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Betaine ester-shell functionalized hyperbranched polymers for potential antimicrobial usage: Guest loading capability, pH controlled release and adjustable compatibility

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ABSTRACT

Betaine ester-shell functionalized hyperbranched polyethylenimines (BEHPEI) were synthesized by Menschutkin reaction between per-N-methylated polyethylenimine (MeHPEI) and alkyl bromoacetate. BEHPEI could play dual antimicrobial roles that were, the betaine ester-shell acted as contact-based antibacterial polycations and the drug-loaded BEHPEI could controllably release the drugs due to the cleavage of the betaine ester groups under weak alkaline condition. The BEHPEI exhibited high transport capacities that per gram of BEHPEI could encapsulate 0.24–2.67 g of dyes or drugs. The model drug release experiment employing methyl orange (MO) showed that the drug release of MO-loaded BEHPEI complex occurred slowly in weak alkaline solutions and the release rate was controlled by varying pH, while the complex kept very stable under weak acid condition (pH = 3.0–7.0). BEHPEI generated from long chain alkyl bromoacetate was compatible with organic resins implying the possible usage in antimicrobial fibers and coatings. Another BEHPEI obtained from short-chain alkyl bromoacetate was water soluble and maybe used in lotion formula. The hydrolysis of BEHPEI afforded zwitterionic shell.

1. Introduction

Microbial contamination and the associated risk are great challenges towards medical implants [1–4], textiles [5,6], food and water security [7–9] and biosensors [10,11]. Till now, antimicrobial materials employing various protection mechanisms have been developed. Among them, contact-based and release-based antimicrobial materials for killing or inhibiting bacteria have gained significant attention.

One typical contact-based antimicrobial material is polycations which can cause damage to the outer membrane of bacteria by interacting with the anionic lipopolysaccharide. However, many contact-based polycations suffer from low sensitivity towards Gram-negative bacteria [12–16].

Release-based antimicrobial materials have long-term antimicrobial effects because of slow release of drugs such as antibiotics, algaecides, preservatives and silver nanoparticles encapsulated in polymer matrix [17–20]. Controlled release property of this sort of material largely depends on property of matrix and compatibility between matrix and drugs. However, because the majority of antimicrobial drugs are water soluble compounds, low compatibility between low polar organic polymer matrix and high polar drugs leads to low drug-loading capacity and uncontrolled release. To solve this problem, various amphiphilic polymer capsules for drug-loading have been developed to enhance compatibility [21–24].

Physical aggregates of amphiphilic macromolecules with liposome or micelle structures are usually used as drug-delivery systems in the past decades [25]. However, these structures are unstable under environment effects like shear force, temperature and pressure [26]. Then, dendritic polymers possessing stable core–shell structures emerged as novel materials for supramolecular encapsulation [27–30]. Among them, pH-responsive, especially acid-responsive, dendritic polymers are promising due to the potential application in in-vivo cancer therapy (faintly acid environment) [31–34]. Haag et al. [35] reported that HPEI linked with poly (ethylene glycol) shells by imine bonds showed high loading capacities for polar dyes and could rapidly release dye molecules under acidic condition (pH = 5). However, there are occasions where acid stability or alkaline lability is needed. For example,

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weak alkaline environment like seawater and human blood and intestines could call for suitable basic degradability of capsules to release drugs, while weak acidic fresh water demands acid stability.

Antimicrobial materials combining contact-based and released-based mechanisms have been reported in several works [13,36–38]. For example, Sen et al. embedded silver bromide into amphiphilic pyridinium polymer matrix to achieve dual actions [36]. Cohen et al. used layer-by-layer technique to fabricate a coating embedded with silver and cationic nanoparticles [13]. These works focused on fabricating antibacterial coatings, while dual-function drug capsules have never been reported.

In this work, weak base-labile betaine ester-shell was utilized to play a contact killing role [39] and to form a labile core–shell structure for drug loading and release [40]. Both dyes and drugs were employed to study the pH-responsive property by means of UV–Vis spectrometry. Long chain shell could endow dye-loaded BEHPEI good compatibility with organic polymer matrix for likely coating application, while short chain shell make the polymer water soluble for possible antibacterial lotion usage.

2. Experimental part

2.1. Materials

Hyperbranched polyethylenimine (M_w = 25,000 Da (LS), M_n = 10,000 Da (GPC)) was purchased from Sigma–Aldrich. Ethanol, formic acid, formaldehyde, bromoacetyl bromide, dodecanol, allyl alcohol, methyl orange, methyl blue (MB), fluorescein sodium (FS), eosin Y (EY), congo red (CR), methyl violet (MV), calcium hydride and anhydrous magnesium sulfate were obtained from Aladdin Chemical Co. China. Sodium sorbate (SS) and tetracycline (TC) were purchased from Chengdu Ai Keda Chemical Technology Co. Diethyl ether, chloroform, methylene dichloride, N,N-dimethylformamide, N,N-diisopropylethylamine, and sodium hydroxide were from Sinopharm Chemical Reagent Co. Dichloromethane and N,N-diisopropylethylamine were dried over CaH_2 before use. All other reagents were used as received.

2.2. Instruments

^1H and ^{13}C NMR measurements were carried out on an Avance III 400 MHz spectrometer at room temperature. The samples were dissolved in $CDCl_3$ or D_2O. Tetramethylsilane was used as an internal reference. Quantitative ^{13}C spectra were recorded using inverse gated decoupling pulse sequence to avoid any influence of the Nuclear Overhauser effect. UV–Vis spectroscopic analysis was recorded on a Lambda 950 UV–Vis spectrophotometer. FTIR spectrum analysis was carried out on a Nicolet 7600 spectrometer.

2.3. Methods

2.3.1. Synthesis of hyperbranched per-N-methylated polyethylenimine (MeHPEI)

Hyperbranched polyethylenimine (10 g, 0.1 mol) was dissolved in distilled water (75 mL) and charged into a round bottom two-neck flask (500 mL). The flask was equipped with a reflux condenser on top of which an oil bubbler was fitted. Excess formic acid (245 g, 5.3 mol) and formalin (36 g, 1.2 mol) were successively added into the flask. After being purged with N_2 gas, the reaction mixture was kept at 100 °C for 5 days under stirring. All the volatiles were removed under reduced pressure. Then, 2 N NaOH aqueous solution was added and the formed sodium formate was precipitated by the addition of ethanol and removed by filtration. The solvent was removed via rotary evaporation and the residue was added with 200 mL ethanol again. After dried over anhydrous magnesium sulfate, ethanol was removed under reduced pressure and MeHPEI (9.68 g, 73.1%) was collected as a yellow viscous material.

