

Supporting Information

Next Generation Strategy for Tuning the Thermoresponsive Properties of Micellar and Hydrogel Drug Delivery Vehicles Using Ionic Liquids

Talia A. Shmool,^{‡a} Anna P. Constantinou,^{‡b} Andreas Jirkas,^a Chen Zhao,^b Theoni K. Georgiou,^b Jason P. Hallett^{a,*}

^a Department of Chemical Engineering, Imperial College London, South Kensington Campus, London SW7 2AZ, UK

^b Department of Materials, Imperial College London, South Kensington, London SW7 2AZ, UK
***E-mail:** j.hallett@imperial.ac.uk **Tel:** +44 (0)20 7594 5388

[‡] These authors contributed equally to this work

Ultraviolet-visible spectroscopy

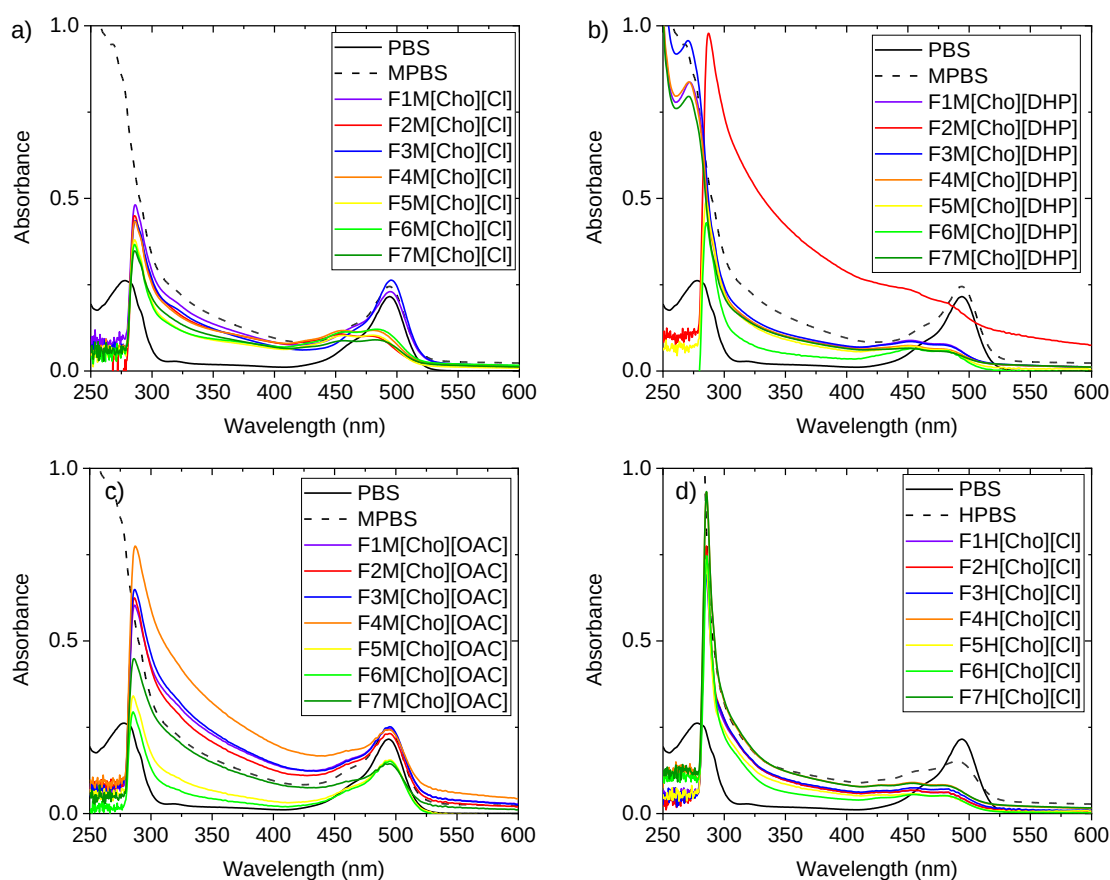


Figure S1. Absorbance spectra of FITC-IgG in micellar-IL formulations (2 w/w% OBDOEGMA300₂₀-*b*-BuMA₂₂-*b*-DEGMA₁₁ (OBD)) a) micellar-[Cho][Cl], b) micellar-[Cho][DHP], and c) micellar-[Cho][OAC] formulations. d) Absorbance spectra of FITC-IgG in hydrogel-IL formulations (20 w/w% OBD). Measurements were recorded at 25 °C, from 800 to 250 nm, at 0.5 nm intervals. In all spectra, the absorbance of the respective controls, FITC-IgG in micellar-PBS (MPBS) and FITC-IgG in hydrogel-PBS (HPBS) is shown by a black dashed line. Each spectrum also includes the absorbance of FITC-IgG in PBS represented by a solid black line.

