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Design of a core-shelled polymer cylinder for potential programmable drug delivery

L.Y. Qiu [a,*], K.J. Zhu [b]

[a] *College of Pharmaceutical Science, Zhejiang University, Hangzhou 310006, People's Republic of China*
[b] *Department of Polymer Science and Engineering, Zhejiang University, Hangzhou 310027, People's Republic of China*

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Abstract

A cylindrical dosage form comprising a laminated composite polymer core and a hydrophobic polycarbonate coating was proposed for programmable drug delivery. In the core, poly[(ethyl glycinate) (benzyl amino acethydroxamate) phosphazene] was synthesized as drug-loaded layers for its strong pH-sensitive degradation (eroded after 1.5 days at pH 7.4 and more than 20 days at pH 5.0 and 6.0). Poly(sebacic anhydride)-*b*-polyethylene glycol or poly(sebacic anhydride-*co*-trimellitylimidoglycine)-*b*-poly(ethylene glycol) was selected as isolating layers for their good processing properties at room temperature and suitable erosion duration. The in vitro drug release studies of these devices were conducted under physiological conditions (pH 7.4). The results revealed that the model drugs (brilliant blue, FITC-dextran, myoglobin) could be released in typical pulsatile manner. Moreover, the duration time of drug release (24–40 h) and the lag time (18–118 h) could be separately regulated by the mass of polyphosphazene and the type or mass of polyanhydride. In this experiment, the cooperative effect of polyanhydrides and pH-sensitive degradable polyphosphazene was specially demonstrated, which offers a new idea to develop a programmable drug delivery system for single dose vaccine and other related applications. © 2001 Published by Elsevier Science B.V.

Keywords: Programmable drug delivery; Polyanhydride; Polyphosphazene

1. Introduction

In the past few decades, much research has been focused on sustained drug delivery to reach a constant drug blood level over a long period of time. But recently the investigations based on clinical cases and chronopharmacology theory have revealed an interesting fact that sustained drug delivery is not fit for all therapeutic agents (Giuseppe, 1991; Forse and Mass, 1995). Instead, pulsed drug delivery is recognized as a satisfactory technology which releases a certain amount of the drug within a short time period after a lag time.

To date, two primary approaches have been used for the development of pulsed drug delivery, namely, programmable drug delivery and intelligent pulsed drug delivery. Making full use of materials responsive to glucose, pH, temperature,

* Corresponding author. Postal address: 60-206 Qiushi Cun, Yuquan, Hangzhou, Zhejiang 310013.
E-mail address: xgaozu@mail.hz.zj.cn (L.Y. Qiu).

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ultrasound, magnetic and electrical fields, intelligent pulsed drug delivery is mainly applied in releasing insulin to maintain the normal blood-sugar concentration according to the physiological need of body (Horbett et al., 1983; Okano et al., 1990). In contrast, programmable drug delivery systems can automatically release drug at predetermined time merely depending on various properties of materials such as molecular weight, hydrophilicity and degradation (Wuthrich et al., 1992; Amer et al., 1994). By this means, hormone substitution theory (Santoro et al., 1986; Giusti and Cavognaro, 1991) and single dose vaccine (Eldridge et al., 1991; Cleland et al., 1998) have been achieved. But how to appropriately control the duration time of drug release and the lag time of each pulse always brings about great puzzles in the research.

With this aim in mind we developed a core-shelled cylindrical polymer device for programmable drug delivery, which is composed of a biodegradable hydrophobic coating and laminated core of polyanhydrides and polyphosphazenes. Polyanhydrides were used as isolating layers attributed to their suitable degradation, which could modulate the lag time of drug release within a broad range (Jiang and Zhu, 1999). As for biodegradable polyphosphazenes, they are a series of relatively new materials in drug delivery systems and have received much attention due to their ease of being widely modified with specific characteristics (Allcock, 1997). When introducing benzyl ester of amino acethydroxamic acid group to the polymer backbone, the resultant polyphosphazene exhibits a pH-sensitive degradation character, which is quite important to a drug-carried layer. Herein, we report some primary results on the manufacture and drug release behavior of these devices.

