Supporting information

Graft Copolymers with Tunable Amphiphilicity tailored for Efficient Dual Drug Delivery via Encapsulation and pH-sensitive Drug Conjugation

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Abstract

Polymer-based drug delivery systems may significantly improve cancer therapy. We developed amphiphilic poly(ε-caprolactone)-*graft*-(poly-*N*-(2-hydroxypropyl) methacrylamide) copolymers (PCL-*graft*-pHPMA) with tunable amphiphilicity intended for efficient dual delivery via simultaneous encapsulation of hydrophobic drug, Bcl-2 inhibitor ABT-199, and pH-sensitive conjugation of other chemotherapeutics, doxorubicin, to desired sites, e.g. tumors. Using controlled RAFT polymerization and click chemistry well-defined PCL-*graft*-pHPMA of diverse M_w and physical properties were prepared. By simple dissolution they self-assembled into highly stable micelles with $D_h \approx 25$ nm and low critical micelle concentration (around 5 μg mL^{-1}). The total drug payload reached 17 wt % while maintaining system solubility. The micelles exhibited long-term stability in buffers, while they were cleaved in the presence of lipase, thus proving degradation and drug release after uptake to lysosomes of cancer cells with minimal drug leakage during blood circulation. PCL-*graft*-pHPMA micelles may serve as a long-circulating drug depo for effective dual therapy of diverse malignancies.

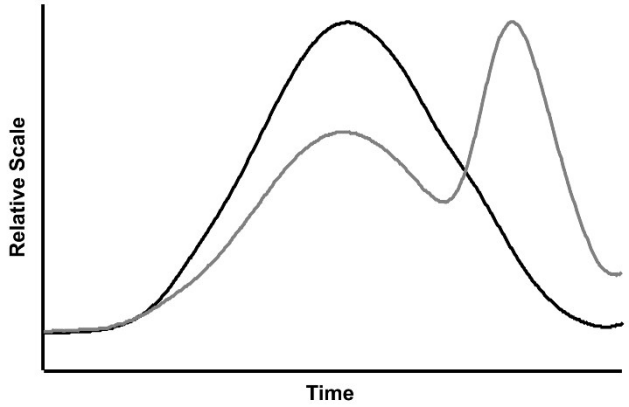
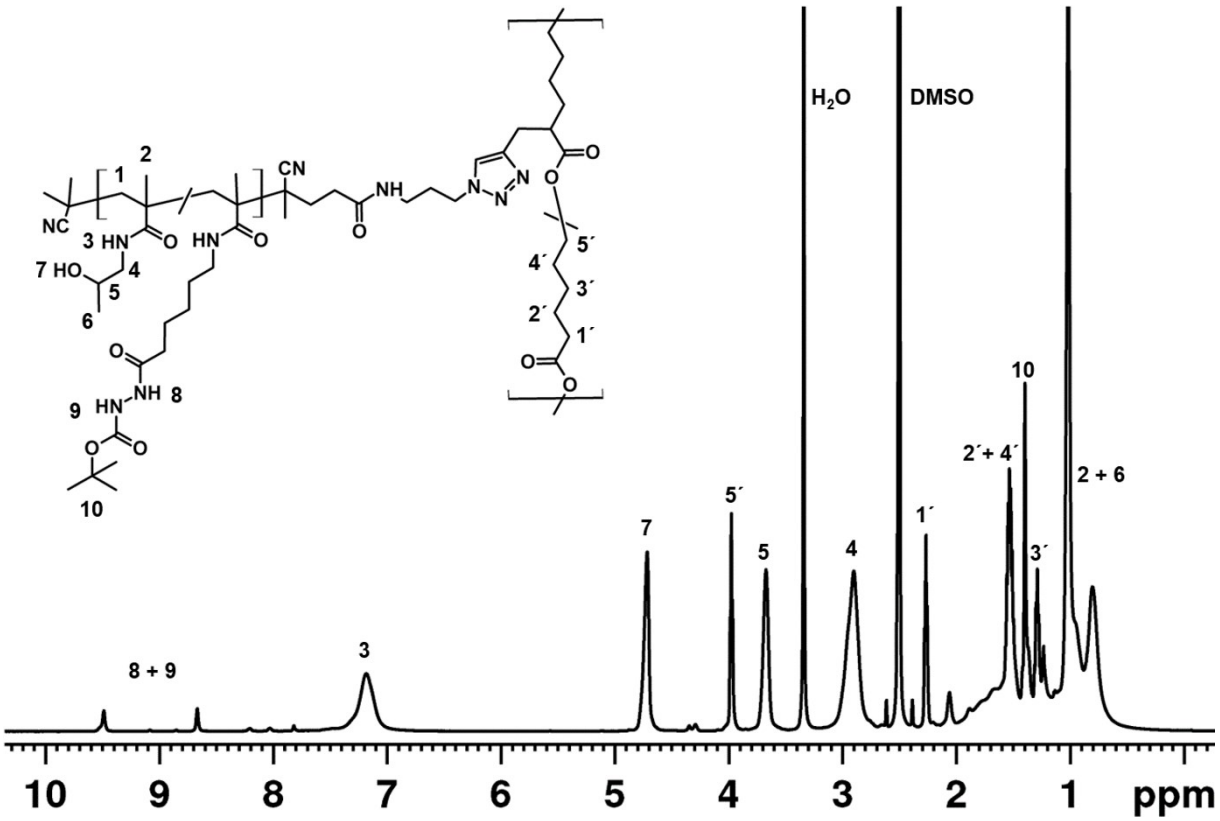


