# Novel Degradable Polyphosphazene Hydrogel Beads for Drug Controlled Release

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**ABSTRACT:** Novel water-soluble polyphosphazene containing carboxylatophenamino groups (PCPAP) was synthesized by the substitution reaction of ethyl *p*-amino benzonate with poly(dichlorophosphazene), followed by alkali hydrolysis. Characterizations by IR, $^1$H-NMR, differential scanning calorimetry, and elemental analysis indicated that the reaction brought about an almost complete introduction of carboxylatophenamino to the polymer side chain. Calcium-crosslinked PCPAP hydrogel beads were accomplished with an extremely mild method. The erosion experiments were conducted in vitro in various pH environments. The erosion duration of the beads at pH 7.4 and 37°C was effectively extended by an increase in the concentration of the PCPAP or $CaCl_2$ solution during the preparation process. Moreover, the bead erosion was sensitive to the pH. The sample dissolved 39.4% in a pH 8.0 buffer within 34 days but only 5.3% in a pH 5.0 buffer. Furthermore, PCPAP underwent degradation into macromolecular segments through the breaking of the backbone, and this could prevent accumulation in the body. These properties of PCPAP may be useful for controlled drug delivery, including intestine-specific oral delivery systems. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 87: 986–992, 2003

**Key words:** polyphosphazenes; degradation; hydrogels

## INTRODUCTION

Spherical hydrogels are currently attracting much attention for bioactive agent protection, sustained release, targeting, responsive release by temperature, pH, or electricity, and so forth.[1–3] Conventional encapsulation techniques involve the use of crosslinking agents, heat, or radiation. These harsh processing conditions may be detrimental to incorporated bioactive therapeutics. Additionally, chemical crosslinking agents, such as glutaraldehyde, for the preparation of gelatin, alginate, and poly(vinyl alcohol) hydrogel beads can cause in vivo toxicity. Therefore, the mild formation of polyelectrolyte complex hydrogel beads by electrostatic interactions between oppositely charged polyelectrolytes has been extensively explored. For example, Tsung and Burgess[4] reported the preparation of heparin/gelatin microcapsules by coacervation under certain conditions. Mi et al.[5] prepared chitosan/polyphosphate complex beads by adding a chitosan solution dropwise to an aqueous polyphosphate solution. However, the procedure for preparing an ionic crosslinking hydrogel bead with small-molecule ions was found to be easier and more convenient. $Ca^{2+}$–alginate beads and $Al^{3+}$–carboxymethylcellulose beads are excellent examples: they can control drug release by the erosion of the hydrogel matrix.[6,7]

Recently, polyphosphazenes have emerged as a new family of biodegradable polymers with inorganic backbones consisting of alternating nitrogen and phosphorous atoms and two side groups attached to each phosphorous atom. Their most significant advantage is the ease of linking specific side groups to the backbone by efficient substitutive techniques.[8] In 1994, Andrianov et al.[9] reported that water-soluble poly[di-(carboxylatophenoxy) phosphazene] (PCPP) had the ability to gelate in the presence of calcium ions under mild condition and release drugs by reversible ion-exchange erosion. However, the synthesis of PCPP was quite complicated. Because of the weak nucleophilicity of the hydroxyl, ethyl *p*-hydroxybenzonate needed to be transferred to sodium alkoxide before the substitution reaction, and tetra-*n*-butyl-ammonium was also required to assist with complete substitution; this may make low yields and high costs unavoidable.

In this article, we report an alternative method for synthesizing a degradable, water-soluble polyphosphazene containing carboxylatophenamino groups (PCPAP) that undergoes a liquid–gel phase transition on contact with an aqueous solution of calcium chloride. We also describe the modulation of erosion behaviors on the basis of the preparation conditions and erosion environment for drug controlled release.

