Main-Chain Polyacetal Conjugates with HIF-1 Inhibitors: Temperature-Responsive, pH-degradable Drug Delivery Vehicles

Sanjoy Samanta†, Chathuranga C. De Silva†, Porakrit Leophairatana, and Jeffrey T. Koberstein*

Department of Chemical Engineering, Columbia University, 500 West 120th Street, New York, New York 10027, United States
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Figure S.1: Polymerization kinetics of (a) PA_{2223} and main-chain PA-drug conjugates prepared from (b) MHQ (c) BIS-A and (d) DES with different drug loading: 5% (circle), 10% (triangle), 15% (square) and 20% (inverted triangle).
Figure S.2: $^1$H NMR (CDCl$_3$, 400 MHz) characterization of polyacetal-based polymer therapeutics: (a) PA$_{222}$$D_3$10V17.6 (entry 1, Table 1) (b) PA$_{222}$$D_3$10V15.1 (entry 6, Table 1) and (c) PA$_{222}$$D_3$10V12.9 (entry 3, Table 1). In the $^1$H NMR spectrum, “*” comes from the presence of trace amount of ethyl acetate, “s*” from the moisture in CDCl$_3$ and “I*” is unknown to us or from impurity.
Table S.1: Characteristics of PA-DES Conjugates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sample</th>
<th>Drug-diol (Dₜ)</th>
<th>% of Dₓ (p)</th>
<th>% of H₂₅</th>
<th>$M_n$thor (kDa)ᵃ</th>
<th>$M_n$exp (kDa)ᵇ</th>
<th>Actual % of incorporated DESᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.2</td>
<td>PA₃₂₂₅D₂₆SV14.1</td>
<td>DES</td>
<td>5%</td>
<td>95%</td>
<td>8.20</td>
<td>14.14</td>
<td>2.81</td>
</tr>
<tr>
<td>S.3</td>
<td>PA₃₂₂₅D₁₅₁₀V12.9</td>
<td>DES</td>
<td>10%</td>
<td>90%</td>
<td>8.28</td>
<td>12.85</td>
<td>6.26</td>
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<tr>
<td>S.4</td>
<td>PA₃₂₂₅D₁₅₁₅V9.3</td>
<td>DES</td>
<td>15%</td>
<td>85%</td>
<td>8.36</td>
<td>9.26</td>
<td>12.84</td>
</tr>
<tr>
<td>S.5</td>
<td>PA₃₂₂₅D₁₂₂₀V6.9</td>
<td>DES</td>
<td>20%</td>
<td>80%</td>
<td>8.43</td>
<td>6.94</td>
<td>12.77</td>
</tr>
</tbody>
</table>

ᵃassuming 100% conversion using the Carothers equation.

ᵇcalculated GPC area mass fraction of DES conjugated onto the main chain.
Figure S.3: Temperature dependent dynamic light scattering study of PA1223-D20V6.9 (heating@1 °C/min) in aqueous PBS (0.1 mM). Polymer concentration = 5g.L⁻¹.
Figure S.4: Temperature induced phase transitions (heating only) for main-chain PA-drug conjugates prepared from (a) MHQ (5, 10, 15, 20, 25, 30 and 40% from right to left), (b) BIS-A (5, 7.5, 10, 15, 20 and 30% from right to left) and (c) DES (5, 10, 15, 20, 30 and 40% from right to left) with increasing drug loading in aqueous PBS (0.1 mM).
**Figure S.5:** GPC analysis of DES content for a PA$_{222}$D$_{10}$V12.9 reaction time (20h). Mass fraction = (area of free DES peak)/(area of main peak)x(total reactant DES added).
Figure S.6: (a) Comparison of degradation rates of PA_{2223D15V} in pH 5 phosphate buffer at 37°C & 42°C, (b) comparison of DES drug release rates from PA_{2223D15V} in pH 5 phosphate buffer at 37°C & 42°C