Figure S1. PCL-*graft*-pHPMA (**G1**) after synthesis (grey curve) and after removal of unreacted linear polymer (black curve); RI detection.

a)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NC
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HN
NH
7 HO
4
5
6
5´
4´
3´
2´
1´
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9 HN
NH 8
10
7
5´
5
4
1´
10
2´+ 4´
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2 + 6
8 + 9
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5
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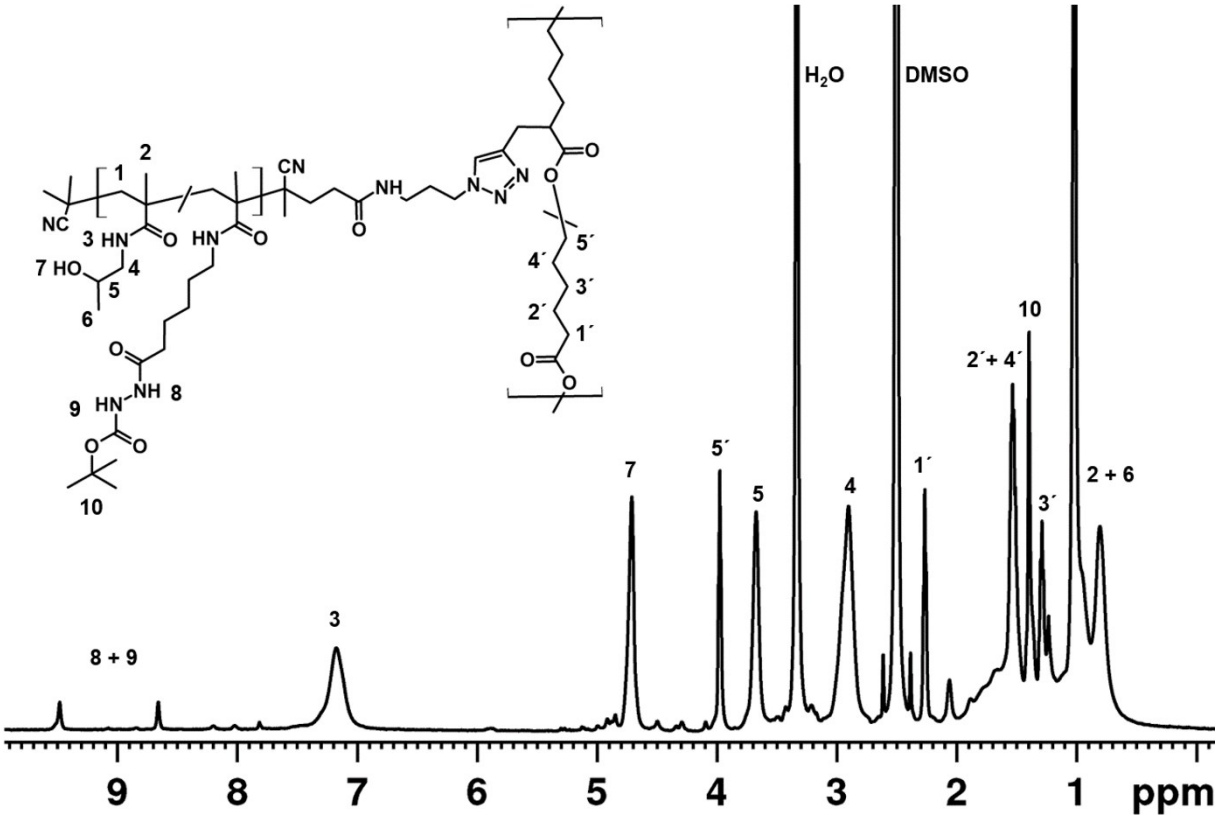
2
1
ppm

