Preparation and Evaluation of Chitosan-Coated Polyphosphazene Hydrogel Beads for Drug Controlled Release

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ABSTRACT: Chitosan-coated polyphosphazene-Ca^{2+} hydrogel beads were fabricated by dropping polyphosphazene into $CaCl_2$/chitosan gelling solution. Polyphosphazene used here was a water-soluble degradable polyanion (PCPAP), which carried almost two carboxylatophenamino groups on each phosphorus atom of the polymer backbone. Two kinds of turbidimetric titration were applied in this study to reveal the interaction between PCPAP and chitosan within the pH range of 4.57≈7.14. The effect of gelling solution pH on the properties of chitosan-coated PCPAP beads was especially emphasized. It was found that the PCPAP/chitosan complex prepared at relatively high pH (pH 6.5) dissociated most slowly in pH 7.4 phosphate-buffered solution (PBS). The erosion of chitosan-coated beads and the release of model drug (Coomassie brilliant blue and myoglobin) in PBS were both obviously prolonged with the increase of gelling solution pH, exhibiting perfect accordance with the behavior of complex dissociation. In addition, the coating of PCPAP/chitosan complex on the bead surface facilitated the improvement of drug loading efficiency. The higher the gelling solution pH, the more the drug loading efficiency improved. At pH 6.5 (PCPAP 5%, $CaCl_2$ 7%, chitosan 0.3%), the loading efficiency of myoglobin in beads reached as high as 93.2%. These results indicate that the chitosan-coated polyphosphazene- Ca^{2+} bead is a potential formulation for drug controlled release. © 2004 Wiley Periodicals, Inc. J Appl Polym Sci 92: 1993–1999, 2004

Key words: polyphosphazene; chitosan; polymer complex; turbidimetric titration; drug controlled release

INTRODUCTION

Currently, spherical hydrogel has been extensively explored as a drug carrier in sustained, targeting, and responsive drug delivery system.[1–3] Conventional encapsulation techniques involve the use of chemical cross-linking agents, heat, or radiation. These harsh processing conditions may be detrimental to incorporated bioactive therapeutics. Furthermore, some chemical cross-linking agents, such as glutaraldehyde, can cause serious cellular toxicity in vivo. To overcome these disadvantages, an alternative encapsulation method of reversible physical cross-linking has received much attention. Based on electrostatic interactions between polyanions and polycations or between polyelectrolytes (polyanions or polycations) and oppositely charged multivalent ions, hydrogel beads can be easily formed under extremely mild conditions. Among these polyelectrolytes, natural polymers play principal roles for potential application in various types of administration due to their excellent biocompatibility and biodegradation. For example, Tsung and Burgess[4] reported the preparation of heparin/gelatin microcapsules by coacervation. Kikuchi et al.[5] prepared alginate-Ca^{2+} beads by adding alginate solution dropwise into an aqueous calcium chloride solution. Carboxymethylcellulose-Al^{3+} bead is also a good example that can control drug release by the erosion of hydrogel matrix.[6] On the contrary, synthetic polymers, mainly referring to polyacrylic acid, polyethylenimine, and their derivations, are used in the limited field of oral formulations because they fail to degrade in vivo.

Polyphosphazene represents a new family of biodegradable polymers with an inorganic backbone consisting of alternating nitrogen and phosphorous atoms and two side groups attached to each phosphorous atom.[7] Its unique characteristic is the ease with which it links specific side groups to the backbone by efficient substitutive techniques. Recently, we have synthesized a novel polyphosphazene containing carboxylatophenamino groups (PCPAP) by the substitution reaction of ethyl *p*-amino benzonate with poly(dichlorophosphazene) and alkali hudrolysis.[8] It undergoes degradation to low-molecule segments under physiological conditions to avoid accumulation in the body. In addition, it is worth noting that PCPAP can dissolve in water in its sodium salt form and has the ability to undergo a liquid-gel phase transition upon contact with the aqueous solution of calcium chloride. We have fabricated calcium cross-linked PCPAP hydrogel beads to extend the drug release, but it was difficult to achieve satisfactory drug loading effi-

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ciency and longer drug release duration. As much work has reported, semipermeable membrane coatings, formed by a polyelectrolyte complex on the surface of hydrogel beads, exhibit many advantages, including the increase of drug payload, prolonged drug release, and improvement of the mechanical strength of beads.[8] Chitosan is a natural polysaccharide, comprising copolymers of glucosamine and *N*-acetylglucosamine. Due to its excellent biodegradability and special polymeric cationic character, chitosan has been widely exploited in the pharmaceutical industry.[9,10] Hence, this study aims to develop chitosan-coated PCPAP-Ca^{2+} hydrogel beads for drug controlled release to overcome those problems of uncoated PCPAP beads.