2. Materials and methods

2.1. Materials

Poly[(ethyl glycinate)(benzyl amino acethydroxamate)phosphazene] (20:80 by molar) (PEBP) was originally synthesized in our lab (Qiu and Zhu, 2000). Poly(sebacic anhydride)-*b*-poly(ethylene glycol) (65:35 by molar, MW_{PEG}200) (PSP) and poly(sebacic anhydride-*co*-trimellitylimidoglycine)-*b*-poly(ethylene glycol) (30:50:20 by molar, MW_{PEG}200) (PSTP) were synthesized by melt-condensation copolymerization. Poly(lactide-*co*-1,3-trimethylene carbonate) (30:70 by molar) (PLCA) was synthesized by ring-opening copolymerization of lactide and trimethylene carbonate using $Sn(Oct)_2$ as catalyst (Cai and Zhu, 1997). The structures of these polymers are illustrated in Fig. 1. Fluorescein isothiocyanate dextran (FITC-dextran) (Mn 71 200) and myoglobin (MW 18 800) were purchased from Sigma (St Louis, MO). Brilliant blue G (BB) was obtained from Fluka Chemie AG (Buchs, Switzerland).

2.2. Polymer degradation

2.2.1. PEBP degradation

Samples of disc shape (2.5 mm in diameter; 2 mm in thickness) were fabricated by compression in a mould under a pressure of 100 kg/cm^2 at room temperature for 2 min. Hydrolysis of the polymers in vitro was performed by immersing samples in each buffer solution (pH 5.0 and 6.0 citric acid/sodium citriate buffer, pH 7.4 and 8.0 boronic acid/borax buffer) at 37°C and the samples were recovered periodically and dried. The weight loss was measured gravimetrically.

2.2.2. PSP and PSTP degradation

Polyanhydride discs (2.5 mm in diameter, 2 mm in thickness) were also prepared by compression under the same conditions. The degradation was operated in a daily-changed pH 7.4 phosphate buffer solution (PBS) at 37°C. The pH change of PBS was monitored by a pH meter. At definite time intervals, the sample was retrieved from the aqueous media and dried under vacuum to constant weight. The degradation rate was evaluated by the weight loss.

The data reported are for the mean weight loss for the three samples, with the deviation approximately 2–6%.

2.3. Drug release from PEBP disc

BB, FITC-dextran and myoglobin were used as model drugs. Prior to making drug-loaded samples by the same method stated in degradation studies, the micronized PEBP was sieved into a particle size range of 90–150 μm and mixed with the same size range of model drugs. Drug-loaded (10%) samples were placed in 5 ml of buffer with different pH at 37°C. The buffer solutions were frequently replaced to maintain perfect sink conditions. BB and myoglobin were respectively monitored by visible absorbance at 590 and 420 nm using a UV–vis spectrophotometer (Smimatz-1201). FITC-dextran release was measured by fluorescence intensity (Hitachi F4000, the excitation wavelength was 496 nm and the emission wavelength was 520 nm).

2.4. Preparation of programmable drug delivery device

Polyanhydride (PSTP or PSP) and 10% drug-contained PEBP powder was individually weighed according to the designed composition in Table 1, then compressed alternately by compression molding at 100 kg/cm^2 pressure at room temperature into a laminated cylindrical core. After quickly dipping into a methylene chloride solvent, the core was tightly coated with one open-end by a PLCA film of 0.5 mm thickness, which was fabricated by compressing beforehand. The entire cylindrical device had a final diameter of 3.5 mm and a height of 11 mm. Fig. 2 gives the longitudinal section structure of this model device for programmable drug release. It can be seen that the device is composed of a thin PLCA coating