Zeta potential and pH measurements

Table S1. Mean zeta-potential for FITC-IgG in micellar-IL formulations (2 w/w% OBD), hydrogel-IL (20 w/w% OBD), and controls of micellar-PBS (MPBS) and hydrogel-PBS (HPBS) formulations, with $\pm$ standard deviation, $n = 3$. Measured pH values for each system prior to adjustment with histidine/HCl buffer to achieve pH 6.5. Measured values for FITC-IgG and IgG from human serum in PBS also included.

Formulation	Mean ζ -potential (mV)	pH $\pm$ 0.5
MPBS	-1.53 ± 0.06	7.2
F1M[Cho][Cl]	-0.27 ± 0.06	8.9
F2M[Cho][Cl]	-0.53 ± 0.06	6.5
F3M[Cho][Cl]	-0.3 ± 0.0	9.3
F4M[Cho][Cl]	-0.17 ± 0.06	6.8
F5M[Cho][Cl]	-0.23 ± 0.06	6.6
F6M[Cho][Cl]	-0.17 ± 0.06	6.3
F7M[Cho][Cl]	-0.13 ± 0.06	6.1
F1M[Cho][DHP]	-4.97 ± 0.06	6.2
F2M[Cho][DHP]	-4.8 ± 0.3	4.9
F3M[Cho][DHP]	-4.7 ± 0.2	6.2
F4M[Cho][DHP]	-3.6 ± 0.1	5.2
F5M[Cho][DHP]	-4.3 ± 0.2	5.0
F6M[Cho][DHP]	-4.5 ± 0.3	4.6
F7M[Cho][DHP]	-4.1 ± 0.1	4.5
F1M[Cho][OAC]	-3.9 ± 0.3	9.3
F2M[Cho][OAC]	-4.60 ± 0.06	6.6
F3M[Cho][OAC]	-4.6 ± 0.3	9.1
F4M[Cho][OAC]	-3.6 ± 0.1	6.4
F5M[Cho][OAC]	-3.3 ± 0.3	6.4
F6M[Cho][OAC]	-3.4 ± 0.3	6.4
F7M[Cho][OAC]	-3.3 ± 0.2	6.4
HPBS	-0.13 ± 0.06	6.3
F1H[Cho][Cl]	-2.8 ± 0.06	5.2
F2H[Cho][Cl]	-0.93 ± 0.06	5.0
F3H[Cho][Cl]	-0.73 ± 0.06	6.1
F4H[Cho][Cl]	-0.17 ± 0.06	6.7
F5H[Cho][Cl]	-0.53 ± 0.06	5.1
F6H[Cho][Cl]	-0.13 ± 0.06	4.9
F7H[Cho][Cl]	-0.3 ± 0.0	6.7
F1H[Cho][DHP]	-5.0 ± 0.06	5.3
F2H[Cho][DHP]	-4.3 ± 0.2	5.0
F3H[Cho][DHP]	-4.73 ± 0.06	5.1
F4H[Cho][DHP]	-3.5 ± 0.1	5.1
F5H[Cho][DHP]	-4.5 ± 0.06	5.1
F6H[Cho][DHP]	-4.1 ± 0.1	4.8
F7H[Cho][DHP]	-3.6 ± 0.01	6.5

F1H[Cho][OAC]	-2.1 ± 0.03	6.0
F2H[Cho][OAC]	-3.0 ± 0.06	5.7
F3H[Cho][OAC]	-2.8 ± 0.2	6.1
F4H[Cho][OAC]	-3.4 ± 0.2	5.1
F5H[Cho][OAC]	-2.0 ± 0.2	5.1
F6H[Cho][OAC]	-1.5 ± 0.06	6.0
F7H[Cho][OAC]	-0.23 ± 0.01	5.3
IgG PBS	-1.3 ± 0.1	7.2
FITC-IgG PBS	-0.26 ± 0.06	7.3

