Electronic Supplementary Information for:

Investigating the Influence of Solvent Quality on RAFT-mediated PISA of Sulfonate-functional Diblock Copolymer Nanoparticles

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Synthesis of 4-cyano-4-(2-phenylethanesulfanyl thiocarbonyl) sulfanylpentanoic acid (PETTC)

The synthesis of the 4-cyano-4-(2-phenylethane sulfanylthiocarbonyl) sulfanylpentanoic acid (PETTC) RAFT agent was conducted according to a modified procedure described by Semsarilar et al.[1] Sodium hydride (60% in oil, 3.0 g, 76 mmol) was gradually added to diethyl ether (150 mL) at 5 °C to obtain a grey suspension. 2-Phenylethanethiol (10.0 g, 72 mmol) was added dropwise to the grey suspension and hydrogen gas was observed. A white viscous slurry of sodium phenylethanethiolate formed over a 30 min period. Carbon disulfide (5.8 g, 76 mmol) was added dropwise to the reaction mixture and slowly transformed into a thick yellow precipitate of sodium 2-phenylethanetrithiocarbonate over 30 min. The precipitate was collected by filtration and subsequently used in the next step without further purification. Sodium 2-phenylethanetrithiocarbonate (15.6 g, 66 mmol) was gradually added to diethyl ether (150 mL) at room temperature to obtain a suspension and then solid iodine (8.8 g, 35 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour and an insoluble white precipitate of sodium iodide was formed and removed by filtration. The yellow−brown filtrate was washed with a sodium thiosulfate aqueous solution to remove excess iodine (three 150 mL portions) and dried over sodium sulfate to remove residual water. The filtrate was further dried under vacuum to evaporate volatiles, and yield bis(2-phenylethanesulfanylthiocarbonyl) disulfide.

A solution of bis(2-phenylethane sulfanylthiocarbonyl) disulfide (9.4 g, 22 mmol) and 4,4’-azobis(4-cyanovaleric acid) (ACVA, 9.3 g, 33 mmol) were dissolved in ethyl acetate (200 mL) and deoxygenated with nitrogen for 30 min. This reaction mixture was immersed in an oil bath at 82 °C and reacted for 18 h under nitrogen. The organic phase was evaporated under vacuum and the crude product was purified by silica chromatography using a mixed eluent (7:3 petroleum ether/ethyl acetate, gradually increasing to 3:7) to isolate 4-cyano-4-(2-phenylethane sulfanylthiocarbonyl) sulfanylpentanoic acid (PETTC) as a viscous yellow oil. The purified yellow oil was further dried under vacuum to obtain a yellow solid (78% yield).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): 7.18−7.36 (m, 5H, aromatic), 3.54-3.62 (t, 2H, $-CH_2$), 2.95-3.04 (t, 2H, $-CH_2$), 2.63-2.75 (t, 2H, $-CH_2$), 2.35−2.60 (m, 2H, $-CH_2$), δ 1.89 (3H, $-CH_3$).

^{13}C NMR (400 MHz, $CDCl_3$, 298 K): 216.28 (C=S), 176.25 (C=O), 126.75, 128.45, 139.02, 139.02 (Ph), 118.71 (CN), 46.21 ($SCCH_2$), 37.85 (SCH_2CH_2Ph), 33.93 (CH_2CH_2COOH), 33.38 (CH_2Ph), 29.26 (CH_2CH_2COOH), δ 24.74 (CH_3).