EXPERIMENTAL

Materials

PCPAP was synthesized as previously described.[8] M_n was 13,570. Chitosan was obtained from Tianbao Chitosan Co. Ltd (China) and refined twice by dissolving in dilute HAc solution and precipitating from dilute ammonia, the degree of deacetylation was 86%, M_v was 460,000. Coomassie brilliant blue R250 (BB, Mw 825) was purchased from Fluka A.G. (Switzerland). Myoglobin (Mb, M_w18,800) was supplied by Sigma Chemical Co. All other chemicals were used as received.

Turbidimetric titration

Turbidity titration was carried out to evaluate the interaction of PCPAP and chitosan.[11–13] Two types of titration were applied: In type I titration, 0.2 g/L PCPAP aqueous solutions, with equivalent amounts of sodium carbonate and 0.2 g/L chitosan solution in dilute hydrochloric acid, were first prepared, respectively. Another mixed solution containing 0.2 g/L PCPAP and 0.2 g/L chitosan was also obtained. Titrant hydrochloric acid or sodium hydroxide was delivered through a microburette into the solution with gentle stirring at 37°C. The pH change of solution was monitored by a digital pH meter with a precision of ± 0.01 during the titration. In type II titration, the pH of 0.2 g/L PCPAP solutions was separately adjusted to 5.0, 5.5, 6.0, and 6.5 by dilute hydrochloric acid. Under mild stirring, 1 g/L chitosan solution with the same pH value was added slowly into PCPAP solution. The consumption volume of chitosan solution was recorded to calculate the weight ratio of PCPAP/chitosan in the corresponding complex. In all cases, the changes in turbidity were examined at 420 nm with an UV-vis spectrophotometer (Shimadzu 1201) and reported as 100-% T which is linearly proportional to the true turbidity for $T > 0.9$. The time between turbidity measurements was 5 min.

Preparation and dissociation of PCPAP/chitosan complex

PCPAP solutions (2 g/L) at pH 5.0, 5.5, 6.0, and 6.5 were prepared first. According to the results of turbidity titration, a certain amount of chitosan was dissolved in dilute hydrochloric acid. The pH of chitosan solution was adjusted by sodium hydroxide to the same value as that of PCPAP solution. PCPAP solution (10 ml) then was mixed with 10 ml chitosan together in a flask under magnetic stirring. After 1 h, the solid resultant was separated by filtration and washed using fresh distilled water three times and then dried under vacuum. The complexes were ground with a mortar and pestle and sieved to the size of 50–125 μm. Complex granules (10 mg) were immersed in 5 mL of 0.1*M* pH 7.4 phosphate-buffered solution (PBS) and incubated in a shaking water-bath at 37°C, 50 rpm. At the appropriate intervals, the sample was centrifuged and 5 ml of supernatant fluid was removed. Another 5 ml of fresh PBS was added to disperse the complex granules well again. After being filtered by a 0.45-μm filtration membrane, the concentration of PCPAP in supernatant fluid was monitored at 258 nm with an UV-vis spectrophotometer, which can reflect the dissociation degree of PCPAP/chitosan complex.

Preparation of chitosan-coated PCPAP-Ca^{2+} beads

The preparation process of chitosan-coated PCPAP-Ca^{2+} bead was similar to that reported by Murata et al.[14] Briefly, a 5 or 10% PCPAP solution was obtained by dissolving 0.5 or 1 g PCPAP in 10 ml of distilled water containing equimolar amounts of sodium carbonate. The solution pH was adjusted to 5.0, 5.5, 6.0, or 6.5, correspondingly. One milliliter of this solution was directly dropped through a syringe needle (0.4 mm diam) into 15 ml gelling solution under gentle agitation. The gelling solution contained 1~10% calcium chloride and 0.1~0.5% chitosan with the pH in the range of 2.0~6.5. Once PCPAP solution met the cross-linking agent, hydrogel beads began to form. After hardening for 1 h in the cross-linking solution at room temperature, the beads were collected by filtration and washed three times with distilled water and then slowly evaporated at 37°C. When the samples were almost dried, they were put on a vacuum line to remove the last trace of water.