Dynamic light scattering measurements

Table S2. Comparison of the mean hydrodynamic diameter and polydispersity index (PDI) values for FITC-IgG and IgG (immunoglobulin G) from human serum in PBS alone and in micellar-IL (2 w/w% OBD) and hydrogel-IL (20 w/w% OBD) formulations, with $\pm$ standard deviation, n = 3.

Formulation	Size (nm)		PDI	
	IgG	FITC-IgG	IgG	FITC-IgG
PBS	13.2 ± 0.1	12.8 ± 0.07	0.14 ± 0.01	0.11 ± 0.02
F7M[Cho][Cl]	22.5 ± 0.5	22.1 ± 0.6	0.39 ± 0.01	0.40 ± 0.01
F6M[Cho][OAC]	23.5 ± 0.4	23.8 ± 0.4	0.40 ± 0.01	0.42 ± 0.02
F4M[Cho][DHP]	21.6 ± 0.7	24.4 ± 0.06	0.39 ± 0.01	0.42 ± 0.06
F7H[Cho][Cl]	38.5 ± 0.6	40.5 ± 0.4	0.28 ± 0.05	0.19 ± 0.03

Table S3. Mean hydrodynamic diameter and PDI values for FITC-IgG in micellar-IL (2 w/w% OBD), and hydrogel-IL (20 w/w% OBD) formulations, and controls of micellar-PBS (MPBS) and hydrogel-PBS (HPBS) formulations, with $\pm$ standard deviation, n = 3, fresh and following 4 months of storage at 4 °C.