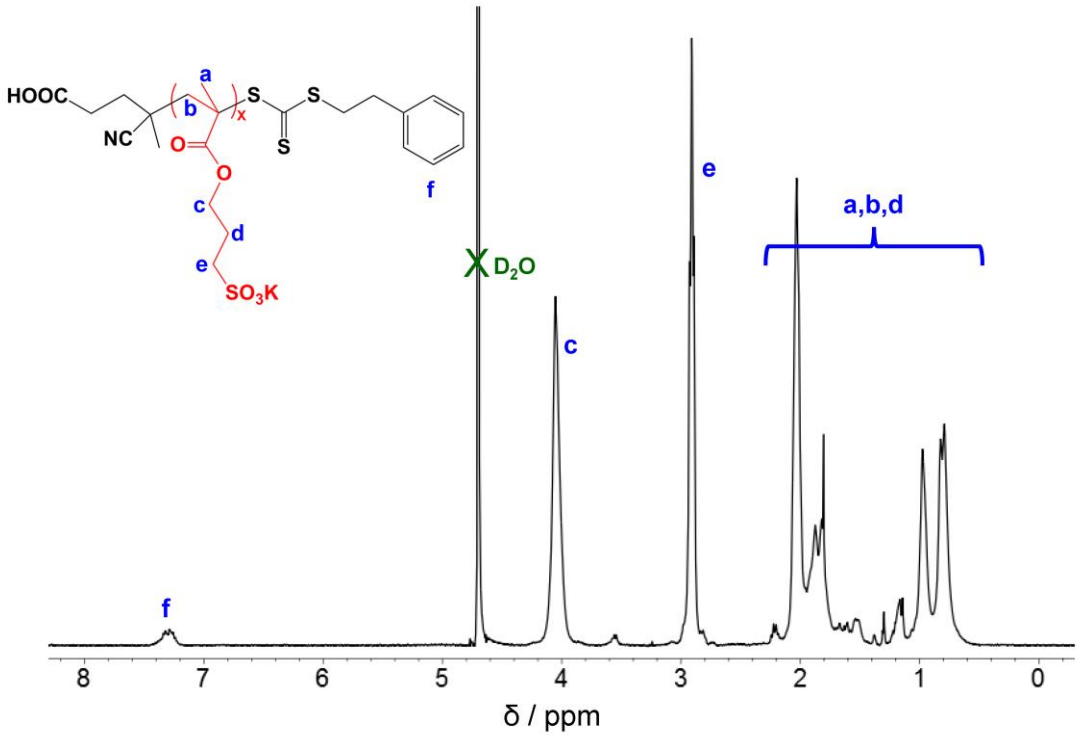

Fig. S1 ^{1}H NMR spectra of a purified and freeze-dried PKSPMA$_{32}$ macro-CTA. The sample was dissolved in D_2O prior to analysis. The degree of polymerisation (DP) for this macro-CTA was calculated by comparing the integrated proton signals corresponding to the methacrylic polymer backbone at 0.4-2.5 ppm with that corresponding to the aromatic protons of PETTC chain end at 7.2-7.4 ppm.

