Supporting Information

Flash Precipitation of Random Copolymers in a Micro-mixer for Controlling the Size and Surface Charge of Nanoparticles

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1.1. Calculation of mixing time in the modular micro-mixer

First, the good solvent with ink is injected into the inner flow of the modular micro-mixer, and the anti-solvent is injected into the outer flow, and the image is taken from the position (0 - 2 ms, 40 - 42 ms, 80 - 82 ms, 120 - 122 ms, and 160 - 162 ms). Second, using Open Source Computer Vision (CV) as a software library developed by Intel, the image obtained at each position is converted to gray scale, and the image in the given time range is altered to pixel value. Each pixel value appears from 0 to 255 according to the degree of gray color. Thirdly, using these values, the degree of mixing can be quantified by the following mixing efficiency.

$$\eta = (1 - \sqrt{\frac{\sigma^2}{\sigma_{initial}^2}}) \times 100$$

Where

$$\sigma = \sqrt{\frac{1}{N}\sum_{l}^{N}(C_l - C_m)^2}$$

standard deviations of grey color code value at total pixels, N is the number of pixels at the position, C_l is a grey color code value of a certain pixel, C_m is the mean grey color code value of the total pixels within each position. Processing grayscale images is computationally more efficient than processing color images. As it involves only one channel (black and white) instead of three (red, green, and blue). $\sigma_{initial}$, σ are the standard deviations of the initial position (0 - 2 ms) and the certain position (0 - 2 ms, 40 - 42 ms, 80 - 82 ms, 120 - 122 ms, 160 - 162 ms).

Figure S1. (A) Mixing efficiency as a function of time. (B) Photograph of system for calculating mixing efficiency and flow regime screening. (C) Schematic representation of experimental setup.

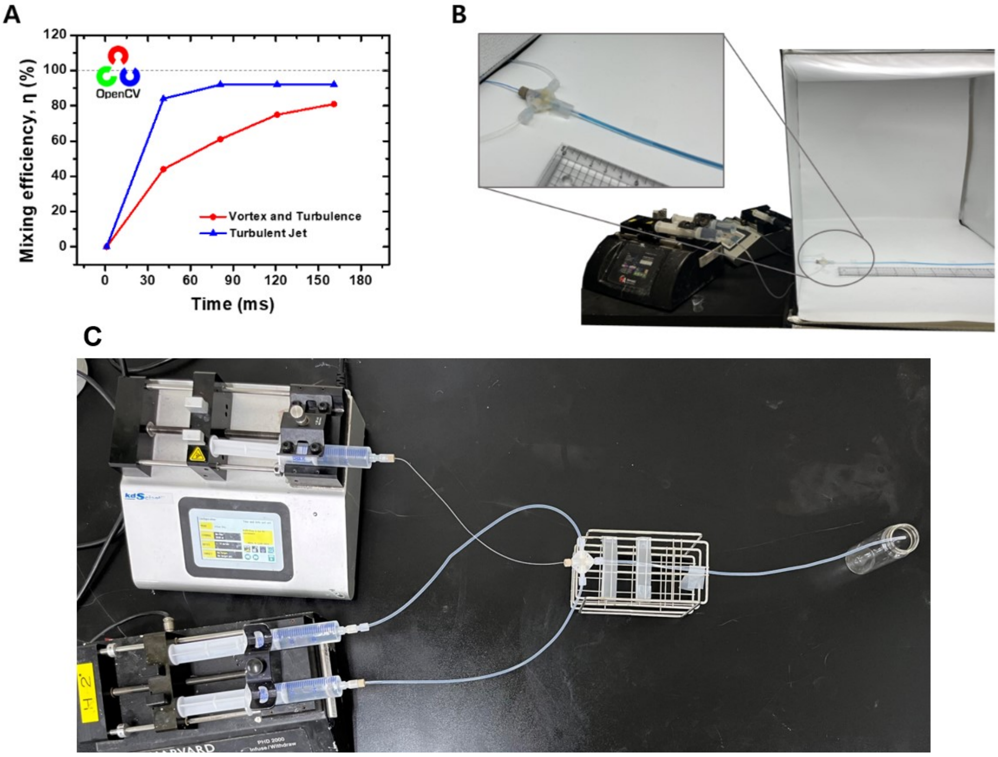
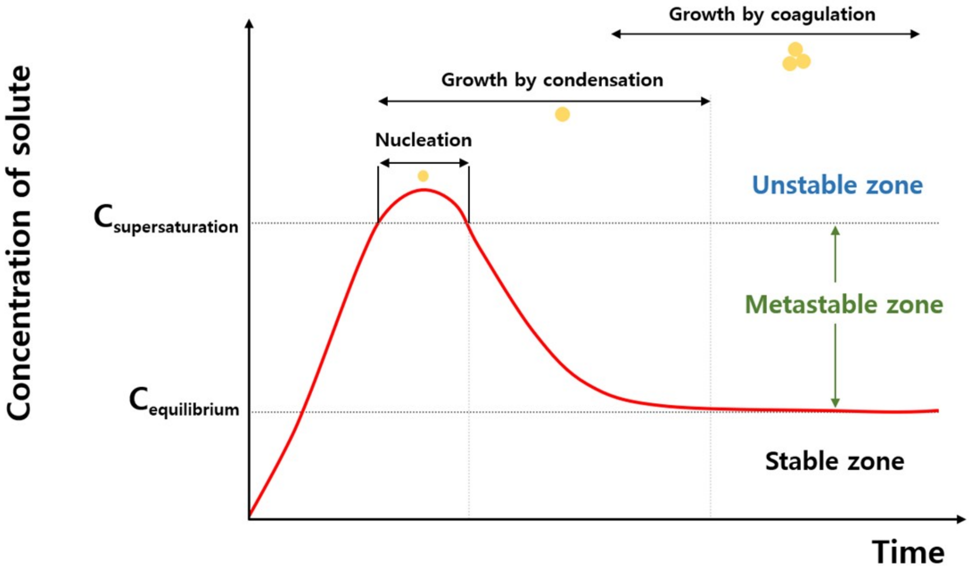