Erosion of chitosan-coated PCPAP-Ca^{2+} beads

A certain amount of dry chitosan-coated PCPAP-Ca^{2+} beads (ca. 20 mg), fabricated under different condi-

tions, were immersed in 5 ml of 0.1*M* pH 7.4 PBS and incubated at 37°C. The erosion rate was evaluated by weight loss of the sample defined as $(W_t - W_0)/W_0$, where W_0 and W_t were the weights at an initial and a specific time.

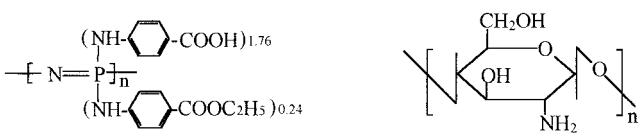
Model drug release

After a model drug (BB or Mb) was dissolved in PCPAP solution (PCPAP/drug weight ratio, 10/1), the drug-loaded beads were fabricated following the same procedure as described in the preparation of chitosan-coated PCPAP-Ca^{2+} beads. To assess the effect of chitosan coating on the drug release, dry drug-loaded beads were immersed in 5 ml of 0.1*M* pH 7.4 PBS and incubated at 37°C. The media were withdrawn at predetermined intervals. The content of BB or Mb was examined by UV-visible spectrophotometric measurements at 590 or 410 nm, respectively. During the bead preparation process, the aqueous phase was collected, and the drug content in it was determined to calculate the drug loading efficiency. Loading efficiency = (the drug given − the drug loss)/the drug given 100.

RESULTS AND DISCUSSION

Preparation and dissociation of PCPAP/chitosan complex

Chitosan is a naturally occurring polysaccharide comprising glucosamine and *N*-acetyl-glucosamine with polycation characteristics, while PCPAP is a polyanion with nearly two carboxylic groups on each constitutional repeating unit (Scheme 1). These properties of chitosan and PCPAP make it feasible to form a polymer complex through electrostatic interactions. Figure 1 shows the type I turbidimetric titration curves of single PCPAP solution, single chitosan solution, and a mixed solution of PCPAP and chitosan. The PCPAP solution remains optically clear irrespective of the decrease of pH until the pH reaches a critical value (pH 4.85), at which point an abrupt increase of turbidity occurs. This turbidity curve is a typical model for a weak acid, indicating the poor solubility of PCPAP at low pH (less than 4.85), resulting from seriously inhibited ionization of carboxyl groups. For chitosan, a weak polybase, the turbidity change also takes place



a. PCPAP b. chitosan

Scheme 1

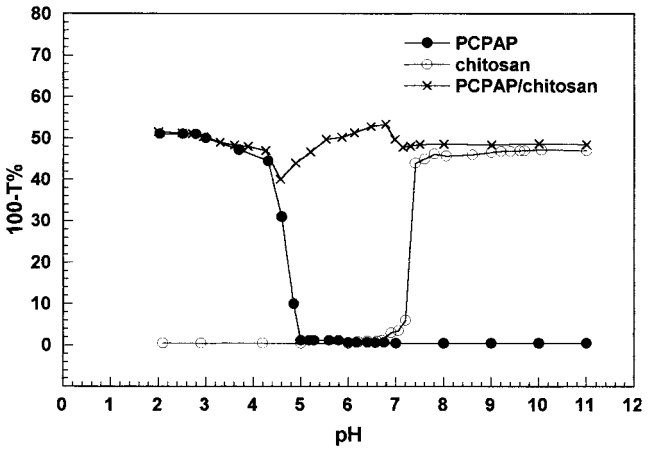


Figure 1 The turbidity changes of PCPAP solution (0.2 g/L), chitosan solution (0.2 g/L), and PCPAP/chitosan mixture solution (0.2 g/L PCPAP and 0.2 g/L chitosan) versus the pH at 37°C.