2.3.2. Synthesis of dodecanyl bromoacetate

Freshly distilled bromoacetyl bromide (26 g, 130 mmol) and dried CH_2Cl_2 (80 mL) were mixed in a 250 mL round-bottom flask in an ice–water bath. A CH_2Cl_2 (50 mL) solution containing dodecanol (18.63 g, 100 mmol) and N,N-diisopropylethylamine (16.77 g, 130 mmol) was dropwise added to the flask with vigorous stirring for 2 h. The reaction was carried out in an ice–water bath for 4 h and then at ambient temperature for 20 h. The precipitates were filtered off, and the filtrate was washed in sequence with 1 M HCl, 1 M NaOH, and saturated NaCl aqueous solution. The organic phase was separated and dried over magnesium sulfate. After removal of CH_2Cl_2 via rotary evaporation, the residual was dried in vacuo at room temperature overnight to afford dodecanyl bromoacetate (26.96 g, 70.0%).

2.3.3. Synthesis of betaine ester wrapped hyperbranched polyethylenimine (BEHPEI)

MeHPEI (2.57 g) and DMF (5 mL) were mixed in a 100 mL round-bottom flask. Dodecanyl bromoacetate (26.51 g) was dissolved in DMF (25 mL) and dropwise added into the flask. Then, the flask was stirred at room temperature for 48 h. Then, DMF was removed under reduced pressure. The residual was cooled to 0 °C, and excess dodecanyl bromoacetate was retrieved carefully by a syringe. The residual was dissolved with 3 mL $CHCl_3$, and poured into 20 mL cold ethyl ether (0 °C) to precipitate a brown solid. After dried in vacuum, BEHPEI was obtained (8.7 g, 73.7%).

2.3.4. Synthesis of water-soluble allyl BEHPEI

Allyl bromoacetate was obtained from allyl alcohol and bromoacetyl bromide. Then, allyl bromoacetate (4.2 g) and MeHPEI (1.0 g) were used to prepare the water-soluble allyl BEHPEI. The reaction was carried out in 10 mL DMF. After 48 h, the reaction solution was poured into 100 mL diethyl ether. The precipitates were collected and dried in vacuum to give a yellow solid (2.99 g, 96.7%).

2.3.5. Determination of the encapsulating capabilities for BEHPEI

Several dyes were dissolved in deionized water to prepare solutions with concentrations of 1×10^{-6} mol L^{-1}, 2×10^{-6} mol L^{-1}, 5×10^{-6} mol L^{-1}, 10×10^{-6} mol L^{-1}, 20×10^{-6} mol L^{-1} and 30×10^{-6} mol L^{-1}. By means of UV–Vis spectra, the absorption maximums (A) of dyes' solutions were detected and plotted versus the concentrations. Linear relationships between A and concentration were observed, resulting in a series of standard work curves.

In the dye transportation experiment, the aqueous solutions of CR and MO were 2×10^{-3} mol L^{-1}, the aqueous solutions of FS, EY, MB and MV were 1×10^{-3} mol L^{-1}, and the $CHCl_3$ solutions of BEHPEI was 0.40 g L^{-1}. Typically, equal volumes of a chloroform solution of BEHPEI and a dye solution were pipetted into a vial and the vial was vibrated fiercely. After phase separation, it was observed that the nether chloroform phase was dyed. The upper water phase was analyzed by UV–Vis spectroscopy to calculate the amount of the remaining dyes in the aqueous phase according to the corresponding standard curve, and thus the amount of the dye transported by BEHPEI was known.

2.3.6. Coloring resins by the dye-loaded BEHPEI via solution blending

Two chloroform solutions of dye-loaded BEHPEI were added with PMMA, respectively. When the solutions became homogenous, they were poured onto petri dishes, dried in a fuming

cupboard for one week and finally dried in vacuum for 24 h to give transparent and homogenous films. In the control experiments, dyes were directly added into the chloroform solutions of PMMA to produce films by following the same procedure.

2.3.7. pH-controlled release of dyes

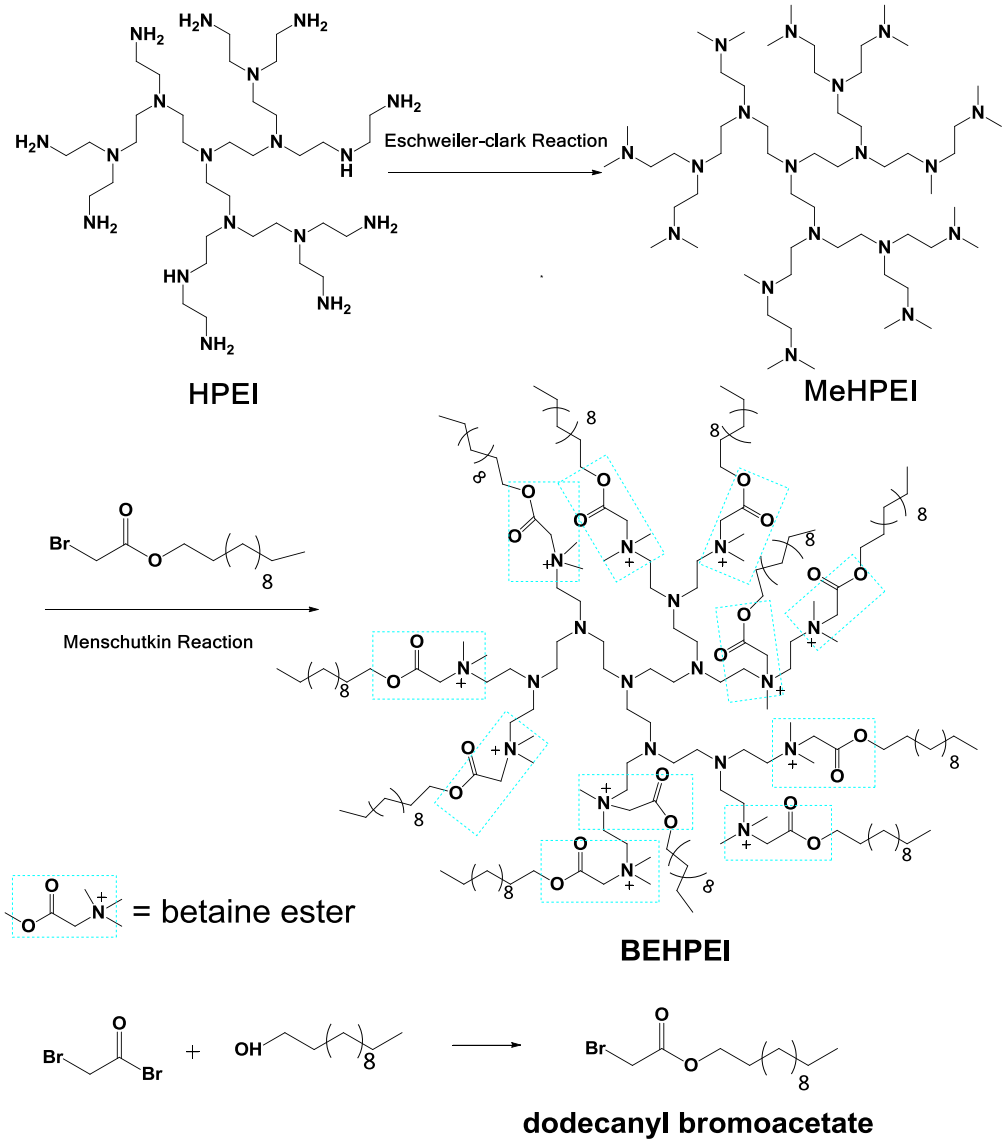
The nether $CHCl_3$ solution of MO-loaded BEHPEI obtained in the dye transportation experiment was dried on a rotary evaporator and then in vacuum for 24 h to yield the supramolecular complex as brown solid, which were subsequently ground into powders. The powder composed of MO and BEHPEI was immersed in a series of buffer solutions of various pH values from 1.0 to 10.4. The release amount of MO at different times was monitored by UV–Vis spectroscopy.