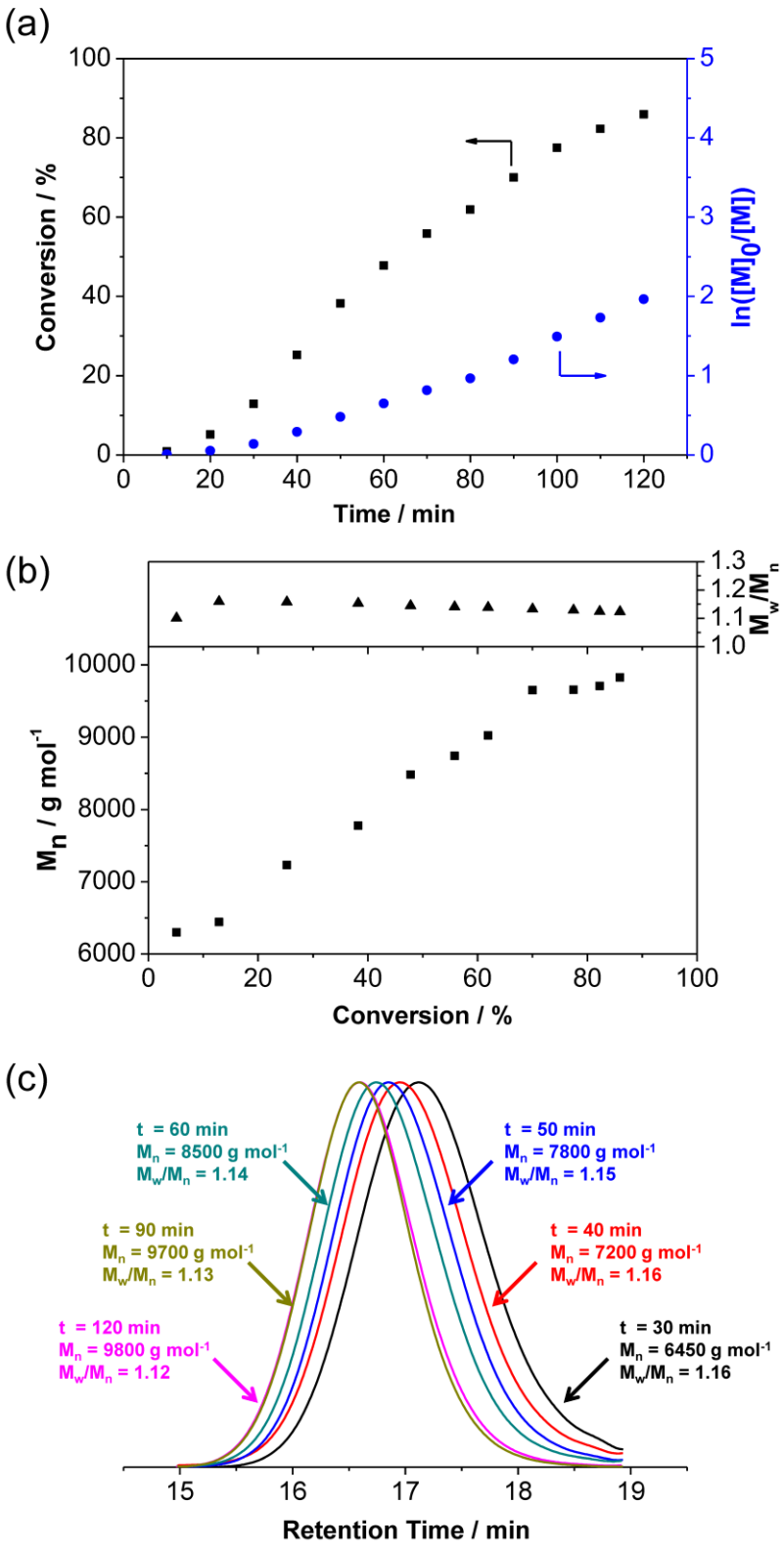

Fig. S2 Kinetic studies for RAFT solution polymerisation of KSPMA with PETTC chain transfer agent in 3:1 water/dioxane at 70 °C (15 % w/w, PETTC/ACVA = 5, target DP = 50): (a) conversion and semi-logarithmic kinetics versus reaction time, (b) molecular weight dispersity (M_w/M_n) and M_n versus monomer conversion, and (c) aqueous GPC chromatograms.

