PH-RESPONSITIVE POLY(BETA-AMINO ESTER) POLYMERS WITH TUNABLE TRANSITION POINT

Zhaohui Tang, Wantong Song, Xuesi Chen.
Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences.
Changchun 130022, China

Statement of Purpose: In recent years, drug delivery system (DDS) has gotten growing attention because of the need to maximize therapeutic activity while minimizing negative side effects. The pH of normal physiological conditions, extracellular fluit of human tumors, early endosome, late endosome, and lysosome is 7.4, 6.5-7.2, 6.0-6.5, 5.0-6.0, 4.5-5.0, respectively.[1] Therefore, the DDS that facilitate triggered release in response to pH stimuli is favarable because it has the potential to deliver drug to targeting compartment according to the pH difference. Biodegradable polymers are usually used as drug carriers materials in DDS. Poly(β-amino ester) (PBAE) is a kind of pH-responsive hydrolytically biodegradable polymer. The solubility of PBAE is directly influenced by solution pH. Consequently, pH-responsive DDS can be obtained using PBAE as carrier material. Because different compartment has different pH in human body, the tunability of pH transition range of carrier materials is important. Therefore, new biodegradable polymers with tunable pH transition point are desirable. Herein, we present a family of pH-responsive PBAEs prepared from primary amine and diacrylate.

Methods: n-Propylamine (Pro), n-pentylamine(Pen), n-octylamine (Oct) and butane-1,4-diol diacrylate (But) were purchased from Sigma Chemical Co. and used as received. PBAEs were synthesized via a Michael-type step polymerization using primary amine and But. The reaction is shown in Scheme 1. The average molecular weights (M_n) and polydispersitys (PDI) of the polymers were measured by a gel permeation chromatography (GPC) apparatus using dichloromethane (DCM) as the eluent at a flow rate of 1mL/min. Polystyrene standards were used to determine the molecular weights. The pKb values of the polymers were measured by the titration method. The soluble-insoluble behavior of the pH-sensitive PBAE was investigated by an ultraviolet (UV) spectrometer in a buffer solution containing 0.1 N borax and potassium phosphate.

Results: ^{1}H NMR spectra of the obtained polymers confirmed the formation of poly(β-amino ester)s. The M_n, PDI, pKb, pH transition point of the obtained PBAEs are shown in Table 1. The M_n of the Pro-But, Pen-But, Oct-But is 2.6, 2.3, 3.8 × 10^3, respectively. The PDI is the range of 1.3-1.8. Compared with the PBAEs prepared from bis(secondary amine) monomers and diacrylates , the M_n is relatively low and the PDI is relatively narrow.[2] The pKb of the Pro-But, Pen-But, Oct-But is 6.35, 5.38, and 3.45, respectively (Fig.1). They are close to the soluble-insoluble transition point of the PBAEs, which is 6.42, 5.39, 2.34 for Pro-But, Pen-But, Oct-But, respectively (Fig.2). The soluble-insoluble transition point of the PBAE decreases with the increase of the size of pendant groups.

Scheme 1. Synthesis of Poly(β-amino ester)s.

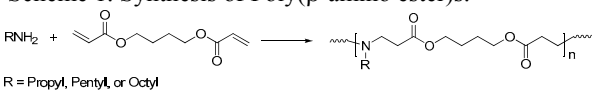

Table 1. PBAE prepared from Pro, Pen, Oct and But.

Sample	$M_n \times 10^{-3}$	PDI	pKb /pH	Transition point/pH
Pro-But	2.6	1.57	6.35	6.42
Pen-But	2.3	1.34	5.38	5.39
Oct-But	3.8	1.73	3.45	2.34

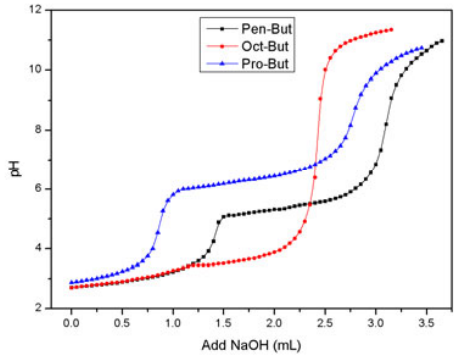

Fig. 1 Acid-base titration profile of PBAEs.

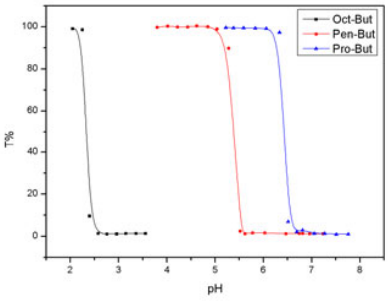

Fig. 2 The UV transmittance of the PBAEs solution.

Conclusions: A comparison of PBAEs bearing hydrophobic pendant groups shows that the soluble-insoluble transition point of pH is highly dependent upon the steric properties of the hydrophobic pendant groups. While the Oct-But has a very low pH transition point, the Pro-But and Pen-But have transition point at pH 6.42 and 5.39, which is fit for the endosome-targeting drug delivery systems.

References:

[1] Bawa P. Biomed Mater. 2009; 4:022001.
[2] Lynn DM. J Am Chem Soc. 2000; 122:10761-10768.