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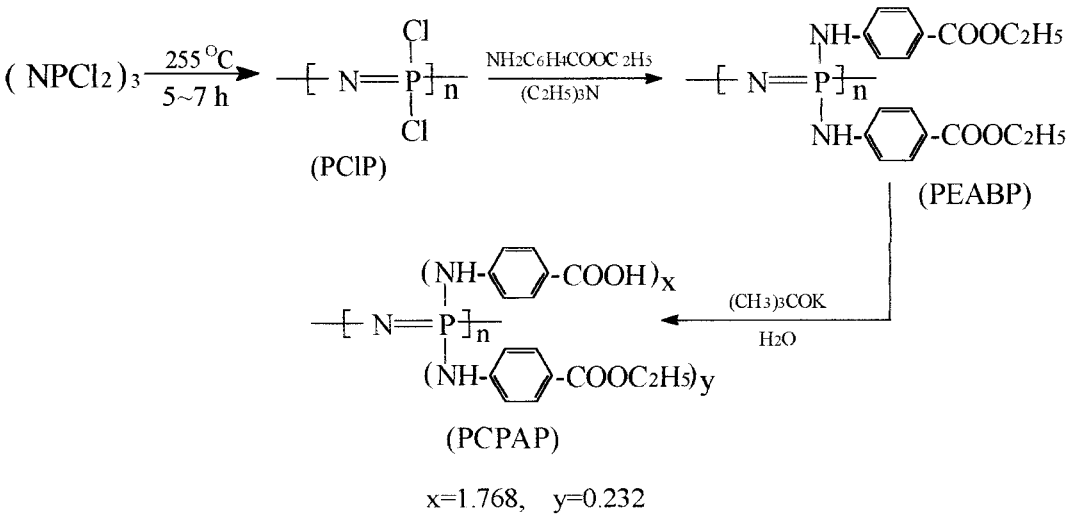



**Scheme 1** Preparation of PCPAP.

## EXPERIMENTAL

### Materials

Hexachlorocyclotriphosphazene (mp = 112–114°C), purchased from Fluka Chemie AG (Buchs, Switzerland), was purified by vacuum sublimation. Ethyl *p*-aminobenzoate (EAB) was obtained from Sigma Co. (St. Louis, MO). Triethylamine and benzene were dried with calcium hydride and distilled before use. Tetrahydrofuran (THF) was freshly distilled from metal potassium. Potassium *tert*-butoxide was freshly prepared by the reaction of potassium with *tert*-butyl alcohol. All other chemicals were used as received.

### Synthesis of PCPAP

The overall reaction is shown in Scheme 1. First, poly(dichlorophosphazene) (PClP) was prepared by the thermal ring-opening polymerization of hexachlorocyclotriphosphazene at 255°C for 5–7 h. Then, the substitution reaction on the polymer backbone was carried out immediately as follows. PClP (1 g, 0.017 mol of P—Cl) was dissolved in 30 mL of benzene in a 250-mL, three-necked flask at 50°C. To this solution, 150 mL of a benzene solution containing EAB (14.025 g, 0.085 mol) and fresh triethylamine (2.2 mL, 0.017 mol) was separately added dropwise through a constant-pressure funnel under a dried nitrogen atmosphere. After the addition was complete, the mixture continued to react for 3 days at 50°C. The insoluble substance was removed by filtration, and the filtrate was concentrated by evaporation in vacuo. The substituted polymer poly[bis(ethyl *p*-aminobenzoate)phosphazene] (PEABP) was isolated and purified by repeated precipitation from benzene into diethyl ether for the removal of excessive EAB.

This product PEABP (0.5 g) was dissolved in 20 mL of THF in a 500-mL, round-bottom flask, and this was followed by the addition of potassium *tert*-butoxide (4 g, 0.04 mol) and water (0.2 mL) to 100 mL of dry THF. The mixture was cooled to 0°C for the first 5 min and then was stirred at room temperature for 40 h. A large quantity of ice water (150 mL) was poured into the mixture. The turbid solution immediately became clear. After it was concentrated by evaporation in vacuo, the solution was dialyzed through a cellulose tube against distilled water for 48 h. Finally, PCPAP was obtained by acidification of the solution with dilute hydrochloric acid. The yield was 83%.

### Characterization

#### IR analysis

IR analysis was performed on a Shimadzu 470 Fourier transform infrared spectrophotometer (Columbia, MD). The samples were film-cast in methylene chloride onto KBr plates or pressed into films with KBr.

#### $^1$H-NMR

$^1$H-NMR measurements were performed at 50°C with an Avance DMX500 instrument (Bruker, Rheinstetten, Germany) with deuterated $CDCl_3$ as a solvent for PEABP or with dimethyl sulfoxide for PCPAP and with internal $Me_4Si$ as a shift reference.

#### Elemental analysis

Carbon, hydrogen, and nitrogen contents in the polymer were obtained by elemental analysis with an EMA EA-1106 elemental analyzer (Milan, Italy).