in the process of titration by sodium hydroxide (pH 7.2), but the trend of turbidity change is the opposite case in that the solubility of chitosan decreases greatly at high pH (above 7.2). Different from PCPAP or chitosan solution, significant turbidity exists in the whole pH region for the mixed PCPAP/chitosan solution, and during the titration, two critical pH points of ca. 4.57 and 7.14 are prominent. When the pH is lower than 4.57, the turbidity curve corresponds to the behavior of the PCPAP solution, while when the pH increases over 7.14, the turbidity curve approaches that of the chitosan solution. Making a comparison among these three turbidity curves, it is reasonable to presume that some interactions occurred between PCPAP and chitosan in the pH region of 4.57~7.14. Furthermore, such interaction was closely related to the solution pH since the turbidity seemed to increase with the increase of pH. Therefore, it was very significant to conduct a type II turbidimetric titration to explore the effect of solution pH on the formation of PCPAP/chitosan complex.

Type II turbidimetric titration curves of PCPAP and chitosan in different pH media, are shown in Figure 2. All of the curves display a three-stage characteristic. At the first stage, a low but measurable turbidity gradually increases and is almost linearly proportional to the consumption volume of chitosan until the transmittance decreases to 82~70% (18% $<$ 100-%T $<$ 30%). Following that, an abrupt increase in turbidity constitutes the second stage of titration. The consumption volume of chitosan at which this phenomenon takes place is defined as the critical volume (V_ϕ). Subsequently, the turbidity was not increased any more. The break point of the curves was designated as V_ϕ', indicating the end point of titration. As in some results that have been published earlier,[15] the degree of solution turbidity was proportional to not only the

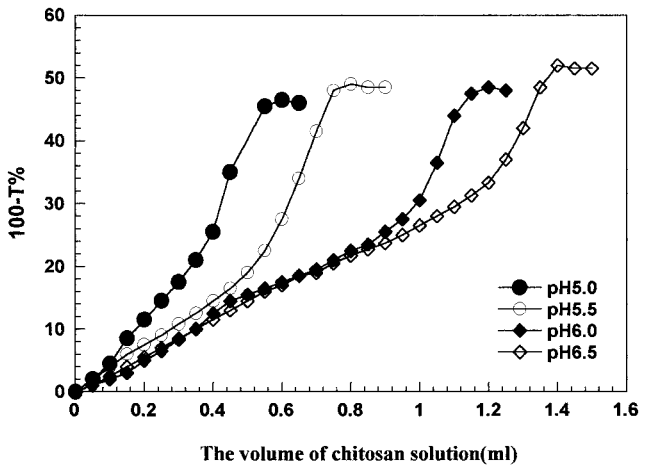


Figure 2 The turbidity changes of PCPAP/chitosan mixture solution during chitosan titriation under different pH conditions at 37°C. Concentration: PCPAP 0.2 g/L, chitosan 1 g/L.

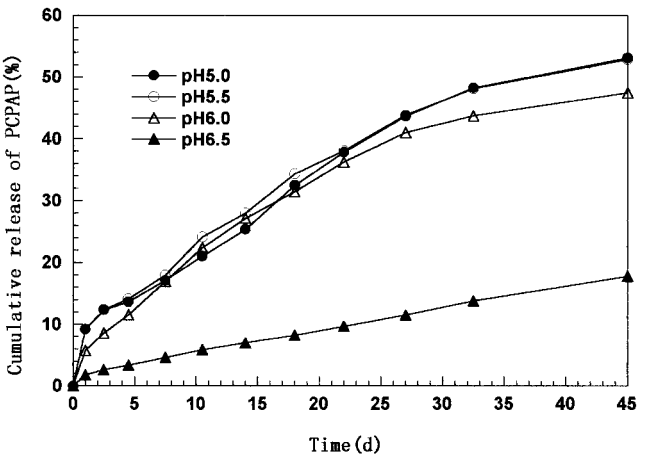


Figure 3 The cumulative release of PCPAP from PCPAP/chitosan complex prepared under different pH conditions in pH 7.4 PBS at 37°C.