3. Results and discussion

3.1. Synthesis of BEHPEI

MeHPEI was chosen on accounts of its high polarity in favor of high encapsulating capacity. Betaine ester groups play a key role, because it has been proved that they own strong antibacterial activity and interesting degradation behavior [39,40]. Compared with normal ester bonds, due to the electron-withdrawing effect of ammonium group adjacent to ester bond, betaine ester bonds undergo much faster cleavage in alkali mediums, but much slower cleavage under acid conditions [40]. Herein, these groups were formed at the outside of HPEI, facilitating them to contact bacteria. As outlined in Scheme 1, Eschweiler–Clark reaction of HPEI yielded MeHPEI, and then highly efficient Menschutkin reaction between MeHPEI and dodecanyl bromoacetate was performed to generate BEHPEI. Polar aprotic solvent, DMF, was chosen to make the nucleophilic reaction proceed rapidly at room temperature and achieve nearly quantitative conversion of methylamino groups into betaine ester groups.

In the ^1H NMR spectrum of MeHPEI (Fig. 1, a_1), the peak at 2.2 ppm was attributed to the proton signal of the formed methyl groups resulted from the Eschweiler–Clark reaction. As a consequence of Menschutkin reaction, in the FTIR spectrum of BEHPEI, the band at 1740 cm^{-1} resulted from the stretching vibration of –C=O groups (Fig. 2), and in the ^1H and ^{13}C NMR spectra of BEHPEI (Fig. 1, c_1 and c_2), the proton signals ascribed to the



Scheme 1. Synthesis of core–shell structured base-labile BEHPEI.

dodecanyl groups appeared at 1.3 ppm, the proton signals assigned to the original PEI moiety emerged at 3.0–5.0 ppm, and all the carbon signals of dimethylamino groups at 44.0 ppm shifted to 51.5 ppm due to the formation of dimethylammonium groups. These results confirmed that BEHPEI was successfully prepared and the conversion of dimethylamino and methylamino groups into betaine ester groups was nearly quantitative. A detailed examination on the BEHPEI structure was presented in the Supporting Information (Fig. 2).

3.2. Encapsulation capacities of BEHPEI for several dyes and drugs

The structures of the employed dyes and drugs were displayed in Fig. 3. According to Lambert–Beer law, when wavelength of