Table S1. Mixing efficiency as a function of time for each flow regime.

Entry	Mixing efficiency at 5 locations (%)				
	0 ~ 2 ms	40 ~ 42 ms	80 ~ 82 ms	120 ~ 122 ms	160 ~ 162 ms
laminar	**Not available**				
vortex and turbulence	0	44	61	75	81
turbulent jet	0	84	92	92	92

Figure S2. General precipitation curve for the anti-solvent process.



The Hoftyzer & van Krevelen equation is:

$$\delta_d = \frac{\sum F_{di}}{V}$$

$$\delta_p = \frac{\sqrt{\sum F^2{}_{pi}}}{V}$$

$$\delta_h = \sqrt{\frac{\sum E_{hi}}{V}}$$

Where δ_d, δ_p, δ_h are parameters defined by dispersions force, polar force, and hydrogen bonding force F_{di}, F_{pi} are dispersive components, polar components of molar attraction constant, E_{hi} is hydrogen bonding energy, and V is the molar volume of the solvent molecule or the structural unit of the polymer.

The Hoy method is as follows.

Additive molar functions:

$$F_t = \sum n_i F_{t,i}$$

$$F_p = \sum n_i F_{p,i}$$

$$V = \sum n_i V_i$$

$$\Delta_T^{(P)} = \sum n_i \Delta_{T,i}^{(P)}$$

Where F_t is the molar attraction function, F_p is the polar component, V is the molar volume of the solvent molecule or the structural unit of the polymer. $\Delta_T^{(P)}$ is similar correction with Lyderson for polymer non-ideality.

Auxiliary equations:

$$\alpha^{(P)} = \frac{777\Delta_T^{(P)}}{V}$$

$$\bar{n} = \frac{0.5}{\Delta_T^{(P)}}$$

Where $\alpha^{(P)}$ is molecular aggregation number for polymer and $\bar{n}$ is the number of repeating units per polymer chain segment.

Expressions for δ and δ-components:

$$\delta_t = \frac{F_t + \frac{B}{\bar{n}}}{V};B = 277$$

$$\delta_p = \delta_t\left(\frac{1}{\alpha^{(P)}}\frac{F_p}{F_t + B/\bar{n}}\right)^{1/2}$$

$$\delta_h = \delta_t\left(\frac{\alpha^{(P)} - 1}{\alpha^{(P)}}\right)^{1/2}$$

$$\delta_d = (\delta_t^2 - \delta_p^2 - \delta_h^2)^{1/2}$$

Where B is base value, δ_t is total Hansen solubility parameter and δ_d, δ_p, δ_h is parameter defined by dispersions force, polar force, hydrogen bonding force.