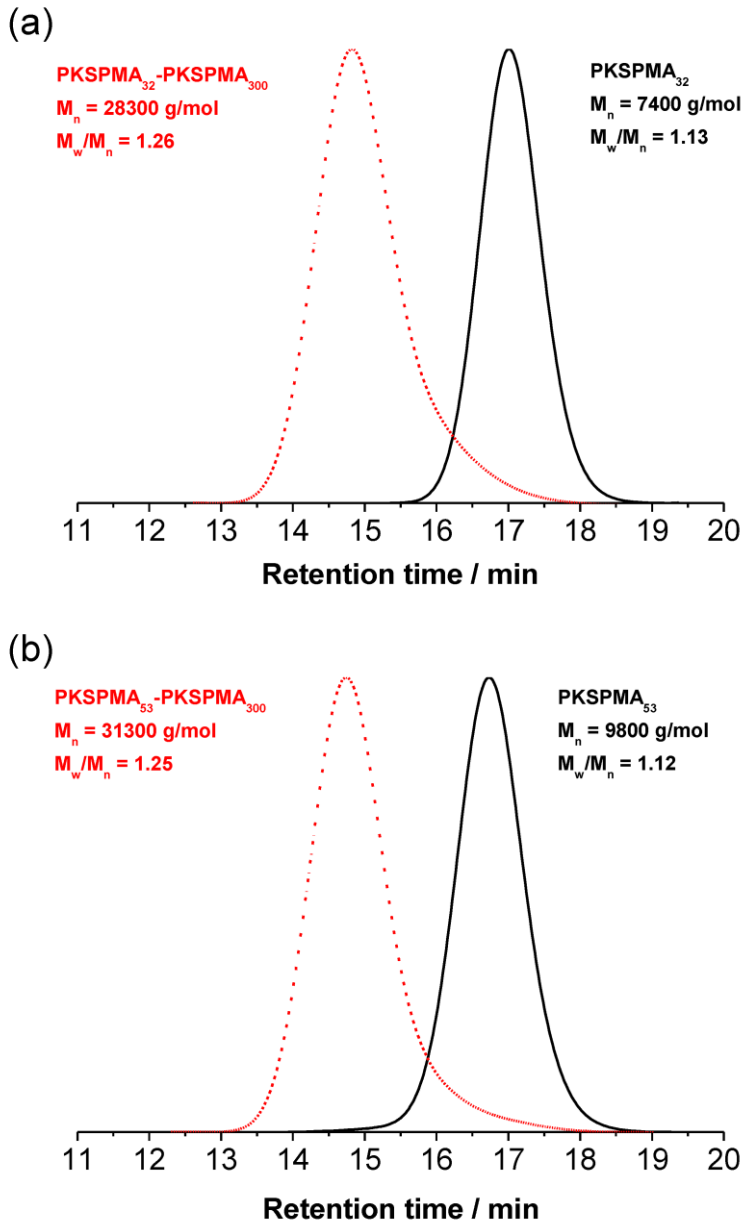

Fig. S3 Aqueous GPC chromatograms obtained for (a) $PKSPMA_{32}$ and (b) $PKSPMA_{53}$ macro-CTAs and their subsequent chain extension *via* RAFT aqueous solution polymerisation using KSPMA at 70 °C (15 % w/w, target DP of second block = 300). In both cases, a relatively high blocking efficiency was achieved, suggesting that the majority of the trithiocarbonate RAFT chain-ends remained intact.

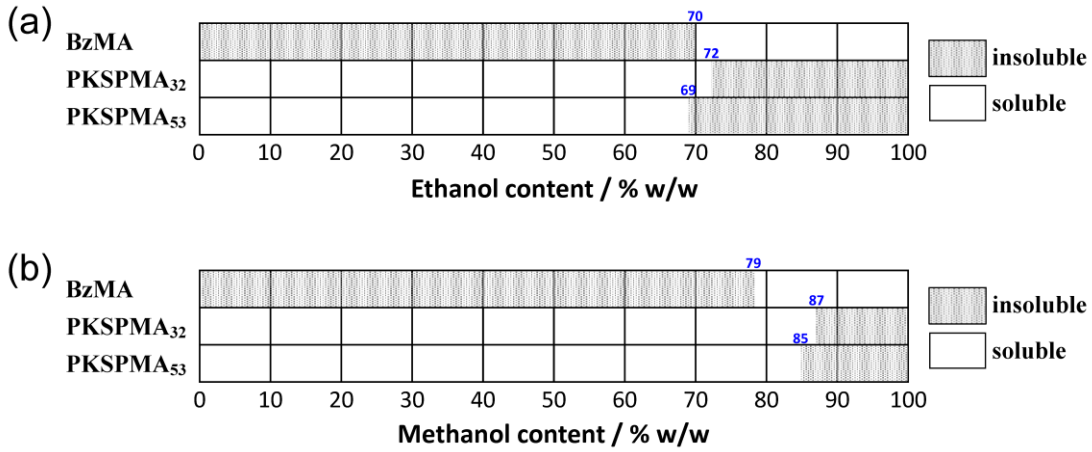

Fig. S4 Solubility of BzMA, $PKSPMA_{32}$ and $PKSPMA_{53}$ in (a) ethanol/water mixtures and (b) methanol/water mixtures. Solubility tests were conducted at 21 °C and at concentrations of 0.3 g mL^{-1} and 5 mg mL^{-1} for BzMA and $PKSPMA_x$, respectively.