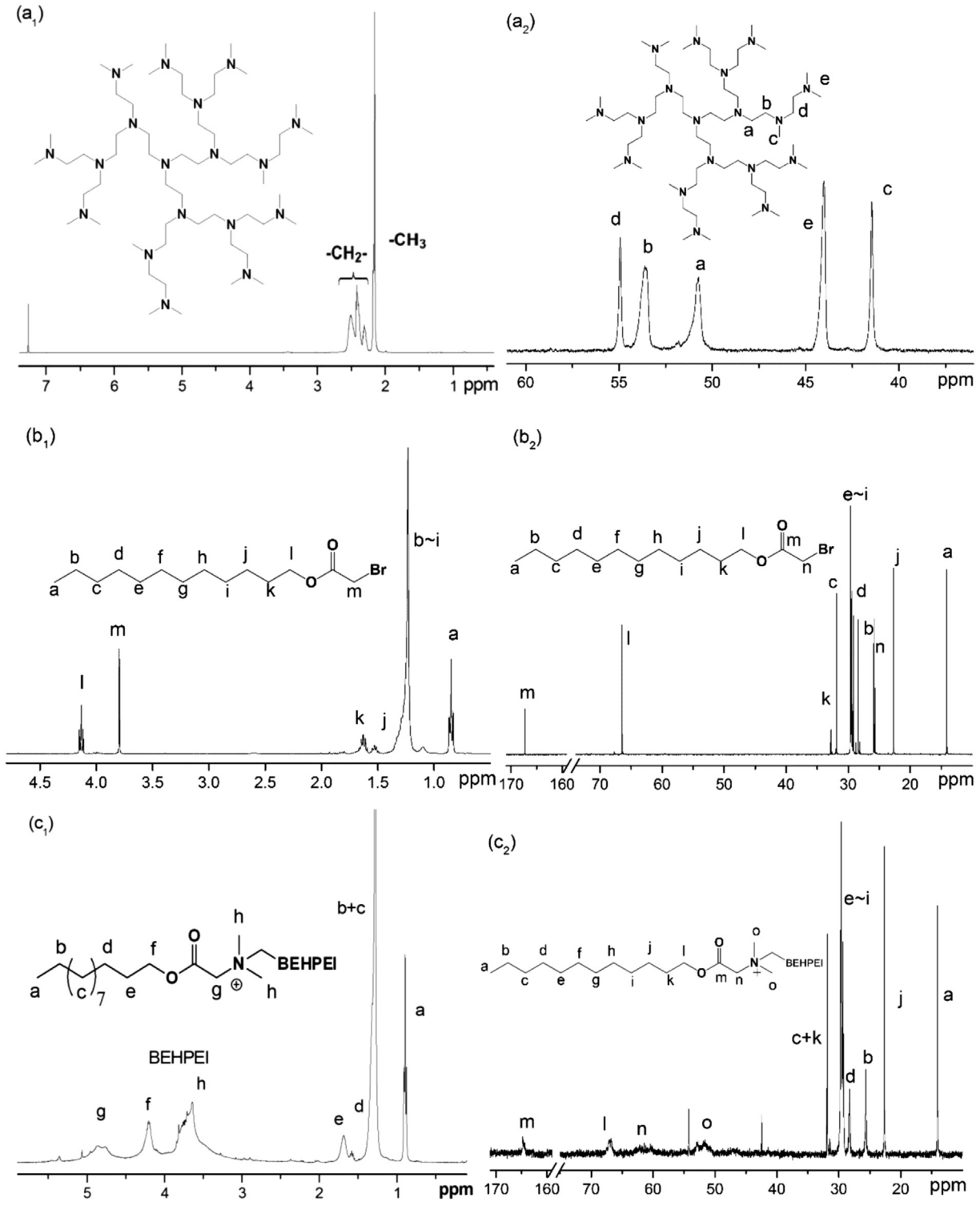


Fig. 1. ^{1}H NMR spectra of MeHPEI (a_1), dodecanyl bromoacetate (b_1) and BEHPEI (c_1); ^{13}C NMR spectra of MeHPEI (a_2), dodecanyl bromoacetate (b_2) and BEHPEI (c_2).

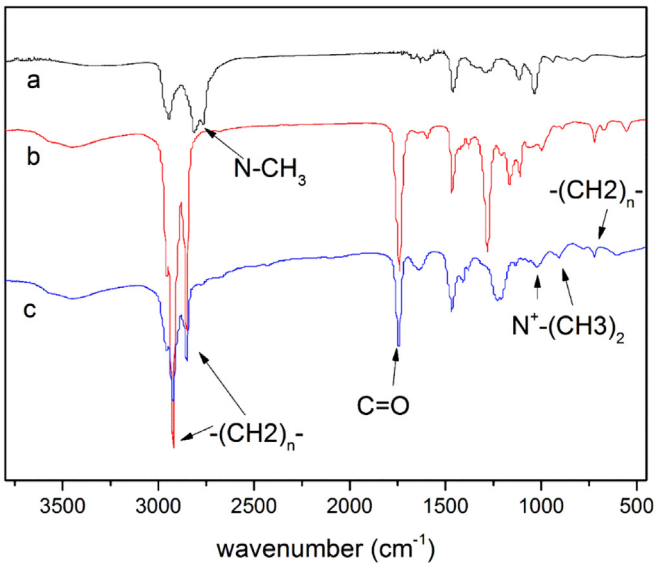


Fig. 2. FTIR spectra of MeHPEI (a), dodecanyl bromoacetate (b) and BEHPEI (c).

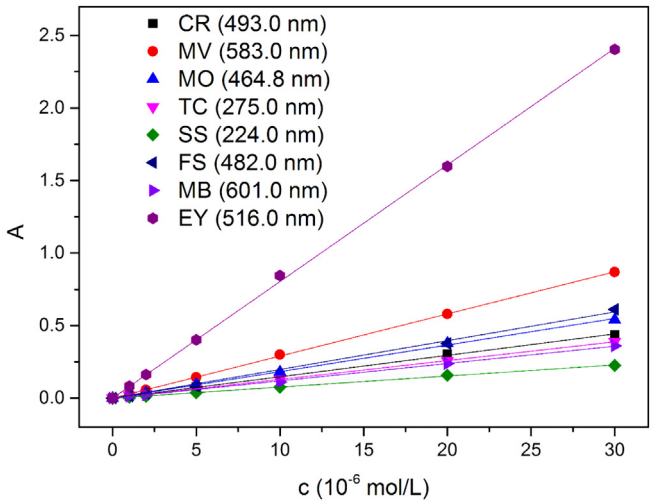


Fig. 4. Standard curves of dyes and drugs.

incident light, liquid layer thickness and temperature of solution were constant, maximum absorbance of solution (A) in a certain range was proportional to concentration following an equation: $A = \varepsilon cl$. Here, c denoted the concentration; l was the thickness of liquid layer which was 1 cm, the size of cuvette; ε was the molar absorption coefficient. In order to determine the proportions between A and c, dyes' or drugs' aqueous solutions of different concentrations were examined by means of UV–Vis spectroscopy and the results were presented in Fig. 4 and Table 1.

Typically, a chloroform solution of BEHPEI was fiercely mixed with a guest's aqueous solutions and after phase separation, the chloroform solution was found to be colorized (Fig. 5). It was explained that BEHPEI accommodated the polar guest molecules within its polar core through electrostatic interaction or hydrophilic interaction [41]. The remaining amount of the guest in the aqueous phase was analyzed using UV–Vis spectroscopy. The