b)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7 HO
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1´
O
9 HN
NH 8
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7
5´
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1´
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2´+ 4´
3´
2 + 6
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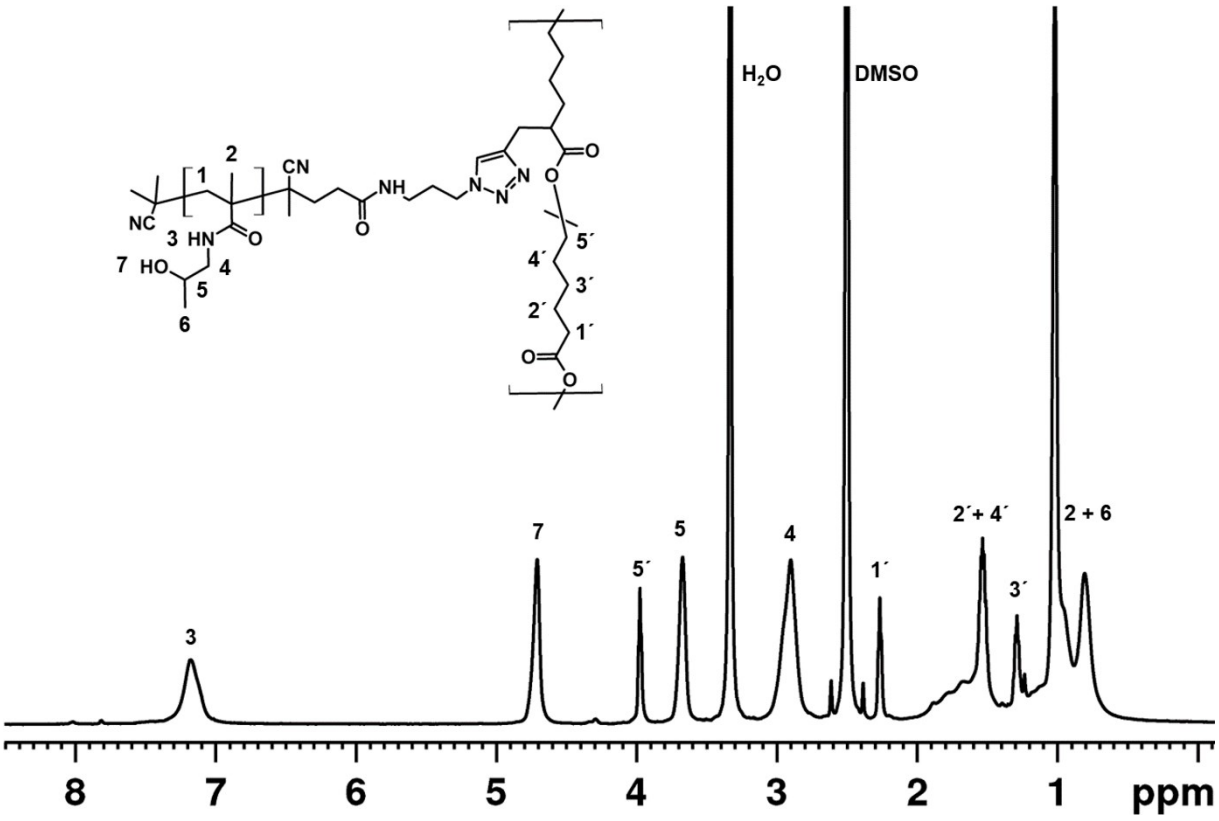
2
1
ppm