concentration of insoluble particles but also to the particle size. When polycations were dropped into the solution containing a large excess of polyanion, they associated to the polyelectrolytes complex with small bulk size. The greater the volume of polycation consumed, the higher was the concentration of complex particle with constant size, which is attributed to the linear increase of turbidity. Once the quantity of titrant exceeded V_ϕ, small complex particles coagulated with each other to bigger aggregates, resulting in the abrupt increase of turbidity until the end point of titration. In addition, it is observed from Figure 2 that the slope of curve in the first phase was reduced with the increase in the solution pH. To understand this situation, we may calculate the weight ratio (α) of the two polymers and the molar ratio (β) of carboxyl groups in PCPAP to amino groups in chitosan at various pH levels (Table 1) according to the following formula:

$$\alpha = (C_{\text{PCPAP}} V_{\text{PCPAP}})/(C_{\text{chitosan}} V_\phi');$$

$$\beta = (n \times C_{\text{PCPAP}} V_{\text{PCPAP}}/W_{\text{PCPAP}}) \div (m \times C_{\text{chitosan}} V_\phi'/W_{\text{chitosan}})$$

TABLE I
Some Properties of PCPAP/Chitosan Complex Prepared under the Different pH Conditions

	V_ϕ	V_ϕ'	α	β	W_c (g)[a]	W_t (g)[b]	Yield (%)
pH 5.0	0.40	0.55	3.64	4.48	0.0201	0.0245	82.0
pH 5.5	0.55	0.75	2.67	3.29	0.0213	0.0261	81.6
pH 6.0	0.96	1.15	1.74	2.14	0.0253	0.0293	86.3
pH 6.5	1.15	1.40	1.43	1.75	0.0304	0.0314	96.8

[a] The experiment value of complex weight.
[b] The theory value of complex weight.

Let $C_{\text{PCPAP}} = 0.2$ g/L, $C_{\text{chitosan}} = 1$ g/L, $V_{\text{PCPAP}} = 10$ ml. n (=1.76) represents the molar substituting ratio of carboxylatophenamino groups in PCPAP. m (=0.86) represents the deacetylation degree of chitosan. W_{PCPAP} (=323.72) and W_{chitosan} (=194.88) are the mean repeating unit weights of PCPAP and chitosan, respectively.

It can be seen that both α and β declined when the solution pH varied from 5.0 to 6.5. Since the ionization of PCPAP was depressed at relatively low pH, a unit of PCPAP bears less negative charges than at high pH, but it is the opposite case for chitosan. As a result, a certain amount of chitosan was able to combine with more PCPAP to form complex particles with a larger size at low pH. This supposition was proved again by the fact that both V_ϕ and V_ϕ' at low pH appear correspondingly ahead of that at high pH in Figure 2.

By making use of α, we fabricated the PCPAP/chitosan complex under different pH conditions and exploited the erosion of each complex in the 0.1*M* pH 7.4 PBS at 37°C. The experimental values of total weight (W_e) for complex were measured and compared with the theoretical value (W_t) in Table 1. It can be found that the change of W_e with pH coincided with that of W_t, but the complex yield, defined as W_e/W_t, can hardly approach 100% except at pH 6.5. Figure 3 illustrates the cumulative PCPAP release from the different polymer complexes. It is obvious that the PCPAP gradually leached from the complex, as the incubation time was prolonged, suggesting dissociation between PCPAP and chitosan. Furthermore, the PCPAP release from the complex prepared at pH 6.5 was rather slower than for the other three complexes. On the basis of our previous experiments, the combination state of PCPAP with chitosan through electrostatic interaction, depended on the pH to a great extent. When α goes toward 1.75 at pH 6.5, a relatively denser inner structure of complex with in-

creased cross-linking points was obtained, which led to greater difficulty in the dissociation of the complex. This property of the complex is the major advantage of this novel vehicle to control the release of incorporated drugs.