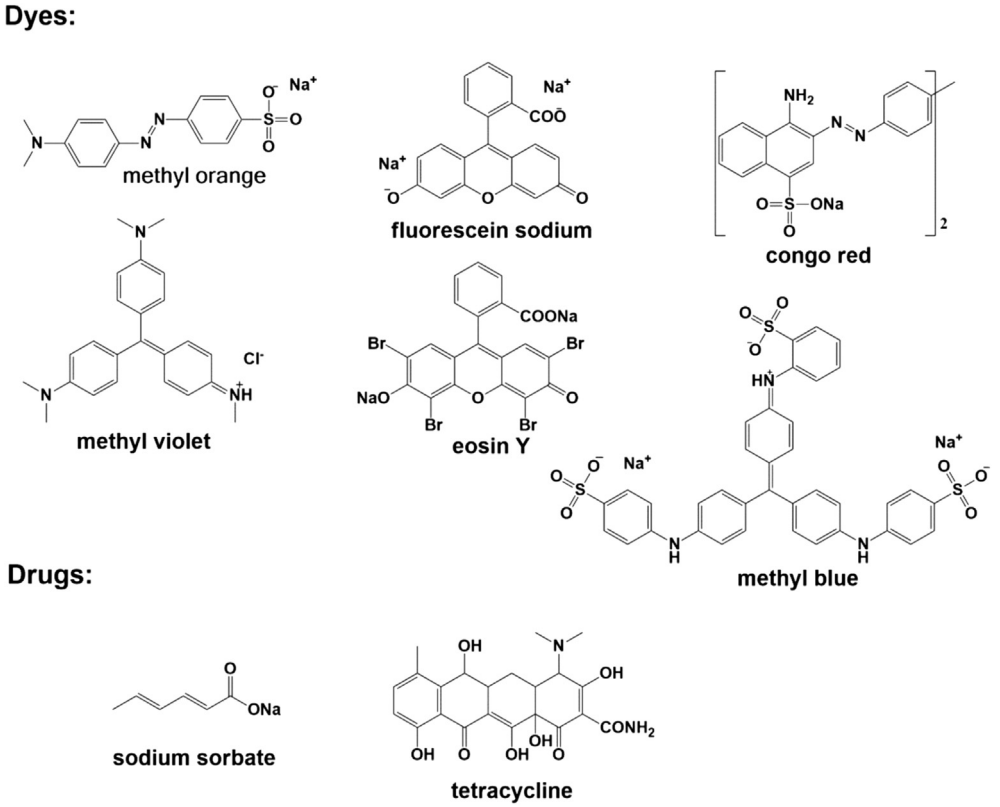


Fig. 3. Structures of the employed dyes and drugs.

Table 1
Standard curve equations and molar absorption coefficients of dyes and drugs.

Dye and drug	$\varepsilon \times 10^{-6}$ [L mol^{-1} cm^{-1}]	R^{2a}	Standard curve equation
FS	0.0198	0.9976	$A = 0.0198c$
MB	0.0120	0.9991	$A = 0.0120c$
EY	0.0804	0.9998	$A = 0.0804c$
CR	0.0148	0.9992	$A = 0.0148c$
MV	0.0290	0.9999	$A = 0.0290c$
MO	0.0181	0.9997	$A = 0.0181c$
SS	0.0076	0.9994	$A = 0.0076c$
TC	0.0130	0.9996	$A = 0.0130c$

[a] R is the linear correlation coefficient.

Table 2
Encapsulation capacities of BEHPEI for different dyes and drugs.

Dye and drug	Encapsulation $\times 10^{-3}$ [mol g^{-1}]	Encapsulation [g g^{-1}]
FS	1.09	0.41
MB	2.29	1.83
EY	1.79	1.24
CR	3.83	2.67
MV	1.94	0.79
MO	2.78	0.91
SS	1.25	0.56
TC	1.82	0.24

results of the transportation capacities were listed in Table 2. BEHPEI exhibited excellent encapsulation capacities towards these guests. For CR and MB, 1 g of BEHPEI could encapsulate 2.67 and 1.83 g, respectively, more than the amounts for other guests. It was explained that there were two or more negatively charged $-SO_3^-$ groups in CR and MB, so they had stronger electrostatic interaction with BEHPEI. Two drugs, antibiotic tetracycline hydrochloride and antiseptic sodium sorbate, were also effectively encapsulated, implying the successful acquisition of two supramolecular complexes possessing two antibacterial weapons, the betaine ester groups and the loaded drugs (Table 2).

3.3. Controlled release of encapsulated dyes by pH stimuli

Photographs of MO-encapsulated BEHPEI immersed in different pH solutions are presented in Fig. 6. Under neutral condition (pH = 7.0), the hydrolysis proceeded very slowly, and an MO concentration in the buffer solution less than 10 μmol L^{-1} was detected. In weak alkaline medium, pH = 8.2, which was in the pH range of natural seawater, the hydrolysis became faster, the buffer solution gradually turned brown and the MO concentration reached 71 μmol L^{-1} in 21 d. The general mechanism was that the alkaline hydrolysis of betaine ester bonds led to the departure of hydrophobic alkyl shell which was proved by the disappearance of the signals at 1.25 ppm ascribed to the long chain alkyl protons (Fig. 8a), gave a hydrophilic zwitterionic shell, made the powders gradually dissolved into the buffer solutions, and in the meantime, MO molecules diffused into water (Fig. 7a). This slow release behavior may be utilized in the design of marine antifouling coating. The hydrolysis speed was accelerated as pH increased to 9.2 and 10.4, and consequently, remarkably visible color change occurred early in 1 d and 4 h, respectively. In 21 d, at pH = 10.4, the MO concentration achieved 250 μmol L^{-1} and the amount of the powders obviously reduced. Hydrolysis behaviors in relatively weak acid medium (pH = 3.4 and 5.0) were interesting. The buffer solutions turned slightly yellow in 1 h, earlier than the time when remarkable color change in the alkaline hydrolysis case was observed, however, the color depth did not intensify as could be seen and the final MO concentrations in 21 d were less than 25 μmol L^{-1}.

As shown in Fig. 7b, the explanation was described as follows. The supramolecular encapsulation included two kinds of mode, intramolecular and intermolecular encapsulation [42]. The remaining tertiary amino groups were quickly transformed into quaternary ammonium groups under acid condition. The intensified electrostatic repulsion effect caused the disassembly of some aggregates of the supramolecular complexes. As a consequence, some MO molecules between the BEHPEI macromolecules were initially released. The ^{1}H spectrum of the BEHPEI after immersion in weak acid solution (pH = 3.4 and 5.0) did not vary much (Fig. 8b), indicating that the betaine ester groups were resistant to acid hydrolysis, and thus most of the MO molecules hold internally and firmly by the BEHPEI could not enter the solution in a very long time. Moreover, by lowering the pH value to 1.0, pH indicative red was seen and hydrolysis rate was remarkably expedited. Nonetheless, the release amount under strong acid condition in 21 d merely equaled that at pH = 8.2 approximately. Therefore, the BEHPEI possessed weak acid stability (pH = 3.0–7.0) and alkaline hydrolysis property, which may be utilized in different pH occasions, such as weak acid freshwater, weak alkaline ocean and so on.

3.4. Compatibility of the supramolecular complex with resins

Compatibility of the supramolecular complex with polymer resins should be taken into account to fabricate antibacterial materials, because it was associated with drug-carrying amount and controllability of release. According to the literatures, a number of antibacterial materials employed polymer resins containing ester bonds, such as poly(lactic-*co*-glycolic acid), poly(ε-caprolactone), PMMA and so on [43,44]. Here, we chose PMMA as model resins to test the compatibility of the supramolecular complex, because PMMA is highly transparent, could make the contrast more distinct.