The R_a, which is the radius between the polymer and the solvent, can be obtained using the Hansen solubility parameter calculated using the average value of two methods.

$$R_a = [4(\delta_{d,P} - \delta_{d,s})^2 + (\delta_{p,P} - \delta_{p,s})^2 + (\delta_{h,P} - \delta_{h,s})^2]^{1/2}$$

Where $\delta_{d,P}$, $\delta_{p,P}$, $\delta_{h,P}$ are for polymer, $\delta_{d,s}$, $\delta_{p,s}$, $\delta_{h,s}$ are for solvent.

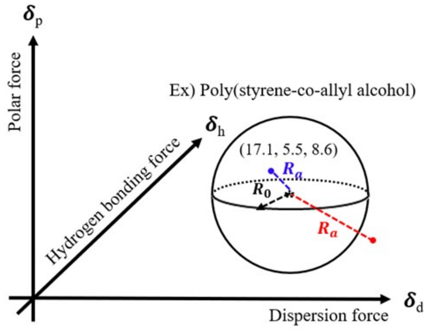
The Hansen solubility parameter was calculated using the Hoftyzer & van Krevelen and Hoy methods. The degree of solubility of the polymer in the solvent was determined through the R_a value. Originally, depending on whether the R_a/R_0 (RED value) is less than or greater than 1, it can be determined whether it is a good solvent that can dissolve the polymer or an anti-solvent that cannot dissolve. If the RED value is greater than 1, it is an anti-solvent, and if it is less than 1, it is a good solvent.

A sphere can be drawn using the intrinsic coordinates of polymer (δ_d,δ_p, δ_h) and its own radius R_0. If the RED value is less than 1, the solvent coordinates exist inside the sphere, and if the RED value is greater than 1, the solvent coordinates exist outside the sphere (Figure 2). Solvent coordinates that are closer to the intrinsic coordinates of the polymer are more soluble, whereas solvent coordinates that are more distant from the intrinsic coordinates of the polymer are less soluble. That is, the smaller R_a in a good solvent, the more soluble it is, and the larger the R_a in an anti-solvent, the better anti-solvent. Because we wanted to compare the solubility of a given polymer between solvents rather than whether the solvent is dissolved, we compared the

R_a between each solvent.

In the case of P(St-AA) polymer, the order of solubility is THF > Chloroform > Acetone > Toluene > DMF > EtOH > MeOH >>> Water. So, Water with the greatest R_a value is the most ideal anti-solvent (Table 2). However, since a good solvent and an anti-solvent must be miscible for precipitation to occur, Chloroform and Toluene, which are both immiscible with Water, are excluded as good solvent options. Using the same process, it is possible to confirm that THF is the best good solvent and water is the best anti-solvent for P(St-MA), P(St-AA), and P(MMA-MAA) (Table 2, 3 and 4).

Figure S3. Index for determining affinity between solvent and polymer using RED



$R_a/R_0 < 1$ → **Good affinity** = Possible for good solvent

$R_a/R_0 > 1$ → **Low affinity** = Possible for anti-solvent

Table S2. Hansen Solubility parameters of solvents and R_a for P(St-MA) polymer.

Solvent	δ	δ_d	δ_p	δ_h	R_a
Poly(styrene-co-maleic acid)	19.3	16.7	7.1	6.6	
Chloroform	19	17.8	3.1	5.7	4.7
Tetrahydrofuran (THF)	19.4	16.8	5.7	8	**2.0**
Dimethylformamide (DMF)	24.8	17.4	13.7	11.3	8.3
Toluene	18.16	18	1.4	2	7.8
Water	47.9	15.5	16	42.3	**36.9**
Ethanol	26.6	15.8	8.8	19.4	13.1
Methanol	29.7	15.1	12.3	22.3	16.9
Acetone	20.1	15.5	10.4	7	4.1

Table S3. Hansen Solubility parameters of solvents and R_a for P(St-AA) polymer.