Preparation and erosion of PCPAP-Ca^{2+} beads

In the previous paper, we reported on the ability of PCPAP to undergo a liquid-gel phase transition upon contact with aqueous solution of calcium chloride. In general, high concentrations of PCPAP and $CaCl_2$ solutions are beneficial to the formation of round beads with excellent properties.[8] But coating chitosan on these bead surfaces rendered the results rather complicated. Since the solution pH greatly influenced the structure of polymer complex of PCPAP and chitosan, the effect of solution pH on the appearance and erosion of beads was closely investigated. No matter whether the pH was varied from 2.0 to 6.5 ($CaCl_2$ 3.5 or 7%; chitosan 0.1, 0.3, or 0.5%; PCPAP 5 or 10%), solid particles were collected. But the bead shape was irregular for pH 2.0 and 4.0, while that of pH 5.0~6.5 was perfectly round in its wet state. In addition, after drying, the beads prepared at pH 2.0 or 4.0 were very brittle and the majority of them were seriously broken, and those of pH 5.0 and 5.5 collapsed somewhat to a disc shape, while the beads with pH 6.5 maintained their spherical shape with a diameter of 0.9 ± 0.1 mm although they had several gaps on the surface. As discussed previously in the bead's preparation process,[8] because of the concentration gradient, Ca^{2+} diffused from the outer solution to the inner solution of the PCPAP droplet while PCPAP moved in the contrary direction. Once they met, cross-linking took place. At the low concentration of PCPAP and Ca^{2+}, the cross-linking between PCPAP and Ca occurred just on the surface of PCPAP droplet. Thus the heterogeneous structure, of a relatively dense surface layer with a loose core was the dominant factor to cause the break or collapse of beads during the drying process. With the addition of chitosan into the gelling solution, PCPAP diffused from the droplet core toward the interface between the droplet and the gelling solution, to form a membrane with calcium ions and chitosan, which resulted in the more heterogeneous structure of beads. But, with the increase of pH in gelling solution from 5.0 to 6.5, α decreased, which meant a unit of chitosan was associated with less PCPAP at high pH. Therefore, the beads prepared at pH 6.5 had the strongest complex coating with a dense structure, which led to the most homogeneous structure and the best appearance.[17] Increasing the concentration of $CaCl_2$ would promote the diffusion rate and helpful to form a homogenous cross-linked structure to strengthen the bead. Increasing the concentration of PCPAP retarded its outward diffusion, which also exerted a positive

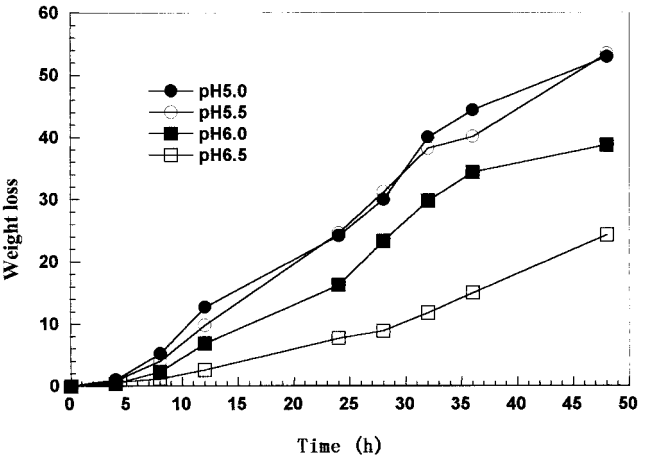


Figure 4 The weight loss of chitosan-coated PCPAP-Ca^{2+} beads prepared under different pH conditions (5% PCPAP, 7% $CaCl_2$, and 0.3% chitosan) in pH 7.4 PBS at 37°C.

effect on the spherical appearance, just like the PCPAP-Ca beads without chitosan coating.[8] For example, when 10% PCPAP was dropped into the gelling solution containing 10% $CaCl_2$ and 0.3% chitosan at pH 5.0, dry spherical beads can be achieved. Compared to pH 5.0~6.5, worse shape and poorer strength of beads at pH 2.0 and 4.0 was possibly attributed to the absence of the PCPAP/chitosan complex on the bead surface. In fact, based on the above discussion of PCPAP/chitosan, the ionization of PCPAP was absolutely depressed at pH below 4.7, thus the solidification of PCPAP at pH 2.0 and 4.0 indicates precipitation in the cross-linking solution instead of cross-linking through calcium ions and chitosan.

During the erosion process, the beads prepared at pH 2.0 and 4.0 disappeared within 10 h in pH 7.4 PBS at 37°C, while those of pH 5.0~6.5 successively underwent swelling, rupture, and diminishing but did not disappear over more than 50 h. Furthermore, the erosion rates of beads are listed in the following order based on the pH of the gelling solution: pH 5.0 > pH 5.5 > pH 6.0 > pH 6.5. It is shown in Figure 4, after 48 h, 52.9, 53.4, 38.7, and 24.3% of initial weight was lost for pH 5.0, 5.5, 6.0, and pH 6.5, respectively. These results accord well with the dissociation behavior of PCPAP/chitosan. The higher the solution pH, the denser the structure of PCPAP/chitosan coating on the surface, which led to the complex dissociating more slowly. As shown in Figure 5, the erosion duration of chitosan-coated PCPAP-Ca beads was prolonged by the increase of chitosan content in the cross-linking solution, due to the improved stability of the chitosan-coated PCPAP-Ca beads. Similarly, the increase of PCPAP concentration (C_p), or $CaCl_2$ concentration (C_{Ca}), extended the erosion duration of the beads, which possibly resulted from the more homogeneous structure of beads with high C_p and C_{Ca} (Fig. 6).