Differential scanning calorimetry (DSC)

The glass-transition temperature ($T_g$) was determined with a PerkinElmer DSC-7 thermal analyzer (Shelton, CT) at a heating rate of 10°C $min^{-1}$ from −70 to 200°C.

### Degradation of PCPAP

Because of interference with assays of the hydrolysis product of polyphosphazene, a phosphorus-free buffer was required. Therefore, the buffers used here were pH 7.4 boronic acid/borax.

PCPAP (15 mg) was dissolved in a 3 mL buffer solution and incubated in a shaking water bath at 37°C and 50 rpm. At the appropriate interval, the number-average molecular weight ($M_n$) was determined with a Shimadzu scl-6A Liquid Chromatopac System (Columbia, MD) with an Alltech Macrosphere GPC 10-7U column as the stationary phase, water as the mobile phase at a flow rate of 0.6 mL/min, a refractive-index detector, and dextran as a reference. The hydrolysis products of PCPAP, phosphate and *p*-aminobenzoic acid, were assayed separately by the ascorbic acid method[10] and high-performance liquid chromatography (Shimadzu scl-6 A Chromatopac System with a $C_{18}$ column, 60/40/2 methanol/water/acetic acid as an eluant, a UV detector with a 258 nm detection wavelength, and *p*-aminobenzoic acid as a reference).

### Preparation of calcium-crosslinked PCPAP (PCPAP–$Ca^{2+}$) beads

The preparation process of PCPAP beads was similar to that reported by Andrianov et al.[9] An aqueous solution of PCPAP with a concentration of 1, 3, 5, or 10% (m/v) was obtained by the dissolution of PCPAP in equimolar amounts of a 4% sodium carbonate solution. The solution was directly dropped through a syringe needle (0.4 mm in diameter) into a 15-mL crosslinking solution containing 1–10% calcium chloride under gentle agitation. Once the PCPAP solution came into contact with the crosslinking agent, hydrogel beads began to form. After hardening for 30 min, the beads were collected and washed three times with distilled water, and then they were slowly evaporated at 37°C. When the samples were almost dried, they were put on a vacuum line so that the last trace of water could be removed.

### Erosion of PCPAP–$Ca^{2+}$ beads

A certain amount of dry PCPAP–$Ca^{2+}$ beads (ca. 20 mg) fabricated under different conditions was immersed in a 5-mL buffer solution and incubated at 37°C. The degradation rate was evaluated by the weight loss of the sample, which was defined as $(W_t - W_0)/W_0$, where $W_0$ and $W_t$ are the weights at initial and specific times. Simultaneously, the erosion product of PCPAP beads was examined by the measurement of ultraviolet–visible (UV–vis) absorption at 258 nm with Shimatz 1201 UV–vis spectrophotometer (Columbia, MD). The media for the erosion study were 0.1*M* citric acid/sodium citrate for pH 5.0 and pH 6.0 and 0.1*M* phosphate for pH 7.4 and pH 8.0. The sodium ion concentration was carefully adjusted to 0.9% (m/v).

### Turbidimetric titration

The solubility of PCPAP in water was investigated by turbidimetric titration. A solution of 0.2 g/L PCPAP with equimolar amounts of sodium carbonate was prepared. The titrant hydrochloric acid was carefully dropped into the solution with gentle stirring at room temperature. The solution pH was monitored with a digital pH meter. The changes in turbidity were measured at 420 nm with a UV–vis spectrophotometer and are reported as 100%*T*, which is linearly proportional to the true turbidity for $T > 0.9$.

## RESULTS AND DISCUSSION

### Polymer synthesis

Several methods have been developed for the preparation of polyphosphazene derivatives. Among them, the most common is the heat polymerization of poly(dichloridophosphazene) followed by a nucleophilic substitution reaction for the introduction of side groups. The generality of this reaction allows it to be applied to the synthesis of novel water-soluble polyphosphazenes containing carboxyl groups. However, free carboxyl groups would result in the serious crosslinking of polymers during the substitution reaction. Therefore, it must be protected by esterification before the substitution reaction. However, the amino group has strong nucleophilicity, leading to a direct reaction with chloride atoms of the polyphosphazene backbone with ease.[11] For these reasons, EAB was chosen as the side group for substitution; its amino groups acted as nucleophiles, whereas ester groups could be further hydrolyzed into free carboxyl groups. Triethylamine, a strong organic alkali, accelerated the reaction of EAB with poly(dichloridophosphazene) by consuming the product of hydrochloride to form benzene-insoluble triethylamine hydrochloride, which itself played an important role as an indicator. During the reaction, white needle crystals were observed after 3 or 4 h of the reaction and accumulated more and more with a prolonged reaction time.