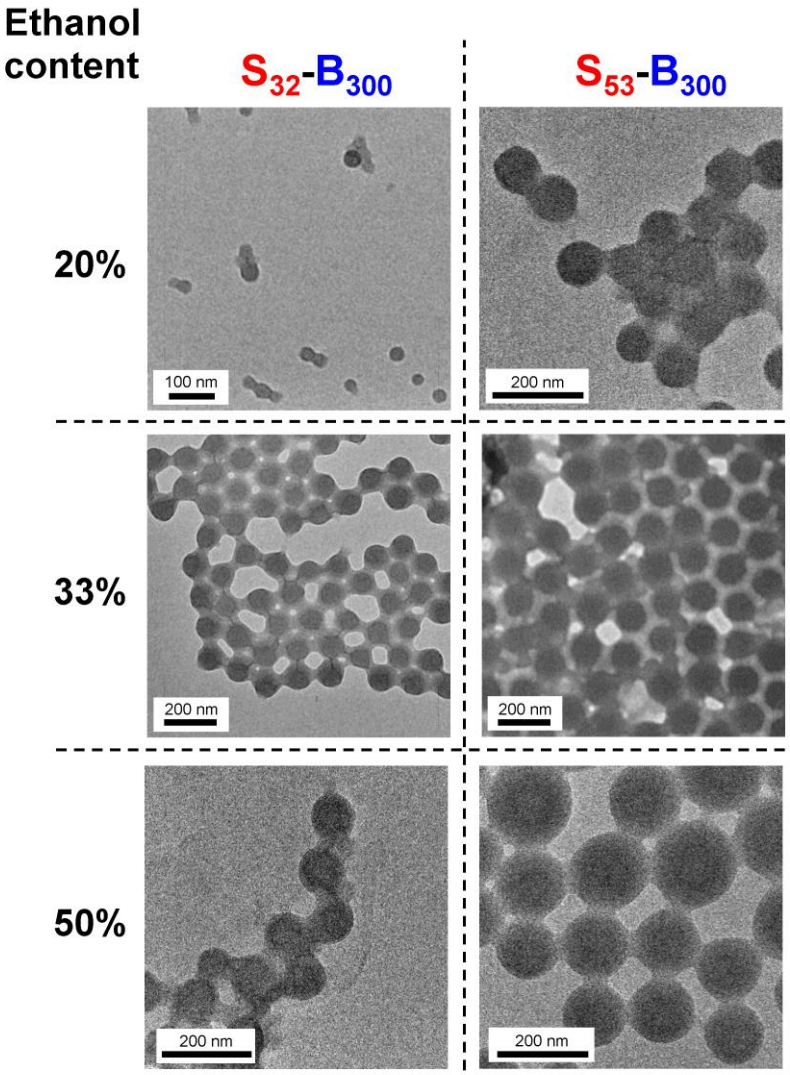

Fig. S5 Representative TEM images of S_{32}–B_{300} and S_{53}–B_{300} diblock copolymer nanoparticles prepared at 10 % w/w solids *via* RAFT-mediated PISA in ethanol/water mixtures at 70 °C.