Solvent	δ	δ_d	δ_p	δ_h	R_a
Poly(styrene-co-allyl alcohol)	19.9	17.1	5.5	8.6	
Chloroform	19	17.8	3.1	5.7	4.0
Tetrahydrofuran (THF)	19.4	16.8	5.7	8	**0.8**
Dimethylformamide (DMF)	24.8	17.4	13.7	11.3	8.7
Toluene	18.16	18	1.4	2	8.0
Water	47.9	15.5	16	42.3	**35.5**
Ethanol	26.6	15.8	8.8	19.4	11.6
Methanol	29.7	15.1	12.3	22.3	15.8
Acetone	20.1	15.5	10.4	7	6.0

Table S4. Hansen Solubility parameters of solvents and R_a for P(MMA-MAA) polymer.

Solvent	δ	δ_d	δ_p	δ_h	R_a
Poly(MMA-co-MAA)	19.3	15.1	6.3	10.2	
Chloroform	19	17.8	3.1	5.7	7.7
Tetrahydrofuran (THF)	19.4	16.8	5.7	8	**4.0**
Dimethylformamide (DMF)	24.8	17.4	13.7	11.3	8.7
Toluene	18.16	18	1.4	2	11.1
Water	47.9	15.5	16	42.3	**33.6**
Ethanol	26.6	15.8	8.8	19.4	9.7
Methanol	29.7	15.1	12.3	22.3	13.5
Acetone	20.1	15.5	10.4	7	5.2

Table S5. Liquid density, viscosity, and diffusion coefficient to water for MeOH,

	Solvent physical properties		
	Density [kg/m^3]	Viscosity [cP]	Diffusion coefficient [cm^2/s]
MeOH	791	0.594	1.35×10^{-5}[28]
EtOH	789	1.144	1.20×10^{-5}[29, 30]
THF	888	0.49	1.05×10^{-5}[31]

Figure S4. Phase diagram of flow regime in terms of R and Re for (A) MeOH, (B) EtOH. (C) Effect of good solvent on the nanoparticles size synthesized from 1 mg/mL P(St-AA) in a turbulent jet flow regime.