c)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DMSO
2´+ 4´
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3´
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8
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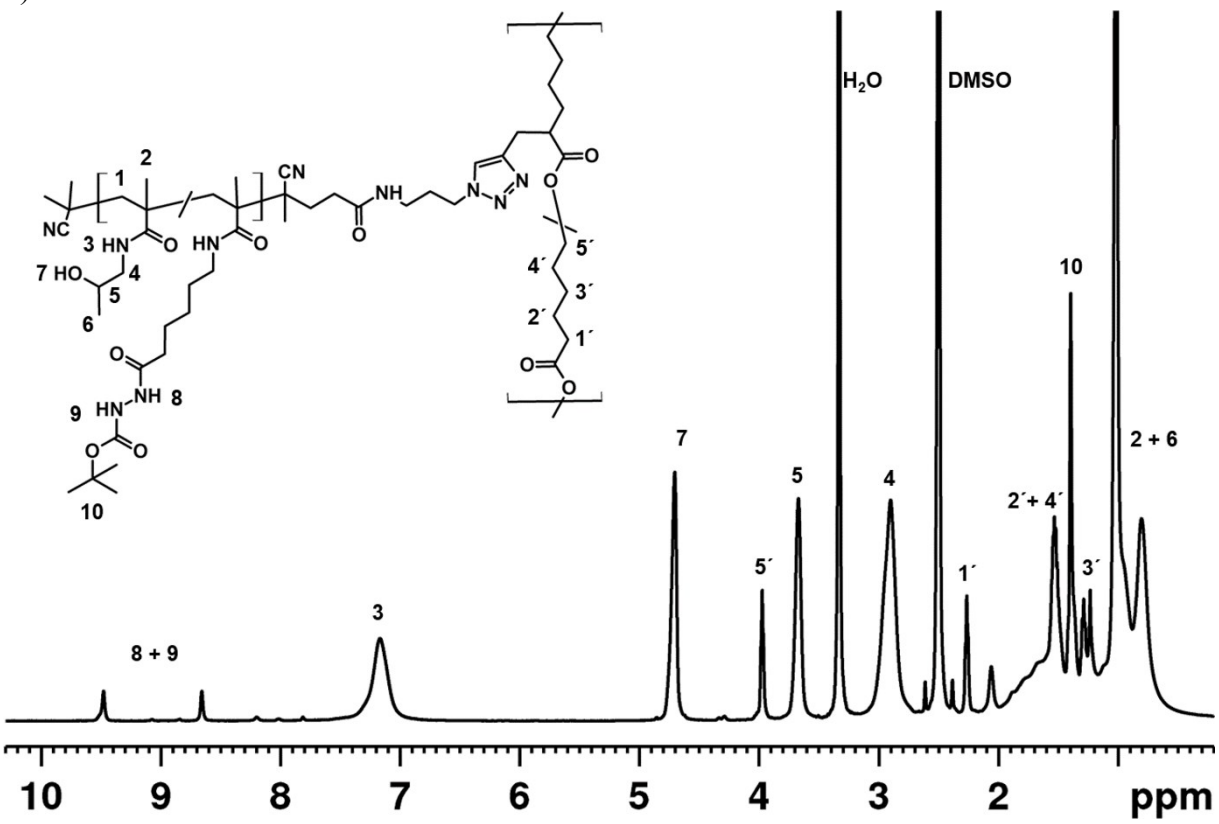
2
1
ppm

d)


H2O
DMSO
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5
4
2´+ 4´
2 + 6
5´
1´
3´
3
8 + 9
10
9
8
7
6
5
4
3
2
ppm

e)