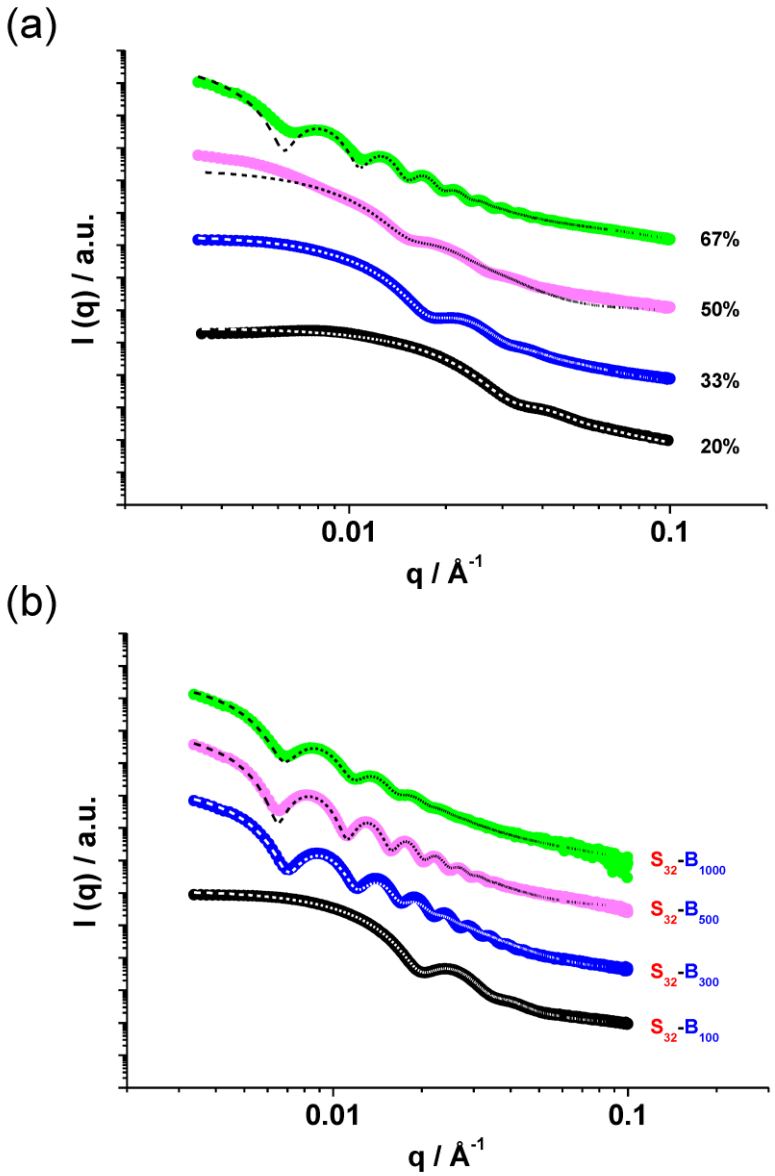

Fig. S6 Selected small-angle X-ray scattering data (coloured circles) recorded for 1.0 % w/w copolymer dispersions of S_x-B_y nanoparticles prepared at 10 % w/w solids *via* RAFT-mediated PISA. (a) S_{53}−B_{300} nanoparticles synthesised at 20-67 % w/w methanol content, and (b) S_{32}−$B_{100\text{-}1000}$ nanoparticles prepared in a 33 % w/w ethanol/water mixture. Dashed lines represent fits to the data using a spherical micelles[2] plus Gaussian polymer chains[3] model.

Table S1 Summary of composition, methanol content and mean diameters obtained for $PKSPMA_x$-$PBzMA_y$ diblock copolymer nanoparticles synthesised at 10 % w/w solids *via* RAFT-mediated polymerisation in methanol/water mixtures.