As for the hydrolysis of side groups of polyphosphazene, Allcock and Kwon[12] attempted several methods, including acidic hydrolysis with hydrochloric

acid or *p*-toluenesulfonic acid or basic hydrolysis with sodium hydroxide. These attempts all failed to give the carboxylic acid derivative without decomposition of the skeleton. However, the use of potassium *tert*-butoxide was achieved. Therefore, potassium *tert*-butoxide was applied to the hydrolysis of PEABP into PCPAP. After 40 h, the reaction mixture became a clear solution by the addition of cold water, and this indicated that the reaction was complete.

## Characterization

The IR spectra of the polymers are consistent with the expected structures. The specific peak assignments of PEABP are listed as follows: 3350 (—NH), 2850–2900 [—$CH_3$, CH(Φ)], 1705 [—O—C(═O)—], 1600, 1510, 1460 (—$C_6H_4$—), 1270 (—O—), and 1240 (—N═P—). The IR spectrum of PCPAP is similar, but a broad peak at 3000–3600 $cm^{-1}$ is very obvious and corresponds to the combination of the amino group and carboxyl.

The $^1$H-NMR spectra of PEABP and PCPAP both consisted of a triplet at 6.4 ppm, a quartet at 4.3 ppm, and two doublets at 6.6 and 7.8 ppm, which are assigned to —$CH_3$, —$CH_2$—, and — $C_6H_4$—, respectively. In addition, the broad singlet at 3 ppm at 50°C moved to 4 ppm at 40°C and corresponded to —NH— or —COOH. Compared with that of PEABP, the ratio of either the methyl or methylene peak to phenyl of PCPAP is much less, and this suggests that some ester groups of PEABP converted into carboxyl groups. The conversion ratio of PEABP to PCPAP calculated from the peak integration was 87.9%.

Elemental analysis is a good method for determining whether or not a result is what was expected. For PEABP, similar results from the theoretical calculations and the experiment (Theory: N, 11.26%; C, 57.90%; H, 5.36%; Experiment: N, 11.27%; C, 57.8%; H, 5.67%) indicate that the substituting degree of EAB was almost 100%. As for PCPAP, the experimental value was also close to the theoretical value when 87.9% of the ester of PEABP was hydrolyzed into carboxyl groups. This result agrees with that obtained from $^1$H-NMR.

DSC analysis was employed to measure the heat properties of the polymers. There was one $T_g$ but no melting point for both PEABP and PCPAP. The $T_g$ value of PCPAP (62°C) was higher than that of PEABP (36°C), and this is ascribed to the increase in the molecular polarity when the ester groups were converted into carboxyl.

## Degradation

Under the physicology condition, PCPAP can completely dissolve in the form of sodium-crosslinked PCPAP (PCPAP–$Na^+$). Therefore, it was necessary to study the degradation of PCPAP in the dissolved state. The degradation of PCPAP is illustrated by the changes in $M_n$ and the release of an erosion product in Figure 1. $M_n$ decreased quickly with increasing incubation time at the initial stage. After 30 days, it decreased to 60.7% of the original $M_n$ value. Then, the degradation rate slowed down. After 60 days, $M_t/M_o$ was 51%, and after 120 days, it was 22.1%. This great change in $M_n$ could be explained as the cleavage of the polymer backbone. Meanwhile, the cumulative release of *p*-aminobenzoic acid increased during the degradation process, and this implied that the breakage of side groups from the backbone took place. However, the breakage was so difficult that only 13% of the *p*-aminobenzoic acid was found after 120 days. The backbone degradation product, phosphate, was also examined by the ascorbic acid method, but little was found. In summary, we concluded that the degradation mechanism of PCPAP mainly referred to the formation of macromolecular segments through the cleavage of the backbone, accompanied by some breakage between the side groups and backbone and little complete hydrolysis of the backbone into small molecules.