Formulation	Size (nm)	PDI	Size (nm)	PDI
	Fresh		Following Storage	
MPBS	50.3 ± 0.4	0.38 ± 0.05	71.2 ± 0.4	0.51 ± 0.01
F1M[Cho][Cl]	30.3 ± 0.3	0.22 ± 0.01	30.9 ± 0.3	0.226 ± 0.005
F2M[Cho][Cl]	30.6 ± 0.2	0.22 ± 0.01	31.6 ± 0.4	0.243 ± 0.008
F3M[Cho][Cl]	30.5 ± 0.3	0.197 ± 0.003	30.2 ± 0.2	0.22 ± 0.01
F4M[Cho][Cl]	20.6 ± 0.6	0.394 ± 0.006	21.3 ± 0.4	0.392 ± 0.007
F5M[Cho][Cl]	28.0 ± 0.1	0.15 ± 0.01	28.3 ± 0.7	0.17 ± 0.01
F6M[Cho][Cl]	23.1 ± 0.6	0.390 ± 0.005	23.6 ± 0.8	0.42 ± 0.02
F7M[Cho][Cl]	22.1 ± 0.6	0.40 ± 0.01	23.0 ± 0.5	0.44 ± 0.08
F1M[Cho][DHP]	31.9 ± 0.9	0.23 ± 0.02	35.1 ± 0.8	0.24 ± 0.02
F2M[Cho][DHP]	32.4 ± 0.9	0.23 ± 0.02	36.4 ± 0.7	0.20 ± 0.04
F3M[Cho][DHP]	31.1 ± 0.7	0.19 ± 0.02	33.7 ± 0.6	0.24 ± 0.008
F4M[Cho][DHP]	24.4 ± 0.06	0.42 ± 0.06	27.7 ± 0.4	0.63 ± 0.03
F5M[Cho][DHP]	30.6 ± 0.7	0.21 ± 0.01	33.8 ± 0.6	0.23 ± 0.04
F6M[Cho][DHP]	30.7 ± 0.8	0.22 ± 0.02	33.8 ± 0.8	0.22 ± 0.03
F7M[Cho][DHP]	29.6 ± 0.5	0.20 ± 0.01	31.8 ± 0.5	0.21 ± 0.02
F1M[Cho][OAC]	32.3 ± 0.4	0.25 ± 0.03	33.9 ± 0.2	0.26 ± 0.02
F2M[Cho][OAC]	30.2 ± 0.6	0.20 ± 0.01	32.0 ± 2	0.25 ± 0.04
F3M[Cho][OAC]	30.9 ± 0.4	0.22 ± 0.01	32.5 ± 0.4	0.23 ± 0.005
F4M[Cho][OAC]	28.0 ± 2	0.28 ± 0.09	31.6 ± 0.6	0.23 ± 0.02
F5M[Cho][OAC]	30.9 ± 0.8	0.17 ± 0.04	32.7 ± 0.3	0.23 ± 0.02
F6M[Cho][OAC]	23.8 ± 0.4	0.42 ± 0.02	25.6 ± 0.2	0.42 ± 0.02
F7M[Cho][OAC]	24.6 ± 0.4	0.43 ± 0.03	25.5 ± 0.6	0.47 ± 0.08
HPBS	67.4 ± 0.3	0.22 ± 0.01	92.4 ± 0.3	0.29 ± 0.004
F1H[Cho][Cl]	46.5 ± 0.2	0.27 ± 0.05	47.2 ± 0.6	0.29 ± 0.03
F2H[Cho][Cl]	45.7 ± 0.1	0.26 ± 0.02	46.5 ± 0.2	0.27 ± 0.05
F3H[Cho][Cl]	45.7 ± 0.06	0.28 ± 0.03	45.7 ± 0.3	0.29 ± 0.03
F4H[Cho][Cl]	41.4 ± 0.3	0.26 ± 0.008	41.5 ± 0.2	0.24 ± 0.006
F5H[Cho][Cl]	41.5 ± 0.2	0.24 ± 0.006	42.3 ± 0.5	0.28 ± 0.01
F6H[Cho][Cl]	40.2 ± 0.2	0.27 ± 0.04	41.5 ± 0.4	0.20 ± 0.03
F7H[Cho][Cl]	40.5 ± 0.4	0.19 ± 0.03	40.5 ± 0.5	0.24 ± 0.02
F1H[Cho][DHP]	44.2 ± 0.8	0.31 ± 0.04	49.2 ± 0.2	0.32 ± 0.08
F2H[Cho][DHP]	45.8 ± 0.5	0.24 ± 0.05	49.1 ± 0.6	0.31 ± 0.08
F3H[Cho][DHP]	47.8 ± 0.24	0.35 ± 0.1	48.72 ± 0.3	0.30 ± 0.05
F4H[Cho][DHP]	41.5 ± 0.3	0.24 ± 0.006	43.7 ± 0.5	0.25 ± 0.012
F5H[Cho][DHP]	41.2 ± 0.2	0.24 ± 0.028	43.4 ± 0.2	0.23 ± 0.008
F6H[Cho][DHP]	41.5 ± 0.3	0.25 ± 0.03	43.7 ± 0.6	0.24 ± 0.01
F7H[Cho][DHP]	40.9 ± 0.1	0.25 ± 0.02	43.4 ± 0.2	0.24 ± 0.02
F1H[Cho][OAC]	45.1 ± 0.4	0.27 ± 0.03	49.2 ± 0.4	0.29 ± 0.04
F2H[Cho][OAC]	44.5 ± 0.3	0.21 ± 0.002	46.1 ± 0.8	0.23 ± 0.01
F3H[Cho][OAC]	44.9 ± 0.8	0.27 ± 0.02	47.7 ± 0.6	0.32 ± 0.06

F4H[Cho][OAC]	40.7 ± 0.3	0.23 ± 0.004	42.8 ± 0.6	0.22 ± 0.018
F5H[Cho][OAC]	42.5 ± 05	0.21 ± 0.005	44.9 ± 0.8	0.27 ± 0.02
F6H[Cho][OAC]	42.8 ± 0.6	0.22 ± 0.02	45.8 ± 0.2	0.28 ± 0.03
F7H[Cho][OAC]	40.5 ± 0.2	0.21 ± 0.04	42.3 ± 0.7	0.24 ± 0.07

Table S4. Mean hydrodynamic diameter and PDI values for IgG from human serum in PBS and FITC-IgG in PBS, micellar (2 w/w% OBD), and hydrogel (20 w/w% OBD) formulations in the absence of IL, with ± standard deviation, n = 3, fresh and following 4 months of storage at 4 °C.