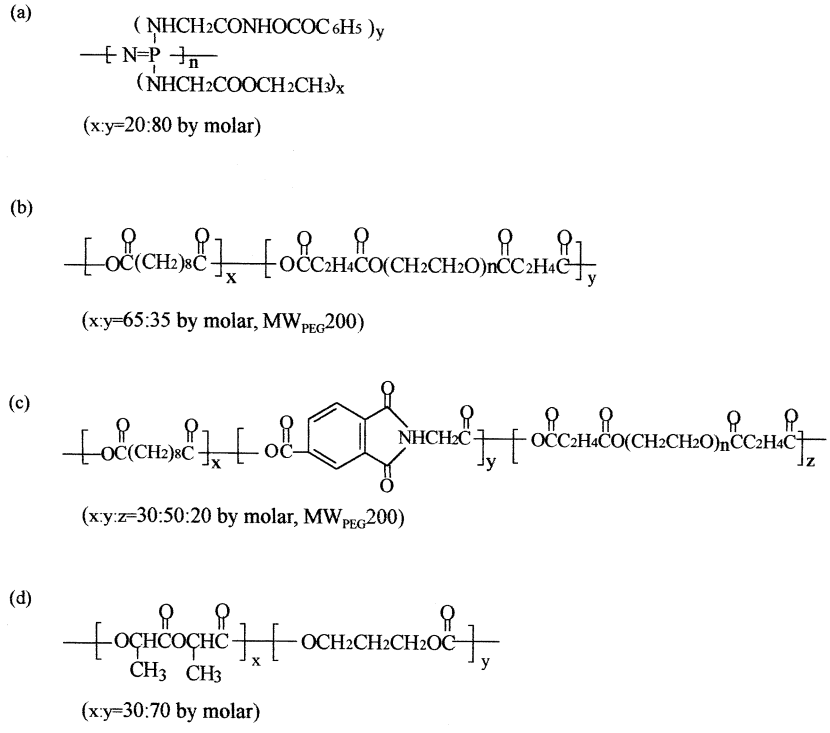

Fig. 1. Chemical structures of (a) poly[(ethyl glycinate)(benzyl amino acethydroxamate) phosphazene] (x:y, 20:80 by molar) (PEBP); (b) Poly(sebacic anhydride)-*b*-poly(ethylene glycol) (x:y, 65:35 by molar, MW$_{PEG}$200) (PSP); (c) poly(sebacic anhydride-*co*-trimellitylimidoglycine)-*b*-poly(ethylene glycol) (x:y:z, 30:50:20 by molar, MW$_{PEG}$200) (PSTP); (d) Poly(lactide-*co*-1,3-trimethylene carbonate) (x:y, 30:70 by molar) (PLCA).

Table 1
The compositions of the devices

Code	Isolating layers	Drug-loaded layers	Model drug
I	PSTP 20[a]	PEBP 18[b]	BB 2[c]
II	PSTP 20	PEBP 18	FITC-dextran 2
III	PSTP 20	PEBP 18	Mb 2
IV	PSTP 30	PEBP 18	Mb 2
V	PSTP 20	PEBP 36	Mb 4
VI	PSP 20	PEBP 18	Mb 2
VII	PSP 20	PEBP 18	Mb 2

[a] Mass of PSTP or PSP (mg).
[b] Mass of PEBP (mg).
[c] Mass of drug (mg).

with one open-end and a cylindrical core containing alternate polyanhydrides isolating layers and drug-loaded PEBP layers.

2.5. Drug release from the device

Each device was placed in 0.1 M pH 7.4 phosphate buffer using temperature regulated shaker baths at 37°C and 100 rev./min. Periodically during the experiment, the solution was separated and the drug concentration was determined by spectrophotometry as described above. All data are expressed as the mean of two samples.

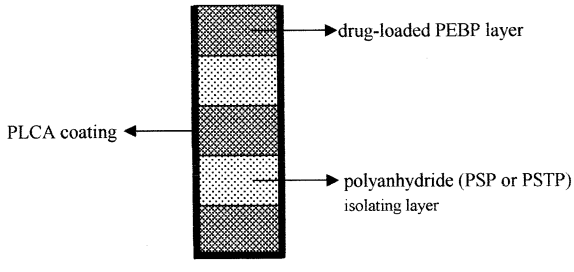

Fig. 2. Longitudinal section structure of the device designed for programmable drug delivery.