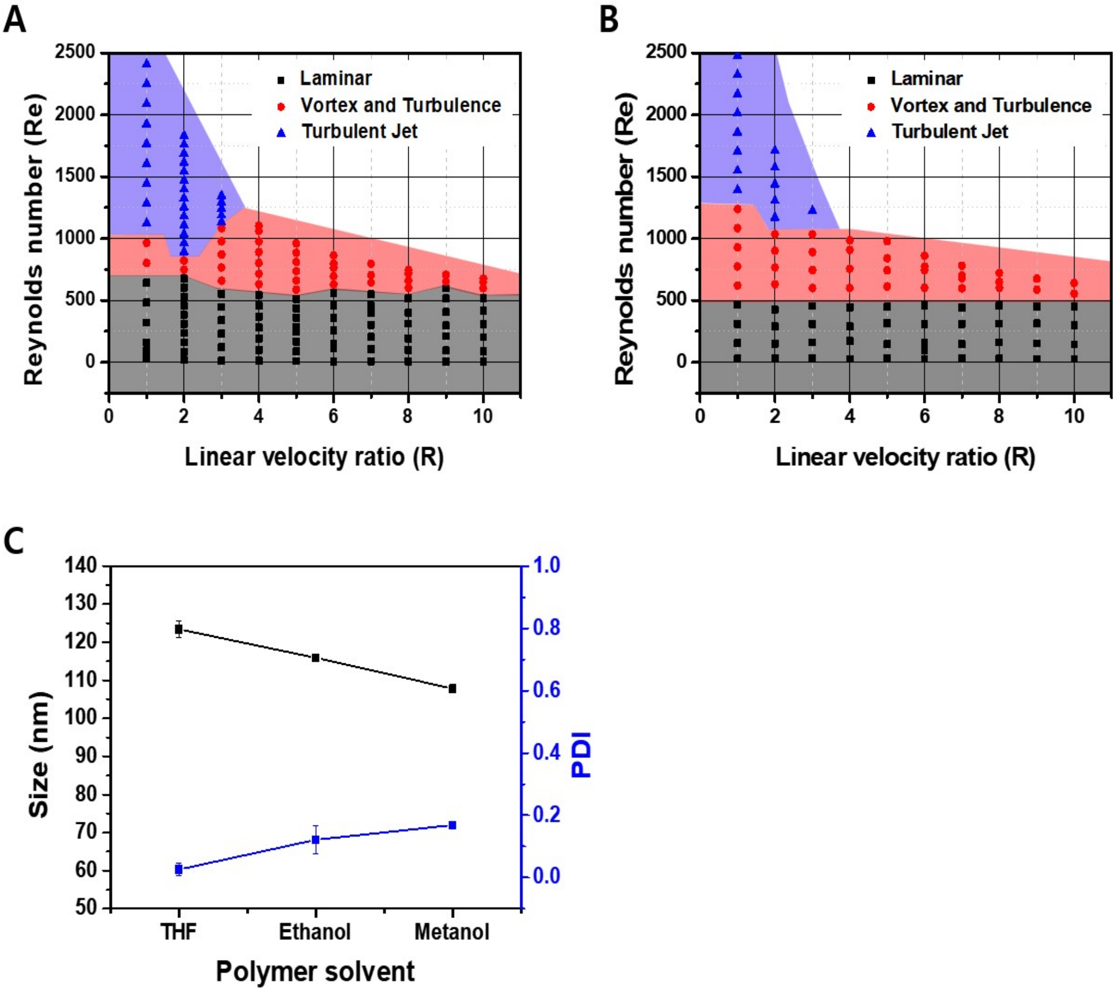
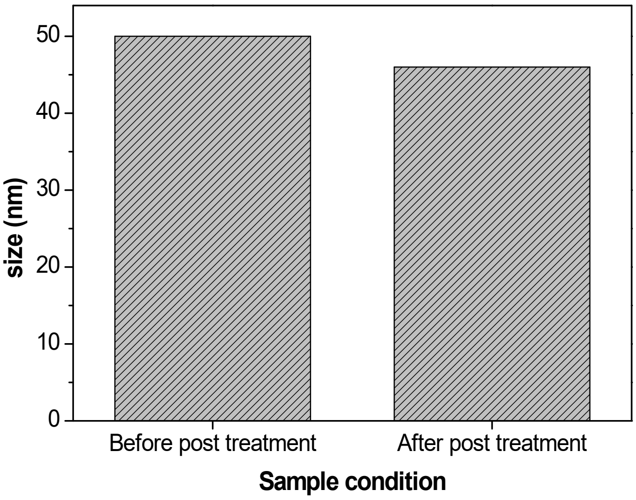


Table S6. R_a value, solubility of P(St-AA) polymer as a function of concentration (0.1mg/ml, 1mg/ml, 10mg/ml).

	R_a	Concentration [mg/ml]		
		0.1	1	10
MeOH	15.8	S*	S	insoluble
EtOH	11.6	S	S	
THF	0.8	S	S	S

* (S) soluble

Figure S5. The particle size difference of P(St-MA) NPs, synthesized at a concentration of 0.1 mg/mL, before and after post-treatment, measured by DLS



1.2. Small-angle X-ray scattering (SAXS) experiments by synchrotron radiation sources.

a. Sample preparation: The nanoparticle dispersed solution was filtered by Amicon® Ultra centrifugal ultrafiltration tube, followed by vacuum drying for overnight, and dispersing in ultrapure water, and sonicating for 5 mins to ensure uniform dispersion of nanoparticles, resulting in a 5 mg/mL aqueous solution of nanoparticles.

b. The experiment protocol of Synchrotron experiment information:
Synchrotron SAXS experiments were performed at 9A beamlines inthe Pohang Accelerator Laboratory (PAL). A monochromatized X-rayradiation source of 11.08 keV monochromated by double crystal monochromator with Si (111) crystal. The distance of sample to detector is 6.4 m. The scattering intensity was monitored by Rayonix Ltd. MX170-HS (1920*1920 pixels, pixel size 0.0886mm) charge-coupled device (CCD) detector. The 1D intensity profiles was extracted from 2D SAXS pattern with circular averaging process as the intensity versus the scattering vector (q), where the magnitude of the scattering vector is given by q = (4pi/lamda)*sin(2theta/2) (lamda : wavelength of photon, 2theta : scattering angle).