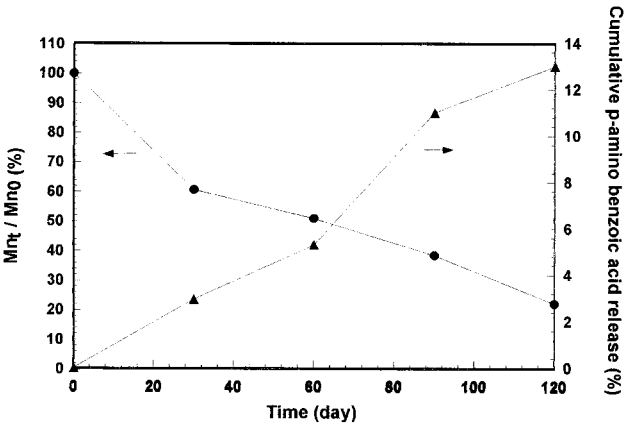



**Figure 1** $M_n$ changes and cumulative *p*-amino benzoic acid release of PCPAP in a pH 7.4 boronic acid/borax buffer solution at 37°C. $M_{n0}$ and $M_{nt}$ are the $M_n$ values of PCPAP at initial and specific times, respectively. $M_{n0}$ was 16,168.

## Preparation and erosion of PCPAP–$Ca^{2+}$ beads

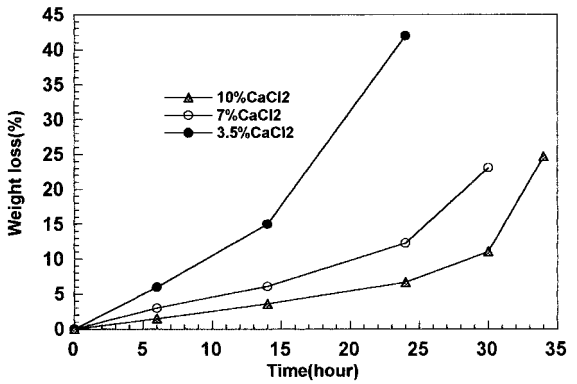
Hydrolyzed from PEABP, PCPAP almost bore two *p*-amino benzoic acid groups on every other nitrogen atom along the backbone. Therefore, in a certain pH region, PCPAP could produce negative charges with a high density by the ionization of carboxyl groups, which facilitated the formation of gel beads with enough strength through electrostatic interactions. However, for the fabrication of gel beads with excellent properties, several other factors of the preparation conditions should be taken into account, including the concentrations of PCPAP ($C_p$) and $CaCl_2$ solutions ($C_{Ca}$). Table I lists several examples reflecting the influence of $C_p$ and $C_{Ca}$ on bead preparation. When $C_p$

**TABLE I**
**Influence of $C_p$ and $C_{Ca}$ on PCPAP–$Ca^{2+}$ Bead Preparation**

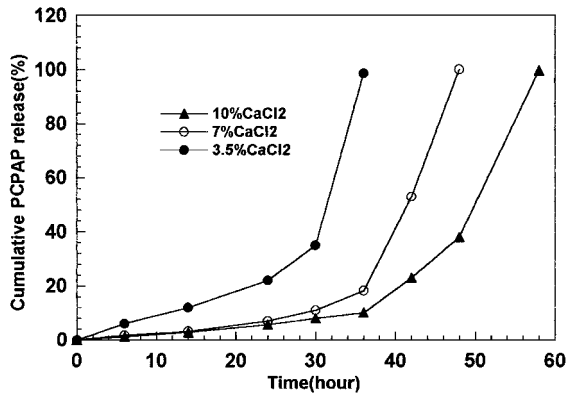
| | $C_p$ (%) | | | |
|---|---|---|---|---|
| $C_{Ca}$ (%) | 1 | 3 | 5 | 10 |
| 1 | Solid particle | Solid particle | Solid particle | Solid particle |
| 3.5 | Solid particle | Solid particle | Irregular bead | Bead |
| 7 | Solid particle | Solid particle | Irregular bead | Bead |
| 10 | Solid particle | Irregular bead | Bead | Bead |

was lower than 5%, no spherical gel could be formed. As $C_p$ increased, the trend to gelate in a spherical form became obvious. When 10% PCPAP was used, only 3.5% $CaCl_2$ could form gel beads with a smooth surface, and the bead strength increased with increasing $CaCl_2$ concentration.