3. Results and discussion

3.1. Polymer degradation

In this new device, polyanhydrides, PSP and PSTP, were selected as isolating layers for their good processing properties as well as suitable erosion duration. From Table 2 it can be found that they have low T_g and crystallinity, which enables the polymers to be easily compressed into a dense layer at room temperature. Fig. 3 shows the degradation behavior of the polyanhydrides. PSP degraded completely within about 110 h. When introducing TMA-gly segments to PSP, the degradation of PSTP accelerated to disappear in 28 h (Jiang and Zhu, 1999). The pH variation of solution was also monitored during the polyanhydride erosion (Fig. 4). pH of PSP ranged between 4.5 and 5.2 and that of PSTP between 3.1 and 6.0 due to the release of small acidic fragments. Mäder et al. (1997) have reported the high water content and porosity in the degrading polyanhydrides. Therefore, it was reasonable to assume that the inner pH values of the device should be below 6.0 during the degrading process of the polyanhydride isolating layer.

PEBP was synthesized by modifying the full glycine ethyl ester substituted polyphosphazene (PGP) with a certain amount of free hydroxylamine to convert partial glycine ethyl ester to amino acethydroxamic acid, followed by further esterification with benzoyl chloride. The whole reaction was conducted under mild conditions and the yield was high ($>72\%$) (Qiu and Zhu, 2000). PEBP is insoluble in water. When the hydrophobicity is evaluated by water content defined as percentage water in dried polymer, its value is 0.32. PEBP also has relatively low T_g (55°C) and no T_m, which facilitates fabrication of the drug formulation under mild conditions, especially for delicate bioactive substances.

The degradation of PEBP in various pH buffers was examined to minimize the degradation behavior of drug-loaded layers in the device. Fig. 5 shows a great dependence of hydrolysis rate of PEBP on pH. It took only 12 h for the sample to dissolute completely in pH 8.0 buffer, 1.5 days in pH 7.4, but more than 20 days in weak acidic

Table 2
Some data for Poly[(ethyl glycinate)(benzyl amino acethydroxamate)phosphazene] (PEBP); Poly(sebacic anhydride)-*b*-poly(ethylene glycol) (PSP); poly(sebacic anhydride-*co*-trimellitylimidoglycine)-*b*-poly(ethylene glycol) (PSTP); Poly(lactide-*co*-1,3-trimethylene carbonate) (PLCA)

Polymer	M_n[a]	T_g (°C)[b]	T_m (°C)[c]	Crystallinity[d] (%)
PEBP (20:80[e])	7400	55	NF[f]	0
PSP[g] (65:35)	3100	−46	66.3	3.0
PSTP[g] (30:50:20)	3200	12	NF	0
PLCA (30:70)	15 600	−7	NF	0

[a] PEBP was measured by vapor pressure osmometer (Knauer) in DMSO, PSP, PSTP and PLCA were measured by GPC (Waters 205) in THF.
[b] Determined by DSC (Perkin Elmer DSC-7).
[c] Determined by DSC (Perkin Elmer DSC-7).
[d] Calculated according to Mathiowitz et al. (1990).
[e] Molar ratio.
[f] Not found.
[g] Molecular weight of PEG is 200.

media (pH 5.0 and 6.0) because of the introduction of hydroxamate group (Ulbrich et al., 1995). This degradation property of PEBP is quite important for the device. During the lag time, the degradation products of polyanhydride formed an acid microenvironment to keep PEBP from degrading and releasing incorporated drug. Once polyanhydride disappeared and saline met PEBP, PEBP degraded quickly and dismissed the drug as a pulse.

3.2. Drug release from PEBP disc

The release rates of three different model drugs from PEBP matrices were individually examined in weak acidic media (pH 5.0 and 6.0) and weak basic media (pH 7.4 and 8.0). This information would help us determine whether the microenvironment changing with the degradation stage of polyanhydrides influenced the drug release from the device. Fig. 6 shows that the release rates of model drugs in weak basic media were indeed faster than those in weak acidic media. But compared with the PEBP degradation profiles in Fig. 5, it was noted that serious burst release occurred for FITC-dextran at pH 5.0 and 6.0 and it was somewhat improved for BB. The explanation might lie in the hydrophilicity of drug. When the drug release was dominated by diffusion, the more hydrophilic the drug, the faster the release rate. But why did the polymer maintain myoglobin quite well at pH 6.0 and 5.0 to show strong pH-dependence, which was in agreement with the corresponding degradation behavior; though it is absolutely water-soluble? This phenomenon may be interpreted as follows. PEBP has negative charges after one of its side groups, glycine ethyl ester, hydrolyzed to glycine (Allcock and Pucher, 1994). Since myoglobin (iso-electric point is 6.9) is an amphoteric polymer, it carried positive charges at pH 5.0 or 6.0, which structured salt bridges with negative charges of PEBP. The formed water-insoluble polyelectrolyte complexes retained myoglobin in the matrix. When the pH was above IEP of myoglobin, such as pH 7.4 or 8.0, it carried negative charges, and the interactions between myoglobin and the polymer turned to electrostatic repulsion, myoglobin was released while the polymer degraded.

