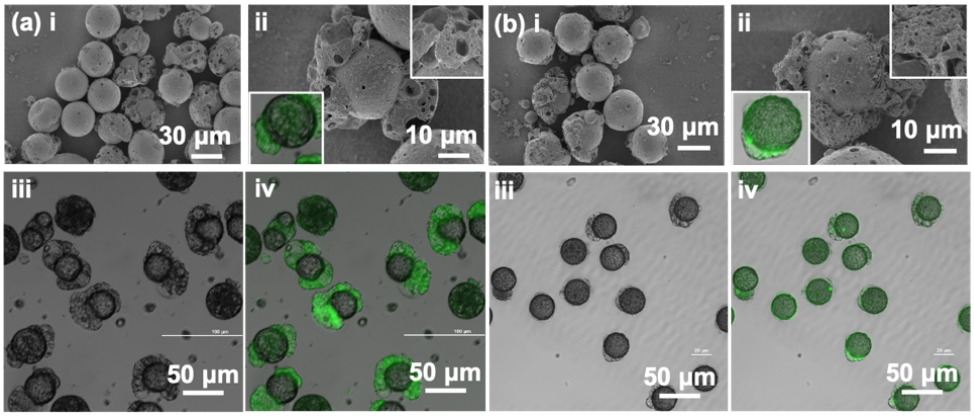

Fig. S5. SEM images (the scale bars in i and ii are 30 µm and 10 µm) and fluorescence confocal microscopy images (iii, brightfield; iv, merged, the scale bars are 50 µm) of PLGA-PEG-FITC/PLGAe7576 microspheres at an $R_{PLGA-PEG/PLGAe7576}$ of 6:4 prepared with DMC/DCM as solvent in 4% PVA (a); 2% PVA (b).

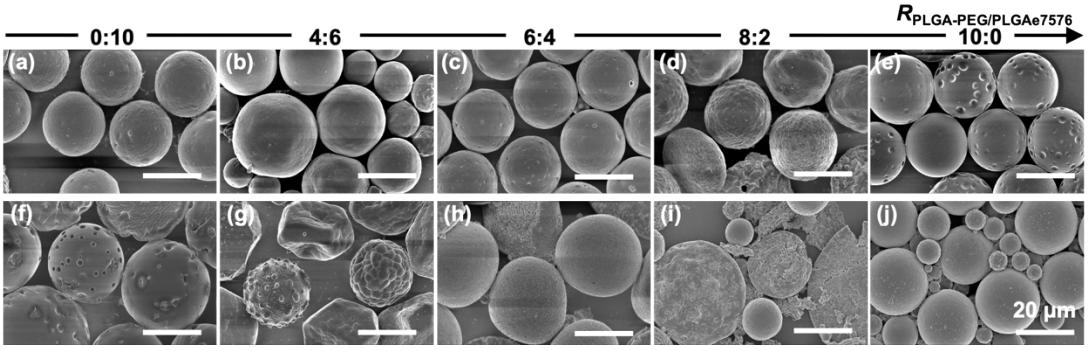

Fig. S6. SEM images of PLGA-PEG/PLGAe7576 microspheres with different $R_{PLGA\text{-}PEG/PLGAe7576}$ prepared with DMC as solvent in 4% PVA (a-e) and DMC/DCM as the solvent, while the continuous phase 2% PVA saturated with DMC (f-j). The scale bars are 20 μm.

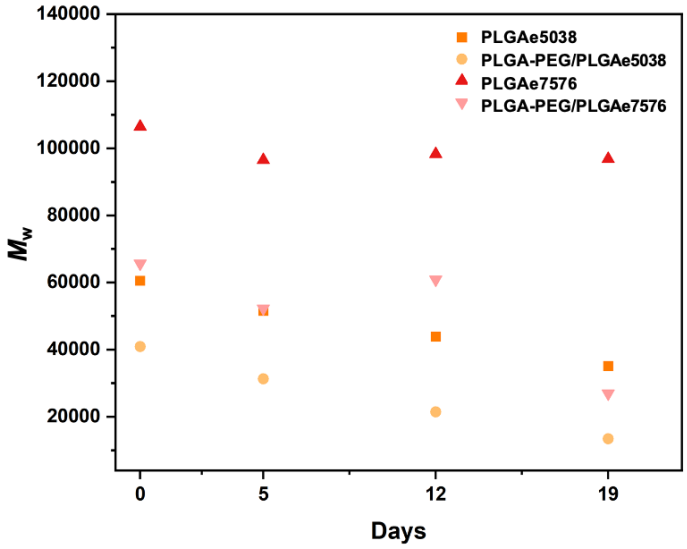

Fig. S7. M_w of microspheres (PLGAe5038, PLGA-PEG/PLGAe5038 at an $R_{PLGA\text{-}PEG/PLGAe5038}$ of 4:6, PLGAe7576, PLGA-PEG/PLGAe7576 at an $R_{PLGA\text{-}PEG/PLGAe7576}$ of 4:6) during degradation.