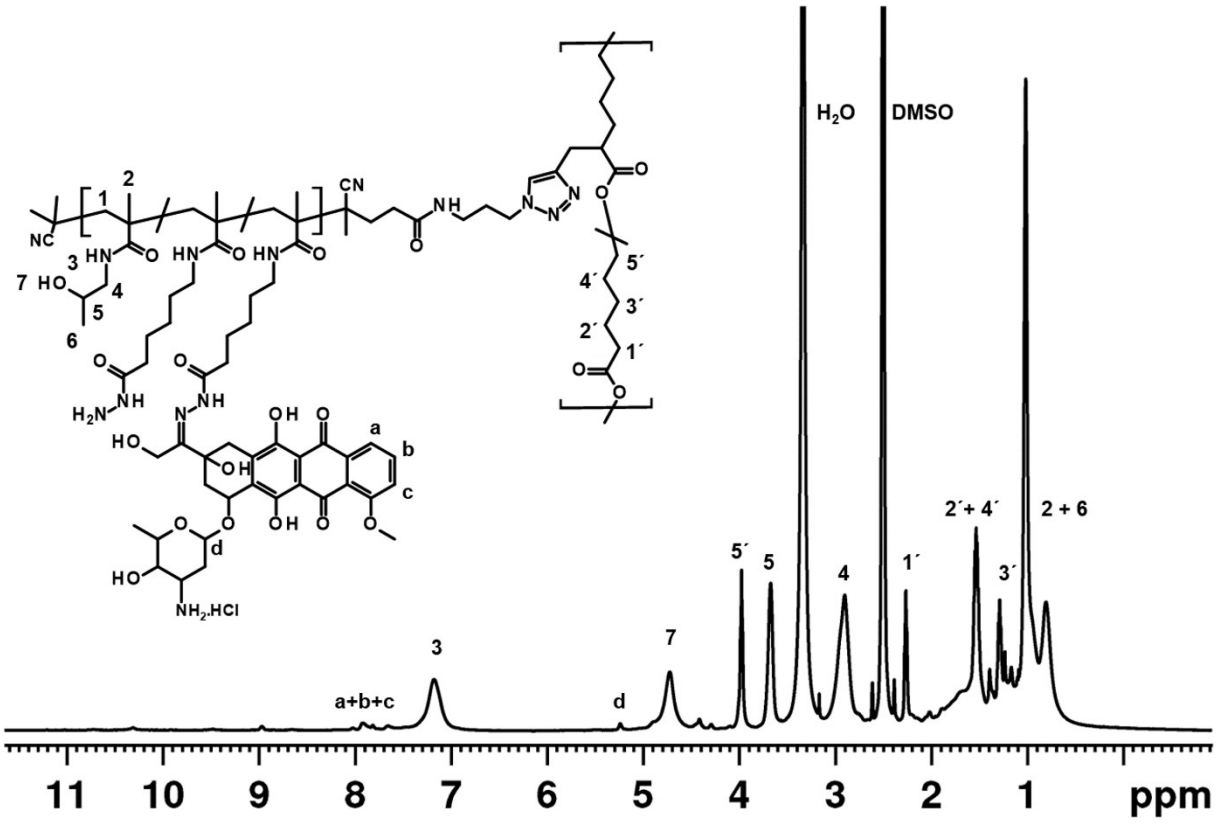

Figure S2. ^{1}H NMR characterization of graft PCL-*graft*-pHPMA a) **G1** b) **G1a** c) **G2** d) **G3** e) **G1a DOX conjugate**

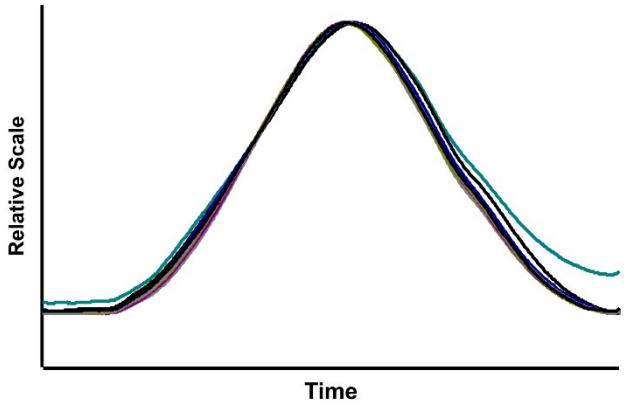

Figure S3. Stability of PCL-*graft*-pHPMA (**G2**) in phosphate buffer (pH 7.4, 37 °C), RI detection; 0 h, 24 h, 48 h, 96 h, 168h, 10 d, 15 d, 21 d, 36 d.

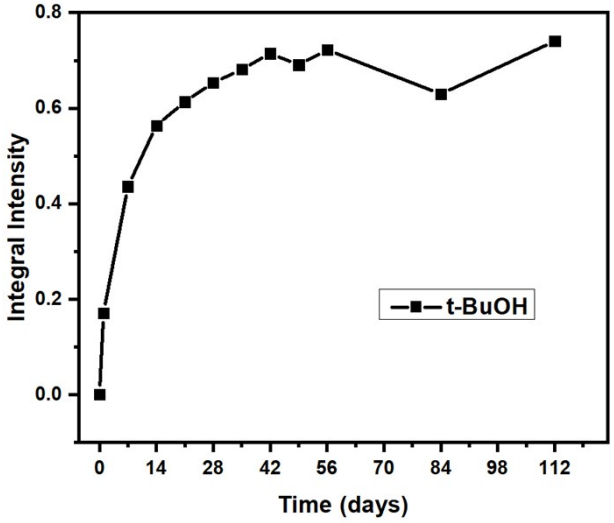

Figure S4. Kinetics of deprotection rate of Boc-protected hydrazide group. On the graph is shown integral intensity of signal related to *t*-BuOH ("**k'**" in Figure 4a in the main text). The signal of CH group of pHPMA ("**d**") was used as internal standard for integration with set value of integral intensity as 1.