3.3. Drug release from the device

The polyanhydrides isolating layers and drug-loaded PEBP layers were alternately compressed into a laminated cylindrical core, then coated by PLCA film with one open-end. PLCA was selected as a coating due to its slow erosion (10% of weight loss within 3 months) and high hydrophobicity (0.027 of water content at equilibrium) (Cai and Zhu, 1997). Moreover dipping the core into a

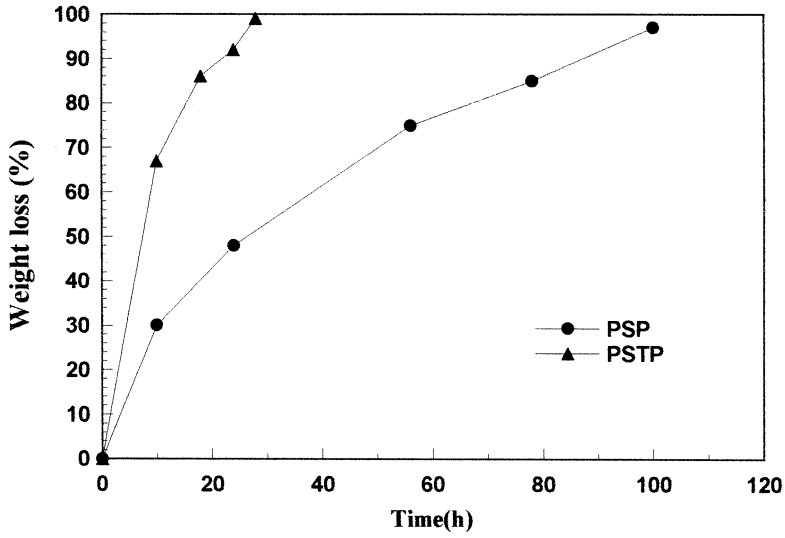

Fig. 3. Cumulative weight loss of polyanhydride PSP and PSTP discs (2.5 mm in diameter, 2 mm in thickness) in 0.1 M pH 7.4 phosphate buffer solution at 37°C.

methylene chloride solvent before coating was beneficial to closer adhesion of the core and the coating. Thus, it can be confirmed that the polymer in the device contacted the outside buffer only at the opening topside. As a result, the composite polymer core was gradually lost from the opening side, but the cylindrical device retained its original shape during the test. As shown in Table 1, several factors including the types and quantity of isolating layers, the quantity of drug-loaded layer and the drug property were taken into account one by one. The results of drug release are illustrated in Fig. 7, which is expressed as the drug release rate versus time. It was observed from all devices that three drug release pulses were separated by two intervals, which is a typical pulsatile release manner. For the device I, the first duration of pulse was about 30 h and the first interval was about 18 h, then followed by the second pulse. But a few of BB extended to the second interval. For device II, some FITC-dextran appeared at both intervals, especially at the second interval. When it turned to myoglobin, the distinctness between drug pulse and interval was very clear. This result was closely related to the hydrophilicity of drugs as discussed above. The more hydrophilic the drug, the more easily the drug diffused out and the more seriously the intervals deformed.