Solution blending method for film formation was adopted. PMMA resin was dissolved in the chloroform solution of MO-loaded BEHPEI and dried in a fume hood to give a uniform and transparent yellow film (Fig. 9 a_2), while another film without using BEHPEI prepared in the same way was hardly dyed (Fig. 9 a_1). This demonstrated that the supramolecular complex was compatible with PMMA and the BEHPEI greatly enhanced the dispersion of MO. Besides, the film containing the complexes showed resistance towards water immersion washing (Fig. 9 b_1). The other film without

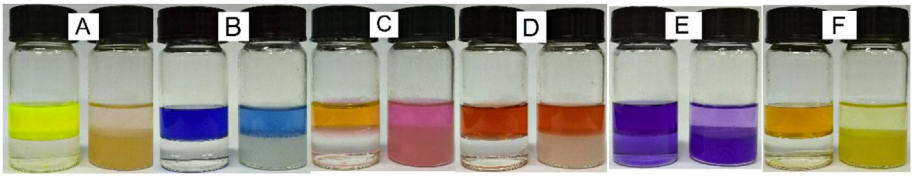


Fig. 5. Photographs of phase transfer——comparison of chloroform and BEHPEI chloroform solution when mixed with FS (A), MB (B), EY (C), CR (D), MV (E) and MO (F) aqueous solution respectively (upper layer: water phase, bottom layer: chloroform phase, left: without BEHPEI, right: with BEHPEI).

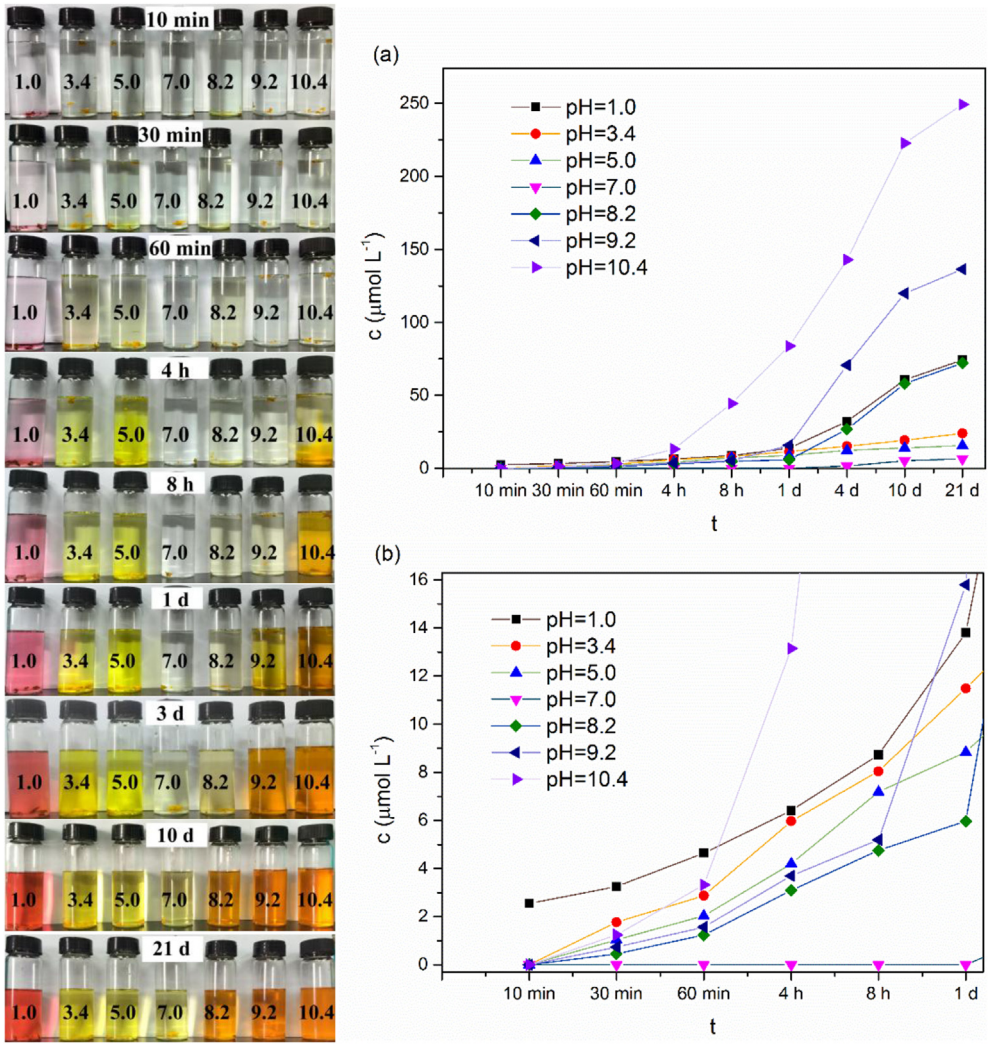


Fig. 6. Photographs of MO-encapsulated BEHPEI immersed in different pH solutions. (Left pictures: from top to bottom, soaking time was 10 min, 30 min, 60 min, 4 h, 8 h, 1 d, 3 d, 10 d and 21 d; from left to right, pH value of the solution was 1.0, 3.4, 5.0, 7.0, 8.2, 9.2 and 10.4. Right pictures: dyes concentration of soaking time from 10 min to 21 d (a) and 10 min to 1 d (b)).

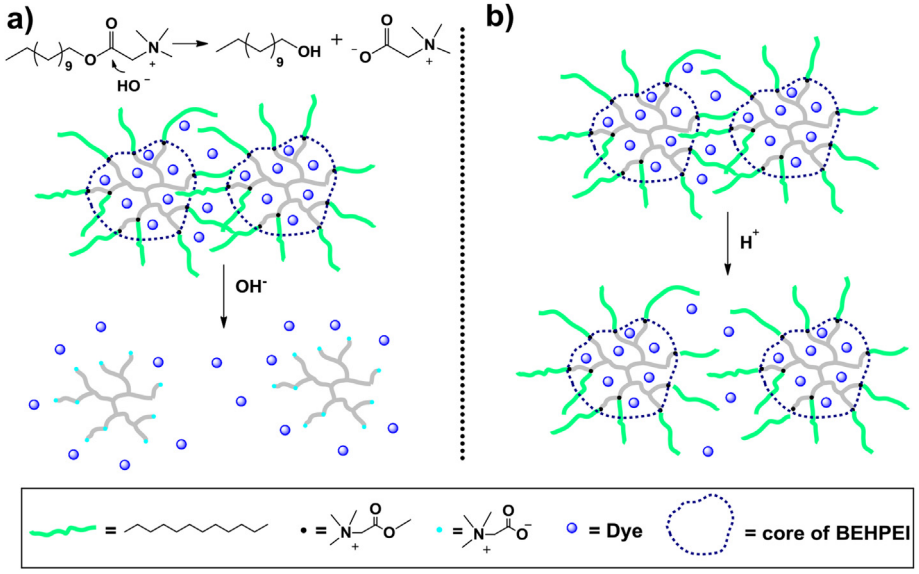


Fig. 7. Schematic showing of the evolution of BEHPEI immersed in alkaline solution (a) and weak acidic solution (b).