Target composition[a]	Methanol content / % w/w	DLS		TEM	SAXS
		$D_{h,\ water}$ / nm[b]	$D_{h,\ methanol/water}$ / nm[c]	D_{TEM} / nm[d]	D_{SAXS} / nm[e]
S_{32}-B_{100}	0	21 (0.431)	21 (0.431)		
S_{32}-B_{100}	20	23 (0.340)	23 (0.317)		
S_{32}-B_{100}	33	33 (0.154)	30 (0.169)	23 ± 4	29 ± 3
S_{32}-B_{100}	50	93 (0.036)	85 (0.026)	43 ± 7	70 ± 9
S_{32}-B_{100}	67	97 (0.026)	88 (0.020)	66 ± 6	73 ± 8
S_{32}-B_{300}	0	40 (0.435)	40 (0.435)		
S_{32}-B_{300}	20	48 (0.192)	42 (0.214)	25 ± 2	40 ± 5
S_{32}-B_{300}	33	96 (0.053)	86 (0.030)	52 ± 5	74 ± 6
S_{32}-B_{300}	50	192 (0.018)	181 (0.061)	147 ± 14	161 ± 9
S_{32}-B_{300}	67	211 (0.016)	204 (0.021)	159 ± 12	179 ± 8
S_{32}-B_{300}	80	197 (0.063)	181 (0.048)	194 ± 17	
S_{53}-B_{100}	0	24 (0.266)	24 (0.266)		
S_{53}-B_{100}	20	26 (0.302)	24 (0.377)		
S_{53}-B_{100}	33	31 (0.237)	30 (0.228)		
S_{53}-B_{100}	50	100 (0.065)	76 (0.049)	60 ± 6	70 ± 10
S_{53}-B_{100}	67	114 (0.364)	89 (0.037)		43 ± 6
S_{53}-B_{300}	0	39 (0.270)	39 (0.270)		
S_{53}-B_{300}	20	57 (0.164)	46 (0.173)	31 ± 4	39 5
S_{53}-B_{300}	33	89 (0.052)	78 (0.066)	51 ± 7	62 ± 9
S_{53}-B_{300}	50	131 (0.070)	119 (0.077)	59 ± 6	65 ± 6
S_{53}-B_{300}	67	174 (0.014)	164 (0.021)	130 ± 13	147 ± 8
S_{53}-B_{300}	80	165 (0.016)	181 (0.086)	145 ± 14	
S_{32}-B_{500}	33	119 (0.014)	113 (0.017)	81 ± 8	101 ± 8
S_{32}-B_{700}	33	158 (0.017)	150 (0.035)	92 ± 11	131 ± 11

[a] All conversions were determined to be >99% *via* gravimetry thus the target composition is assumed to be the actual obtained copolymer composition.

[b] DLS analysis using water as dispersant. DLS polydispersity index vales are indicated in brackets.

[c] DLS analysis using methanol/water mixtures corresponding to the synthetic conditions. DLS polydispersity index vales are indicated in brackets.

[d] Mean TEM particle diameters were calculated by analysing 200 particles using ImageJ software.

[e] SAXS diameters were calculated using $D_{SAXS} = 2R_{core} + 4R_g$.

Table S2 Summary of target copolymer composition, ethanol content and mean diameters obtained for $PKSPMA_x$-$PBzMA_y$ diblock copolymer nanoparticles synthesised at 10 % w/w *via* RAFT-mediated polymerisation in ethanol/water mixtures.

Target composition[a]	Ethanol content / % w/w	DLS		TEM	SAXS
		$D_{h,\ water}$ / nm[b]	$D_{h,\ ethanol/water}$ / nm[c]	D_{TEM} / nm[d]	D_{SAXS} / nm[e]
S_{32}-B_{100}	0	21 (0.431)	21 (0.431)		
S_{32}-B_{100}	20	32 (0.243)	28 (0.288)		
S_{32}-B_{100}	33	68 (0.051)	61 (0.029)	38 ± 4	52 ± 5
S_{32}-B_{100}	50	139 (0.032)	123 (0.071)	113 ± 10	
S_{32}-B_{300}	0	40 (0.435)	40 (0.435)		
S_{32}-B_{300}	20	71 (0.152)	58 (0.159)	32 ± 4	
S_{32}-B_{300}	33	157 (0.011)	150 (0.078)	101 ± 8	132 ± 7
S_{32}-B_{300}	50	196 (0.059)	164 (0.057)	156 ± 34	
S_{53}-B_{100}	0	24 (0.266)	24 (0.266)		
S_{53}-B_{100}	20	26 (0.379)	24 (0.339)		
S_{53}-B_{100}	33	64 (0.069)	57 (0.062)	29 ± 3	39 ± 5
S_{53}-B_{100}	50	140 (0.055)	122 (0.070)	110 ± 7	
S_{53}-B_{300}	0	39 (0.270)	39 (0.270)		
S_{53}-B_{300}	20	137 (0.017)	132 (0.043)	119 ± 9	
S_{53}-B_{300}	33	173 (0.033)	169 (0.040)	139 ± 13	144 ± 9
S_{53}-B_{300}	50	214 (0.016)	194 (0.094)	174 ± 23	
S_{32}-B_{500}	33	171 (0.016)	153 (0.053)	112 ± 11	144 ± 6
S_{32}-B_{1000}	33	180 (0.024)	135 (0.035)	115 ± 9	141 ± 11

[a] All conversions were determined to be >99% *via* gravimetry thus the target composition is assumed to be the actual obtained copolymer composition.