In devices VI and VII, PSP took the place of PSTP as isolating layers. Considering that PSP degraded more slowly than PSTP, the lag time was prolonged to about 100 h for BB and 118 h for myoglobin, which almost correlated with the polyanhydride degradation shown in Fig. 3. In addition, the lag time also depended on the quantity of polyanhydride. For example, the lag time of device IV increased to 24 h when increasing the

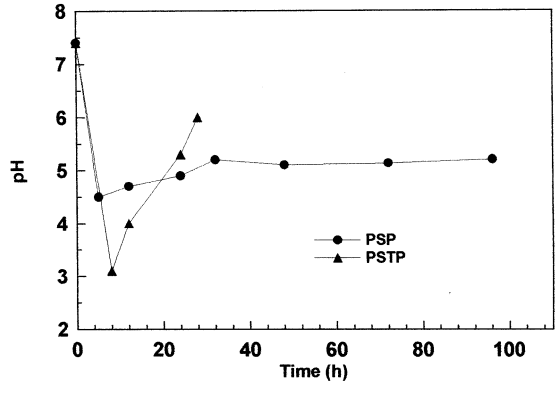

Fig. 4. pH change of 0.1 M pH 7.4 phosphate buffer solution at 37°C when polyanhydrides PSP and PSTP eroded.

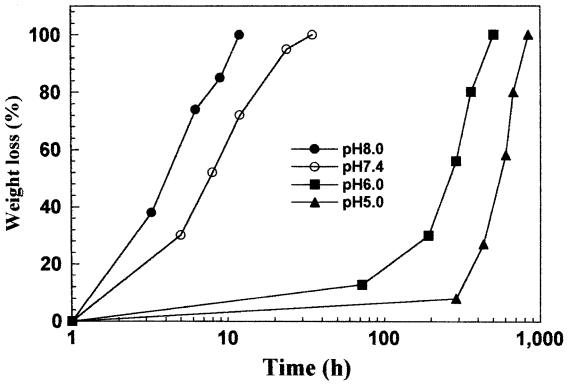

Fig. 5. Cumulative weight loss of PEBP discs (2.5 mm in diameter, 2 mm in thickness) in pH 7.4 and 8.0 boronic acid/borax buffer, and pH 5.0 and 6.0 citric acid/sodium citriate buffer at 37°C.

mass of PSTP from 20 to 30 mg. It was thus evident that the lag time of drug release can be modulated by the type and mass of polyanhydride. Similarly, the duration of drug release can also be regulated by the mass of drug-loaded PEBP layers, e.g. myoglobin took about 30 h to release completely in device III, and about 40 h in the device V, which did not interfere with the lag time of drug release.

As a contrast test, a similar device was examined, which was composed of polyanhydride isolating layers and drug-loaded PEG6000 layers. It was found that myoglobin was released in an irregular pattern, an initial burst within ca. 5 h, then a sustained release phase instead of the second pulse (Jiang and Zhu, 2000). Considering the dissolution of PEG6000, the outer water penetrated into the inner drug-loaded PEG layer through the polyanhydride isolating layer to make the drug diffuse out. This result powerfully proved the necessity for the pH-sensitive degradation and hydrophobicity of PEBP as well as the organic combination of drug-loaded PEBP layers with polyanhydride isolating layers.

4. Conclusions

A core-shelled cylindrical dosage form was designed composed of a hydrophobic coating and a