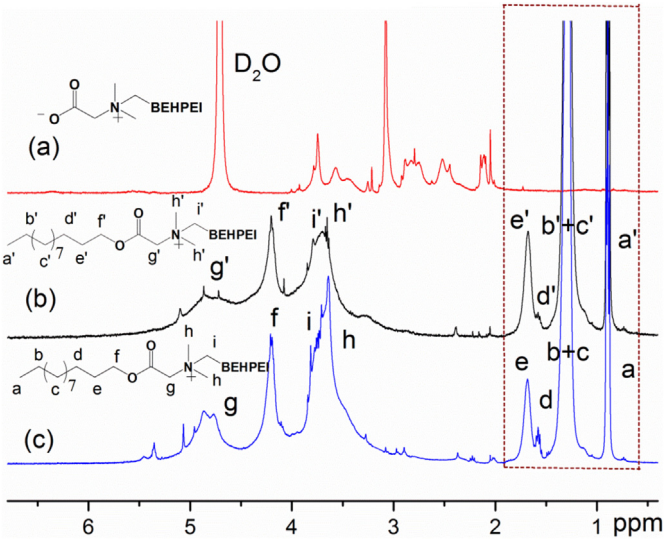


Fig. 8. (a) ^{1}H NMR spectrum of hydrolysis product of BEHPEI after long time immersion in alkaline solution (D_2O); (b) ^{1}H NMR spectrum of BEHPEI after immersion in weak acid solution (pH = 3.4 and 5.0) in 21 d ($CDCl_3$); (c) ^{1}H NMR spectrum of pristine BEHPEI ($CDCl_3$).

using BEHPEI had many visible dye particles lying on the film surface and thus the dye could enter water easily (Fig. 9 b_2). After immersing the film in water for 1 h, water exhibited yellow color, and in 2 days, the concentration of MO dye in water reached 0.039 mmol/L. Examination of the washing water by means of UV–Vis spectroscopy confirmed that trace amount of dyes was released by the BEHPEI-containing sample (Fig. 9c). Thus, the supramolecular complex enhanced the dispersion of guests.

3.5. Water-soluble allyl BEHPEI

Long chain alkyl shell offered BEHPEI the compatibility with resins, while short chain shell endowed BEHPEI with water solubility. Because allyl group normally show its proton signals at 5.6–6.0 ppm and it could make the study of hydrolysis process easier, allyl 2-bromoacetate was used here. The Menschutkin reaction between allyl 2-bromoacetate and MeHPEI yielded the target polymer (Scheme 2). Solubility test showed that it could be mixed with water in all proportions at 29 °C. The dissolution speed was fast. 5 mL water was added into a 25 mL beaker, and was stirred by a magnetic stirrer at a speed of 200 r/min. A piece of 0.2 g polymer was put into the beaker and it was totally dissolved in 105 s. Immersing the polymer in a buffer solution of pH = 8.4 led to