[b] DLS analysis using water as dispersant. DLS polydispersity index vales are indicated in brackets.

[c] DLS analysis using ethanol/water mixtures corresponding to the synthetic conditions. DLS polydispersity index vales are indicated in brackets.

[d] Mean TEM particle diameters were calculated by analysing 200 particles using ImageJ software.

[e] SAXS diameters were calculated using $D_{SAXS} = 2R_{core} + 4R_g$.

Table S3 Summary of viscosity, refractive index, and dielectric constant values of methanol/water mixtures at 25 °C for DLS hydrodynamic diameter calculations. All parameters were obtained by fitting literature data.[4-6]

Mixture type	Alcohol content / % w/w	Viscosity / cp	Refractive index	Dielectric constant
Methanol/water	20	1.394	1.337	69.21
Methanol/water	33	1.565	1.339	62.82
Methanol/water	50	1.524	1.340	54.78
Methanol/water	67	1.269	1.339	46.71
Methanol/water	80	0.994	1.336	40.24
Ethanol/water	20	1.808	1.344	67.01
Ethanol/water	33	2.257	1.351	59.06
Ethanol/water	50	2.386	1.357	49.15

Table S4 Summary of fitting parameters used for modelling SAXS data obtained for $PKSPMA_x$-$PBzMA_y$ nanoparticles. SAXS data were fit using a two-population spherical micelles[2] plus Gaussian polymer chains[3] model.

X-ray scattering length density (ξ) of polymers[a] / x 10^{10} cm^{-2}		
PKSPMA		11.69
PBzMA		10.71
X-ray scattering length density (ξ) of alcohol/water mixtures[a]		
Mixture type	**Alcohol content / %**	**ξ / x 10^{10} cm^{-2}**
Ethanol/water	33	8.80
	50	8.49
Methanol/water	20	9.05
	33	8.80
	50	8.49
	67	8.17
Calculated volume of polymer chains		
Polymer Chain	**DP**	**V / $Å^3$**
PKSPMA	32	8470
	53	14029
PBzMA (V_{co})	100	24819
	300	74456
	500	124093
	700	173730
	1000	248185

[a] X-ray scattering length densities were calculated using programming tools within Irena SAS macros for Igor Pro.[7] Density values used in these calculations were taken as ρ_{PKSPMA} = 1.300 g cm^{-3}, ρ_{PBzMA} = 1.179 g cm^{-3}, $\rho_{Ethanol}$ = 0.789 g cm^{-3}, $\rho_{Methanol}$ = 0.792 g cm^{-3}, ρ_{Water} = 1.000 g cm^{-3}.

Notes and references

1. M. Semsarilar, V. Ladmiral, A. Blanazs and S. Armes, *Langmuir*, 2011, **28**, 914-922.
2. J. S. Pedersen, *J. Appl. Crystallogr.*, 2000, **33**, 637-640.
3. B. Akpinar, L. A. Fielding, V. J. Cunningham, Y. Ning, O. O. Mykhaylyk, P. W. Fowler and S. P. Armes, *Macromolecules*, 2016, **49**, 5160-5171.
4. J. V. Herráez and R. Belda, *J. Solution Chem.*, 2006, **35**, 1315-1328.
5. E. J. Wensink, A. C. Hoffmann, P. J. van Maaren and D. van der Spoel, *The Journal of chemical physics*, 2003, **119**, 7308-7317.
6. G. Akerlof, *J. Am. Chem. Soc.*, 1932, **54**, 4125-4139.
7. J. Ilavsky and P. R. Jemian, *J. Appl. Crystallogr.*, 2009, **42**, 347-353.