During the erosion process, all PCPAP–$Ca^{2+}$ gel beads successively underwent swelling, rupture, and disappearance. However, the duration of the bead erosion was dependent on the preparation conditions and the buffer solution pH. We evaluated the bead erosion by measuring the weight loss of the bead and the erosion product content. Attributed to the slow degradation of PEABP, as discussed previously, the erosion product of the bead was thought to be PCPAP–$Na^+$.




(a)




(b)

**Figure 2** (a) Weight loss of and (b) cumulative PCPAP release from PCPAP–$Ca^{2+}$ beads prepared with $CaCl_2$ solutions of different concentrations. The concentration of PCPAP was 10%.

Figure 2(a) shows the effect of the $CaCl_2$ concentration on the weight loss of PCPAP–$Ca^{2+}$ beads in pH 7.4 phosphate-buffered saline at 37°C. Because of the difficulty of weighing the broken beads, the latest period of weight loss could not be displayed in the curves. There existed a weight loss for each bead. In addition, the weight loss rate was faster with the decrease in $C_{Ca}$. In Figure 2(b), the cumulative PCPAP release was almost proportional to the time until the bead was broken, after which PCPAP burst out to 100%. For instance, the bead with 3.5% $CaCl_2$ released 35% PCPAP within 30 h but all of the PCPAP after 36 h because the bead was broken after 31 h. With increasing $C_{Ca}$, the erosion duration was obviously extended. When 10% $CaCl_2$ was used as a crosslinking agent, a 35% PCPAP release needed approximately 46 h. This character of the cures was consistent with that shown in Figure 2(a).

During the preparation process of PCPAP–$Ca^{2+}$ beads, because of the concentration gradient, $Ca^{2+}$ diffused from the outer solution to the inner solution of PCPAP droplets, whereas PCPAP moved in the other direction. Once they met, crosslinking took place. However, when $C_{Ca}$ was low, the crosslinking just occurred on the surface of PCPAP droplets, and this resulted in poor shapes and poor mechanical strength for the beads. Increasing $C_{Ca}$ promoted the diffusion rate, and this was helpful for forming homogeneous crosslinking structures to strengthen the beads. Similarly, increasing $C_p$ retarded itself from diffusing out, and this also strengthened the beads.

It is well known that the erosion of $Ca^{2+}$–alginate gel beads is dominated by an ion exchange of sodium ions in phosphate-buffered saline and calcium ions bound to carboxylates in alginate molecules. From the results for weight loss and erosion product release, we concluded that PCPAP–$Ca^{2+}$ gel eroded by the same mechanism. Sodium ions diffused toward the bead core and displaced the bound calcium ions, leading to the dissolution and release of PCPAP and the weight loss of the beads. As discussed previously, the higher $C_{Ca}$ or $C_p$ was, the sturdier PCPAP–$Ca^{2+}$ beads were. Therefore, when the concentration of PCPAP was

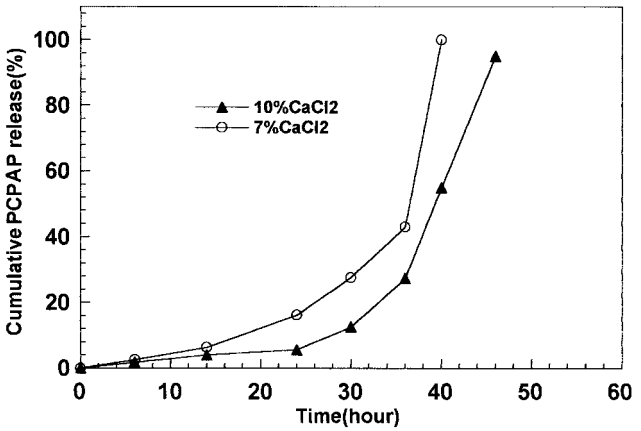



**Figure 3** Cumulative PCPAP release from PCPAP–$Ca^{2+}$ beads prepared with a 5% PCPAP solution.

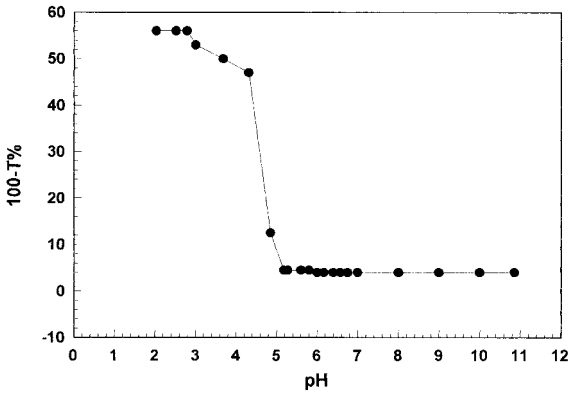



**Figure 5** Turbidity titration curves of aqueous PCPAP solutions with the addition of hydrochloric acid ($\lambda$ = 420 nm).