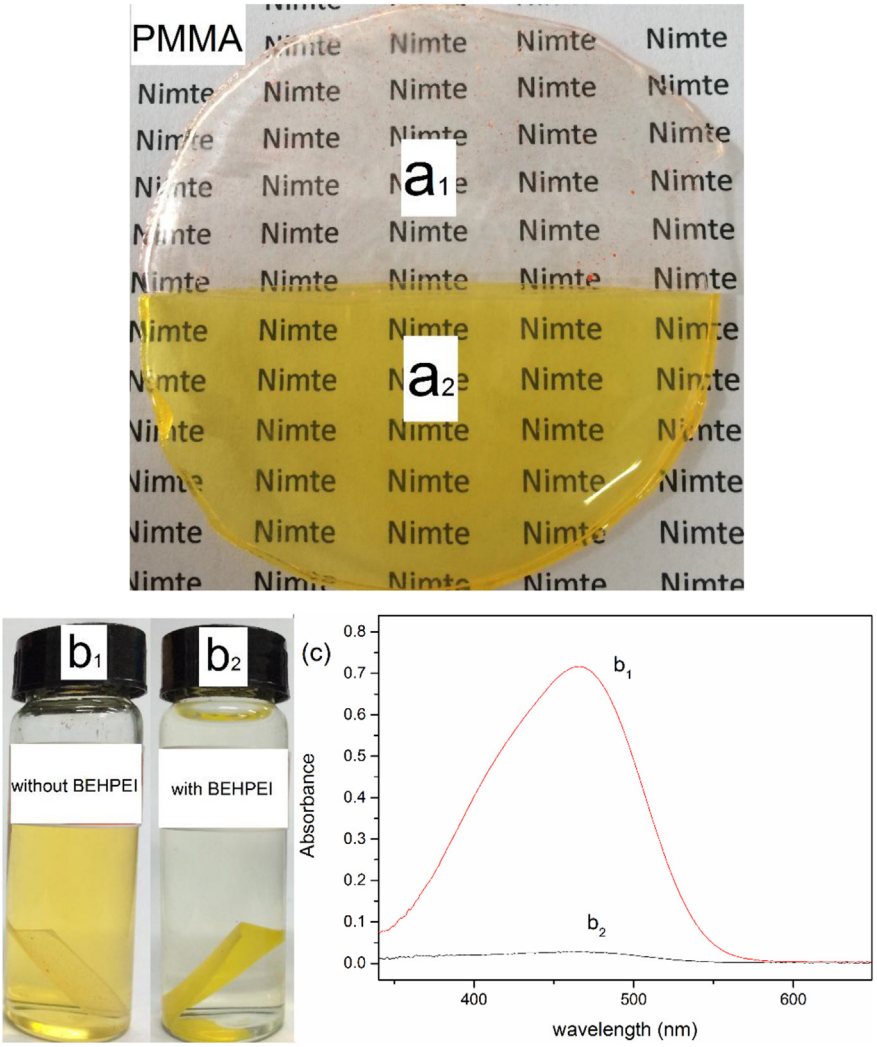
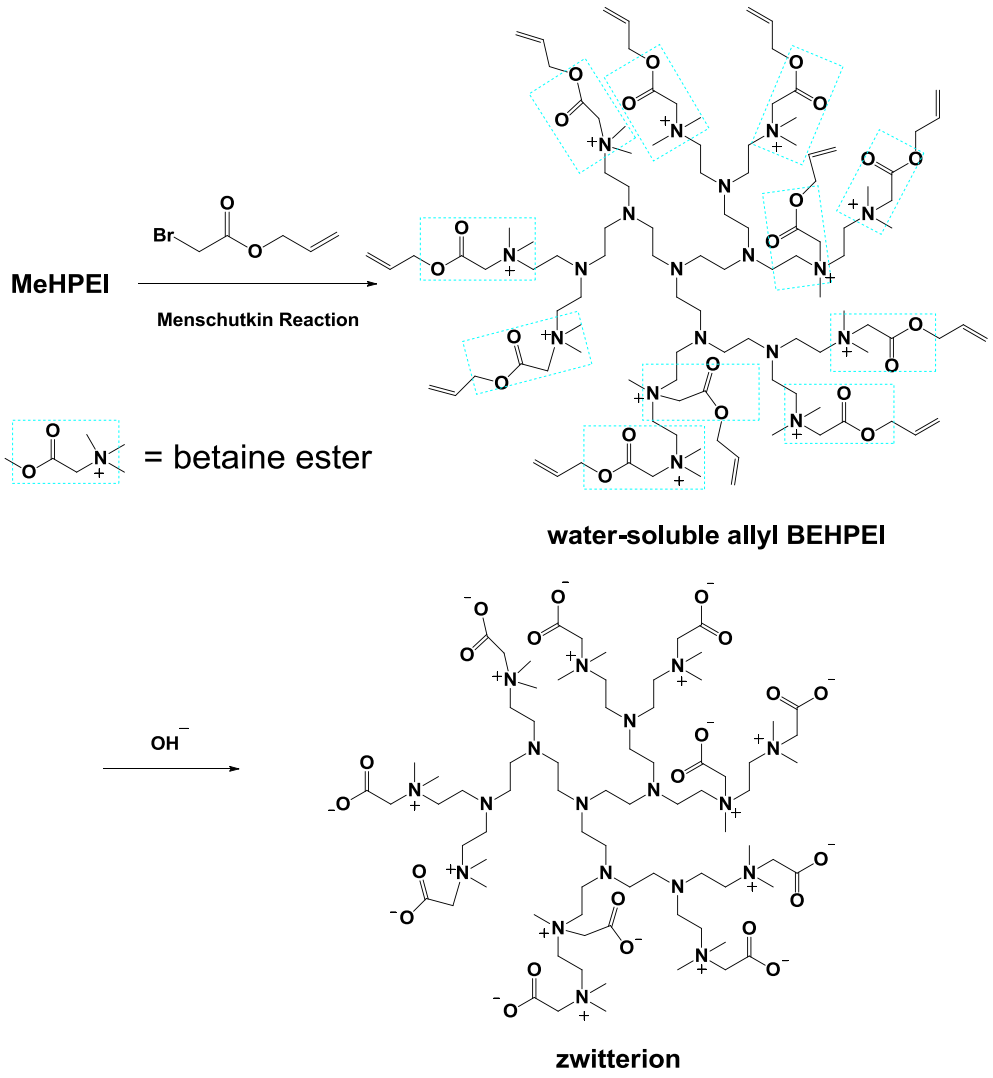


Fig. 9. Photographs of MO-coloring PMMA membranes placed on a paper (a_1 without BEHPEI, a_2 with BEHPEI) and immersed in water for 2 d (b_1 without BEHPEI, b_2 with BEHPEI); the corresponding UV–Vis spectra of aqueous solution after immersing dyed PMMA films (c).



Scheme 2. Synthetic route of water-soluble allyl BEHPEI.

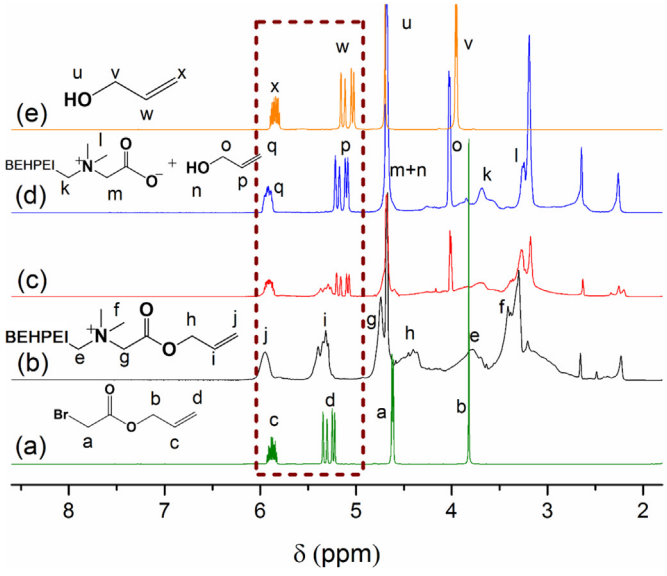


Fig. 10. ^{1}H NMR spectra of allyl 2-bromoacetate (a), water-soluble allyl BEHPEI (b), allyl BEHPEI immersed in alkaline solution for 10 h (c), BEHPEI immersed in alkaline solution for 24 h (d) and allyl alcohol (e) in D_2O.

the carboxybetaine-functionalized product in 24 h (Fig. 10). The short chain poly (betaine esters) has been found excellent activity against bacteria like *Escherichia coli* K12 [45], and the carboxybetaine groups are nontoxic to cells and resistant to nonspecific protein adsorption [46], so the prepared water soluble allyl BEHPEI maybe found usage in hand washing lotion, mouth rinse and etc.

4. Conclusion

A general avenue to prepare betaine ester-shell functionalized hyperbranched polyethylenimine (BEHPEI) in large scale was presented. The BEHPEI possesses these functions: firstly, betaine ester-shell could act as antibacterial polycations; secondly, the core–shell structure of opposite polarity could encapsulate large amount of antibiotic TC and antiseptic SS (0.24 and 0.56 g g^{-1}, respectively); thirdly, betaine ester shell could be controllably degraded under weak alkaline conditions (pH = 7–9) to realize a controlled release operation while kept stable under neutral and weak acid environments (pH = 3.0–7.0); fourthly, varying the chain length of betaine ester-shell could adjust the compatibility with organic resins or water for different usages. Based on these investigations, antimicrobial applications of drug-loaded BEHPEI in biodegradable polymer coatings and lotions are in process in our lab.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.polymer.2014.10.020.

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