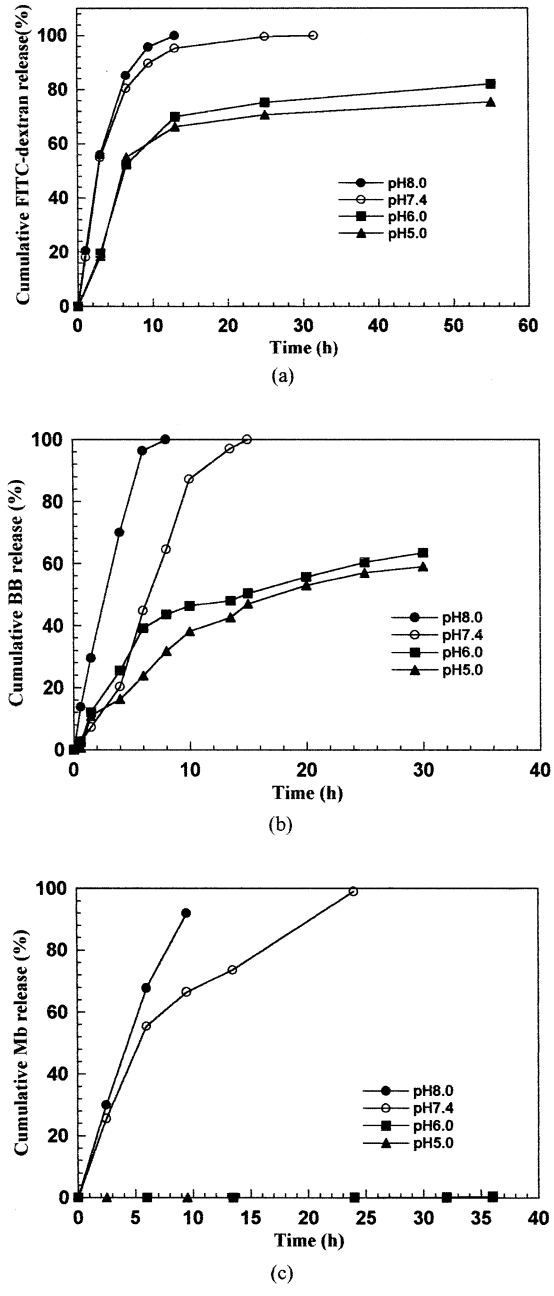

Fig. 6. Cumulative release of (a) FITC-dextran; (b) BB; (c) myoglobin from 10% drug-loaded PEBP discs in pH 7.4 and 8.0 boronic acid/borax buffer, and pH 5.0 and 6.0 citric acid/sodium citriate buffer at 37°C.