Formulation	Size (nm)	PDI	Size (nm)	PDI
	Fresh		Following Storage	
IgG PBS	13.2 ± 0.1	0.14 ± 0.01	53.0 ± 3	0.45 ± 0.03
FITC-IgG PBS	12.8 ± 0.07	0.11 ± 0.02	52.7 ± 0.07	0.35 ± 0.04
F1M	44.3 ± 0.7	0.43 ± 0.05	53.3 ± 0.5	0.39 ± 0.02
F2M	39.8 ± 4	0.28 ± 0.07	51.8 ± 1	0.25 ± 0.02
F3M	45.0 ± 1	0.31 ± 0.05	49.7 ± 0.1	0.21 ± 0.02
F4M	34.0 ± 1	0.34 ± 0.03	47.0 ± 1	0.33 ± 0.03
F5M	36.9 ± 0.4	0.29 ± 0.02	47.4 ± 0.3	0.43 ± 0.01
F6M	37.0 ± 1	0.24 ± 0.006	48.4 ± 0.7	0.21 ± 0.009
F7M	34.9 ± 0.4	0.22 ± 0.004	38.6 ± 0.6	0.28 ± 0.05
F1H	56.5 ± 0.7	0.39 ± 0.05	76.0 ± 0.07	0.52 ± 0.008
F2H	52.0 ± 1	0.25 ± 0.02	80.0 ± 1	0.53 ± 0.01
F3H	50.8 ± 0.7	0.24 ± 0.004	75.9 ± 0.8	0.43 ± 0.01
F4H	56.0 ± 2	0.26 ± 0.03	66.0 ± 3	0.44 ± 0.03
F5H	55.8 ± 0.4	0.43 ± 0.02	76.00 ± 0.07	0.52 ± 0.008
F6H	53.0 ± 3	0.45 ± 0.03	66.0 ± 1	0.47 ± 0.04
F7H	52.6 ± 0.6	0.34 ± 0.03	68.0 ± 1	0.41 ± 0.05

Table S5. Mean hydrodynamic diameter and PDI values for FITC-IgG in micellar-IL (2 w/w% OBD) and hydrogel-IL (20 w/w% OBD) formulations, fresh and following heating to 60 °C and 50 °C, respectively, at one-degree intervals, with $\pm$ standard deviation, n = 3. Controls of micellar-PBS (MPBS) and hydrogel-PBS (HPBS), are included.

Formulation	Size (nm)	PDI	Size (nm)	PDI
	Fresh		Following Heating	
F4M[Cho][Cl]	20.6 $\pm$ 0.6	0.39 $\pm$ 0.006	23 $\pm$ 0.7	0.40 $\pm$ 0.01
F4M[Cho][OAC]	28.0 $\pm$ 2	0.28 $\pm$ 0.09	31.6 $\pm$ 0.6	0.22 $\pm$ 0.01
F7M[Cho][OAC]	24.6 $\pm$ 0.4	0.43 $\pm$ 0.03	24.7 $\pm$ 0.8	0.44 $\pm$ 0.01
F7M[Cho][Cl]	22.1 $\pm$ 0.6	0.40 $\pm$ 0.01	25.7 $\pm$ 2	0.43 $\pm$ 0.02
MPBS	50.3 $\pm$ 0.4	0.38 $\pm$ 0.05	70.9 $\pm$ 2.5	0.72 $\pm$ 0.02
F7H[Cho][Cl]	40.5 $\pm$ 0.4	0.19 $\pm$ 0.03	41.2 $\pm$ 2.1	0.28 $\pm$ 0.1
F4H[Cho][Cl]	41.4 $\pm$ 0.3	0.26 $\pm$ 0.008	41.5 $\pm$ 2.1	0.25 $\pm$ 0.01
F3H[Cho][Cl]	45.7 $\pm$ 0.06	0.28 $\pm$ 0.03	48.9 $\pm$ 2.1	0.32 $\pm$ 0.03
HPBS	67.4 $\pm$ 0.3	0.22 $\pm$ 0.01	80.9 $\pm$ 0.74	0.53 $\pm$ 0.01