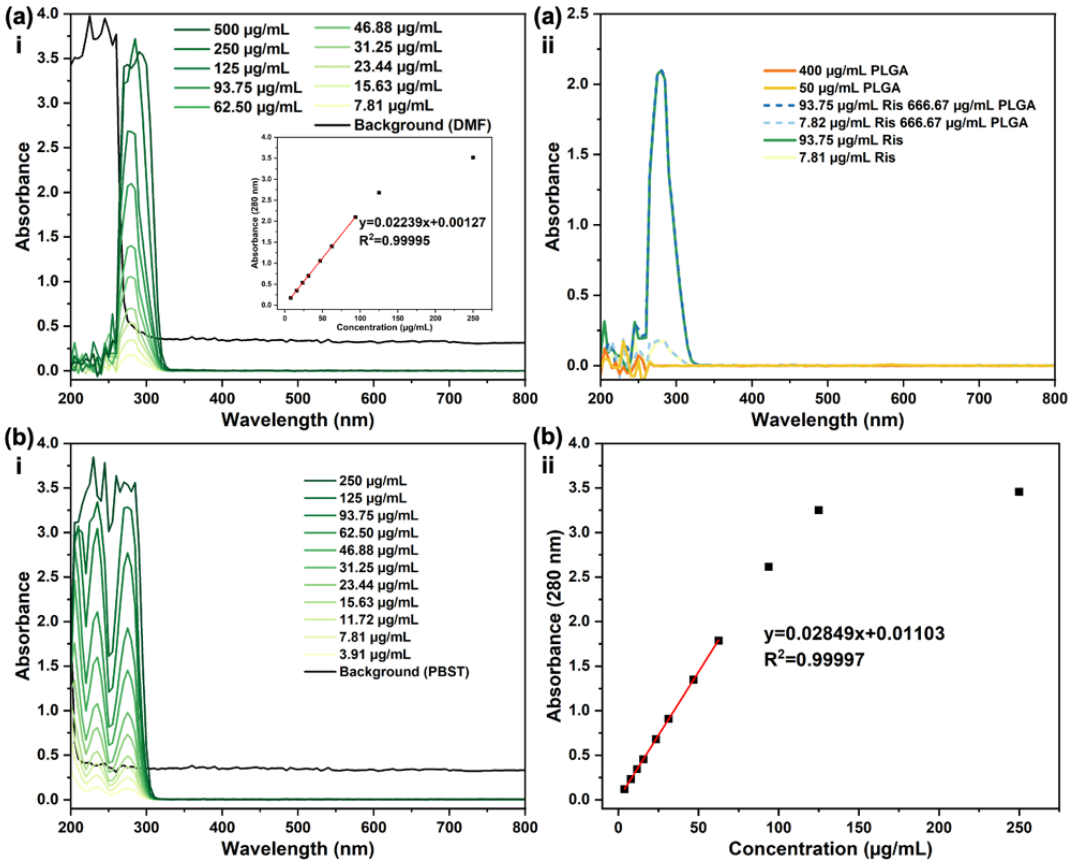

Fig. S8. UV absorption curves and standard curve of Ris/DMF (a) and Ris/PBST solutions (b). In addition, multiple concentrations of Ris/PLGA/DMF solutions were measured to inspect whether PLGA affected the UV absorption of risperidone ((a)ii).

Tab. S2. Preparation of drug-loaded microspheres.

Formation	Polymer	Solvent	TDL %	Continue Phase	Q_d/Q_c (mL/min)	Droplet Size (μm)
Fig. 6a	PLGAe5038	DMC/ DCM	16.67	3% PVA	0.005/0.020	73.39 ± 1.58
Fig. 6b	PLGAe7576				0.005/0.015	78.92 ± 2.86
Fig. 6c	PLGA-PEG/			4% PVA	0.010/0.025	83.92 ± 1.53
Fig. 6d	PLGAe7576 6:4			2% PVA	0.008/0.033	86.04 ± 2.18

The yield of microspheres prepared by microfluidic approaches approximately 99%, with minimal losses occurring during subsequent treatments such as washing. The duration required to accumulate a specific mass of microspheres is mainly depends on the flow rate. For example, 10 mg of microspheres typically require 100 minutes at a dispersed phase flow rate (Q_d) of 0.01 mL/min.

Tab. S3. Properties (size, DL %, and EE %) of drug-loaded microspheres.

Formation	Size (μm)	DL %	EE %
Fig. 6a	25.63 ± 0.56	0.49	2.96
Fig. 6b	27.89 ± 1.55	0.56	3.34
Fig. 6c	35.80 ± 0.86	2.69	16.13
Fig. 6d	34.69 ± 1.81	2.45	14.70