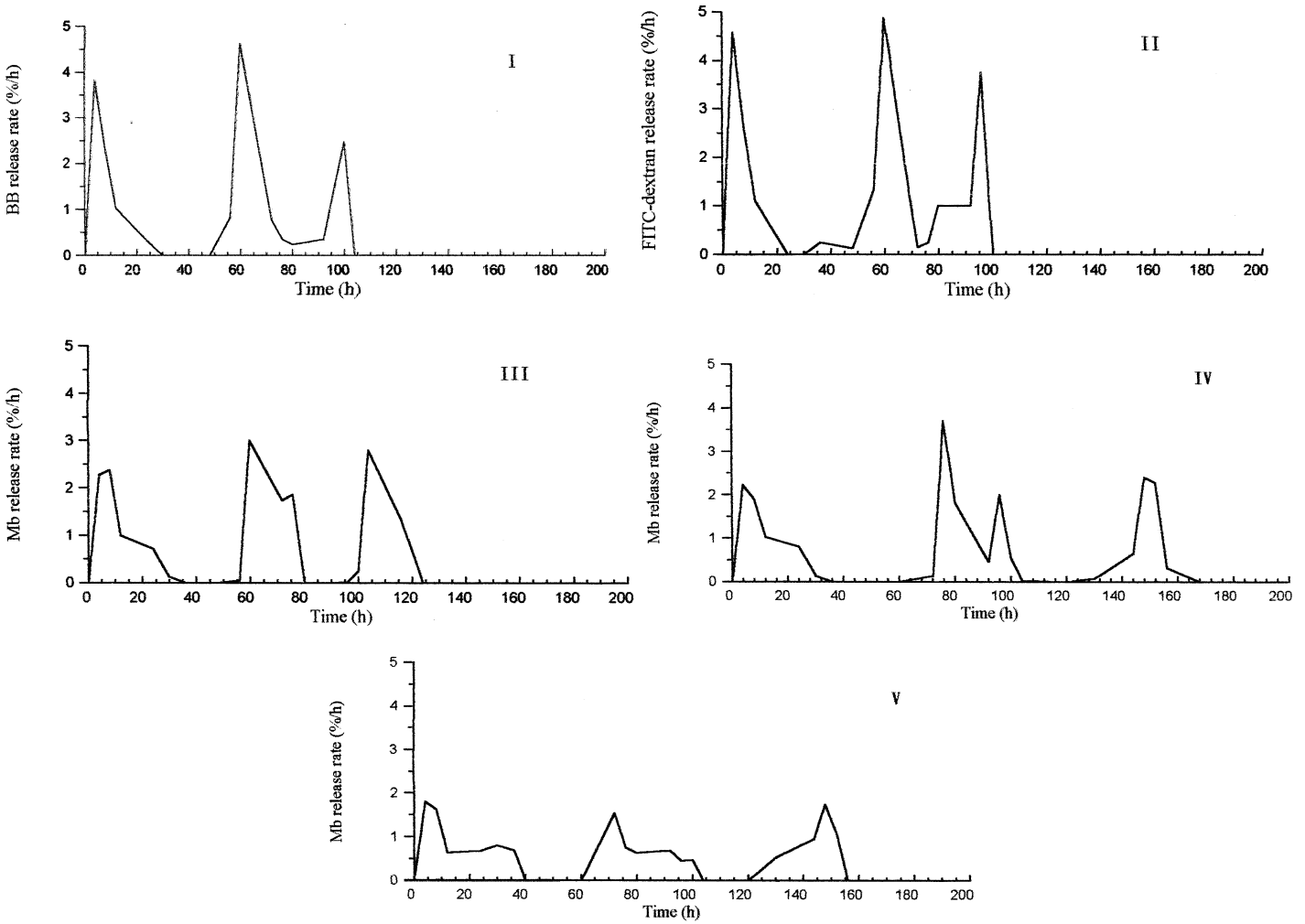

Fig. 7. The release rates of model drugs from the devices I–VII in 0.1 M pH 7.4 phosphate buffer solution (PBS) at 37°C.

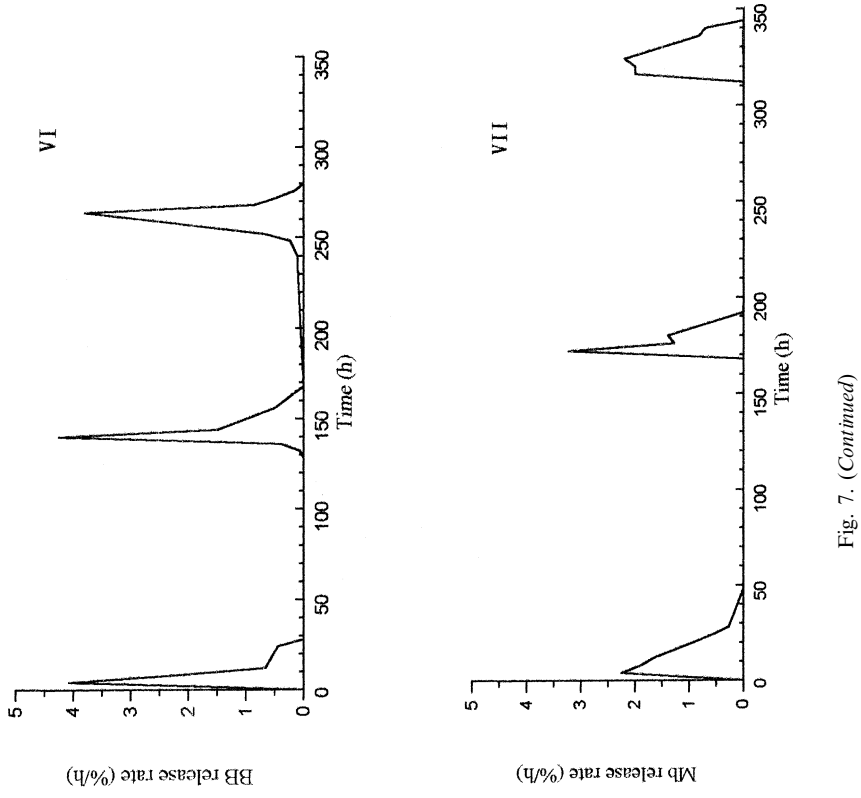

Fig. 7. (*Continued*)

cylindrical core of alternating polyanhydride isolating layer and drug-loaded PEBP layer. The pulsatile drug release pattern was achieved on the basis of the pH-sensitive degradation of PEBP and its cooperative interaction with polyanhydrides. Moreover, the lag time and the duration period of drug release can be respectively regulated by selecting the types or quantities of polyanhydrides and the quantity of PEBP. The feasibility of this model drug delivery system will encourage further pursuit of the development of a proper system for single dose vaccine or other related applications.

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