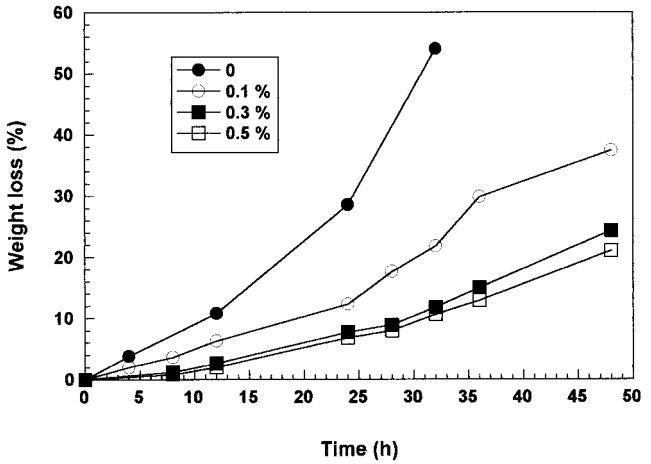


Figure 5 Weight loss of chitosan-coated PCPAP-Ca^{2+} beads prepared at pH6.5 using 5% PCPAP, 7% $CaCl_2$, and 0~0.5% chitosan in pH 7.4 PBS at 37°C.

As shown in previous research,[8] the erosion mechanism of PCPAP-Ca^{2+} beads was dominated by the ion exchange of sodium ions in PBS and calcium ions bound to PCPAP. In other words, sodium ions diffused toward the bead core and displaced the bound calcium ions, leading to dissolution of PCPAP. But, in the case of chitosan-coated PCPAP-Ca^{2+} beads, it is reasonable conclude that the erosion mechanism is the synergistic effect between Ca^{2+}-Na^+ ion exchange and dissociation of PCPAP/chitosan complex. Due to the poor solubility of chitosan in pH 7.4 PBS, the chitosan-coated beads can't erode completely like uncoated PCPAP-Ca^{2+} beads.

Drug loading efficiency and drug release

Table 2 shows the influence of chitosan coating on BB and Mb loading efficiency in beads. Generally, compared to PCPAP-Ca^{2+} beads, chitosan coating facilitated the improvement of drug-loading efficiency. As the concentration of chitosan increased to 0.5%, the loading efficiency of BB and Mb reached 75.6 and 89.2%, respectively, which were evidently higher than those of PCPAP-Ca beads without chitosan coating. Moreover, the pH values of the cross-linking solution obviously influenced the loading efficiency (Table 3). The loading efficiency at pH 2.0 or 4.0 is very low and almost equal, but those at pH in the range of 5.0–6.5 improved more than 1.5 times and became higher with the increase of pH. These results suggested the fact that significant drug loss inhibition for PCPAP-chitosan complex was associated with the preparation process. Also in accordance with the above discussion, the densest structure of coating at pH 6.5 resulted in the highest drug-loading efficiency. In all cases, the loading efficiency of Mb was higher than that of BB because the diffusion out of the droplet of Mb with greater molecular weight was more difficult.

TABLE II
Effect of Chitosan Concentration on the Drug-loading Efficiency (%) of BB and Mb in Chitosan-coated PCPAP-Ca^{2+} Beads (PCPAP 5%, $CaCl_2$ 7%, pH 6.0)

	Chitosan concentration (%)			
Model drug	0	0.1	0.3	0.5
BB	58.3	67.8	72.5	75.6
Mb	75.6	80.2	83.6	89.2