fixed at 10%, increasing $C_{Ca}$ effectively maintained the bead integrity to some extent, and this made sustained drug release feasible. For the same reason, with the concentration of PCPAP decreasing, the beads ruptured earlier, and the erosion of the beads was fast. This assumption was confirmed in Figure 3.

Recently, responsive controlled release systems have attracted interest. Several kinds of polyelectrolyte hydrogels have been proven to be pH-sensitive for oral delivery. Here, the effect of the buffer solution pH on PCPAP–$Ca^{2+}$ bead erosion was also investigated. In Figure 4, the erosion rate of PCPAP–$Ca^{2+}$ beads is shown to have decreased greatly in weak acid solutions. After 34 h of incubation, the weight loss was 39.4% in pH 8.0 phosphate-buffered saline but only 5.3% in pH 5.0 phosphate-buffered saline. To understand this phenomenon, we performed the turbidimetric titration of PCPAP in water. Figure 5 shows the titration curve obtained from the titration of an aqueous PCPAP–$Na^+$ solution with dilute hydrochloric acid. A significant increase in the turbidity appeared around pH 5.18–4.85. This indicated that at a pH lower than 4.85, the ionization of carboxyl groups of PCPAP was seriously depressed, leading to a decrease in solubility and even precipitation from water. PCPAP is a weak polyacid. As PCPAP–$Ca^{2+}$ beads were immersed in a pH 5.0 buffer solution, both the hydrion and sodium ions diffused inward. On one side, sodium ions promoted bead erosion by exchanging with calcium ions. On the other side, the hydrion decreased the solubility of PCPAP and inhibited bead erosion by depressing the ionization of carboxyl. This negative effect was further strengthened by the hydrogen-bond action between free carboxyl groups in the beads. This finding was similar to the findings of a recent study by Hodsdon et al.[13] They observed the swelling properties of alginate–$Ca^{2+}$ hydrogels with low-temperature-cooling scanning electron microscopy. A large area of icy crystals existed in the sample in simulated intestinal fluid, but there was little in simulated gastric acid; this indicated that at low pHs hydrogel hydration was prohibited by the transformation of soluble alginate–$Na^+$ into insoluble alginate. Therefore, the PCPAP–$Ca^{2+}$ beads exhibited pH-dependent erosion characteristics.

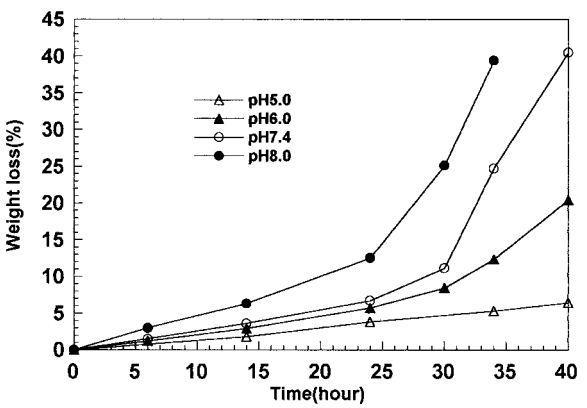



**Figure 4** Weight loss of PCPAP–$Ca^{2+}$ beads in pH 5.0 and 6.0 citric acid/sodium citrate buffers and in pH 7.4 and 8.0 phosphate buffers at 37°C,

## CONCLUSIONS

The novel water-soluble polyphosphazene derivative PCPAP was synthesized by the substitution of EAB and alkali hydrolysis. It gelled into calcium-crosslinked beads in $CaCl_2$ solutions with an easy method. The hydrolytic erosion of gel beads based on the bead structure could be regulated by the bead preparation conditions, such as the concentration of PCPAP or $CaCl_2$. The obvious pH sensitivity of erosion for PCPAP–$Ca^{2+}$ beads was observed. Additionally, PCPAP could be degraded mainly through the breakage of the backbone, which could prevent accumulation in the body. Because of these properties, this novel polyphosphazene may be useful for drug controlled release, especially for oral delivery.

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