The release curves of Mb from chitosan-coated PCPAP-Ca beads are shown in Figure 7. It was observed that Mb release was prolonged in comparison with the PCPAP-Ca beads, and the release rates were proportional to the decrease of pH during the preparation. For example, the release percentage of Mb reached almost 100% for pH 5.0 after 24 days, while that for pH 6.5 was only 36.1% (PCPAP 5%, $CaCl_2$ 7%, chitosan 0.3%). Similar release behavior of BB under the same preparation conditions was obtained (not shown). Thus it is suggested that the coating of PCPAP and chitosan with dense complex structure can effectively retard the release of incorporated drug. Also the Mb release rate decreased with the increase in the concentration of chitosan, but the difference was not very

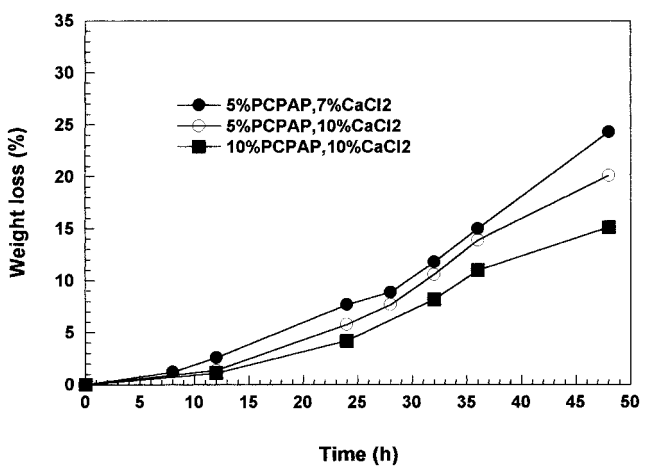


Figure 6 Weight loss of chitosan-coated PCPAP-Ca^{2+} beads prepared at pH 6.5 using 5 or 10% PCPAP, 7 or 10% $CaCl_2$, and 0.3% chitosan in pH 7.4 PBS at 37°C.

TABLE III
Effect of pH on the Drug-loading Efficiency (%) of BB and Mb in Chitosan-coated PCPAP-Ca^{2+} Beads (PCPAP 5%, $CaCl_2$ 7%, chitosan 0.3%)

Model drug	pH					
	2.0	4.0	5.0	5.5	6.0	6.5
BB	45.2	42.1	66.8	68.4	72.5	78.6
Mb	56.2	58.0	80.2	83.5	88.6	93.2

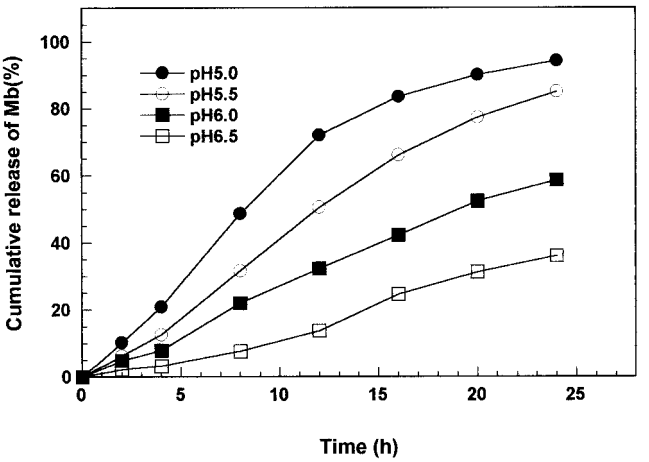


Figure 7 The cumulative release of Mb from chitosan-coated PCPAP-Ca^{2+} beads prepared under different pH conditions (5% PCPAP, 7% $CaCl_2$, and 0.3% chitosan) in pH 7.4 PBS at 37°C.

distinct. At 24 days in the experiment, 33.7% Mb diffused out, in beads using 0.5% chitosan, and 40.3% in beads using 0.1% chitosan (PCPAP 5%, $CaCl_2$ 7%).

CONCLUSION

Chitosan coating on PCPAP-Ca^{2+} hydrogel beads was accomplished by an extremely mild method. The pH modulation of gelling solution during PCPAP/chitosan complex formation was the predominant factor to influence the erosion, appearance, drug-loading efficiency, and drug release of beads as well. In general, when pH was relatively high, a complex coating with a dense structure aggregated on the bead surface. Therefore, good appearance and high drug-loading efficiency can be achieved. Also, the duration of bead erosion and drug release can be efficiently prolonged. These results indicated that chitosan-coated polyphosphazene-calcium bead is a potential formulation for drug controlled release.

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