Preparation of Polyethersulfone–Alginate Microcapsules for Controlled Release

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Received 4 March 2008; accepted 18 August 2008
DOI 10.1002/app.29122
Published online 12 October 2008 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: In this study, polyethersulfone (PES)–alginate microcapsules were prepared for drug-controlled release, and vitamin B_{12} (VB_{12}), rifampicin (RFP), and bovine serum albumin (BSA) were used as model drugs. Different microcapsules were prepared by the variation of the crosslinking degree of alginate and the variation of the chemical components of the microcapsule membrane, including the PES and polyethylene glycol (PEG) contents. Systematic experiments were carried out to study their influences on the release profile of the model drugs. The results showed that with the increase of the crosslinking degree of the alginate, the drug release rate increased; whereas with the increase of the PES concentration used to prepare the microcapsule membrane, the drug release rate decreased. The contents of the PEG in the microcapsule membrane also affected the drug release. This study enriched the methodology of the fabrication of the microcapsules, and the microcapsules may have a potential use for controlled release. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 111: 651–657, 2009

Key words: polyethersulfone; alginate; microcapsule; controlled release; phase separation

INTRODUCTION

Conventional drug administration usually does not provide rate-controlled release or target specificity. Controlled-release technologies allow for effective use of existing drugs and successful development of new drug candidates. Nowadays, new methods of drug delivery are possible, desired drug release can be provided by rate-controlling membranes or by implanted polymers containing dispersed medication.

Recent past has witnessed tremendous research work on naturally occurring polymers like sodium alginate (SA) and chitosan, which are gaining importance in the pharmaceutical field because of their properties such as good biocompatibility,[1,2] nontoxicity,[3,4] biodegradability,[5,6] and antimicrobial property.[7] Their capability of undergoing gelation in aqueous medium at room temperature,[8,9] minimizes the chances of loss of activity or the damage of delicate protein/peptides drugs loaded in the polymeric carriers for the purpose of oral drug delivery along the gastrointestinal (GI) tract. However, the drug release rate from the carriers (such as from calcium alginate) is fast and is difficult to be controlled by changing the preparing conditions.

Liquid–liquid phase separation process (nonsolvent-induced phase separation) is usually used for the preparation of membranes,[10–12] and there are many investigations focused on the effects of the thermodynamic conditions and process dynamics on the membrane structures and performances.[13–15] Polyethersulfone (PES) membranes, which are usually prepared by using the phase inversion technique, have been widely employed in advanced separation technology and biomedical fields such as artificial organs and medical devices used for blood purification (hemodialysis, hemodiafiltration, hemofiltration, plasmapheresis, and plasma collection).[16–19] PES membrane presents a unique architecture having a continuous wall with a porous interior, which exhibits unique encapsulation and delivery properties.[20,21] Thus, it has potential application in the field of drug delivery.

In this study, PES microcapsule encapsulating calcium alginate was prepared and used for drug-controlled release. This strategy has not only widened the drug delivery system but also perfected the methodology of fabricating new container for drug

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Contract grant sponsor: National Natural Science Foundation of China; contract grant numbers: 50403028, 50673064.
Contract grant sponsor: State Education Ministry of China.
Contract grant sponsor: SRF (for ROCS); contract grant number: 2004527-16-14.
Contract grant sponsor: Doctoral Program for High Education; contract grant number: JS20061116506327.
Contract grant sponsor: The Program for New Century Excellent Talents in University; contract grant number: NCET-05-0791.

TABLE I
Chemical Components Used to Prepare the Polyethersulfone-Alginate Microcapsules

	Calcium alginate		Outer wall membrane			Drugs		
	Alginate (g/100 mL)	$CaCl_2$ (g/100 mL)	PES (%)	PEG (%)	DMAC (%)	VB_{12}	RFP	BSA
A_1	1.5	6.0	12		88	√	–	–
A_2	1.5	6.0	16	–	84	√	–	–
A_3	1.5	6.0	20	–	80	√	–	–
A_4	1.5	6.0	24	–	76	√	–	–
B_1	1.5	3.0	16	–	84	√	–	–
B_2	1.5	9.0	16	–	84	√	–	–
C_1	1.5	6.0	16	2	82	√	–	–
C_2	1.5	6.0	16	6	78	√	–	–
C_3	1.5	6.0	16	10	74	√	–	–
D_1	1.5	6.0	16	–	84	–	√	–
D_2	1.5	6.0	16	2	82	–	√	–
D_3	1.5	6.0	16	6	78	–	√	–
D_4	1.5	6.0	16	10	74	–	√	–
E_1	1.5	6.0	16	–	84	–	–	√
F_1	1.5	6.0	–	–	–	√	–	–

delivery. And, the effect of the preparation condition on the microstructure of the microcapsule membrane and the release profile were systemically studied.

EXPERIMENTAL

Materials

Polyethersulfone (PES, Ultrason E6020P, CAS Number: 25608-63-3, BASF Aktiengesellschaft) was used to prepare the membrane of the microcapsule. Polyethylene glycol (PEG-20000, Kelong Chemical Reagent, Chengdu, China) was used as additives to modulate the hydrophilicity of the membrane. *N*,*N*-dimethylacetamide (DMAC, Kelong Chemical Reagent, Chengdu, China) was used as the solvent. Sodium alginate (SA; Sinopharm Chemical Reagent, Shanghai, China) was used as the material to fabricate the drug-loaded hydrogel beads. Anhydrous calcium chloride ($CaCl_2$, Kelong Chemical Reagent, Chengdu, China) was used as the crosslinker. Vitamin B_{12} (VB_{12}, Kelong Chemical Reagent, Chengdu, China), rifampicin (RFP, Ronghai Biotechnical, Chengdu, China), and bovine serum albumin (BSA; fraction V, Sigma Chemical) were used as the model drugs to test the release profile of the microcapsules.

Preparation of drug-loaded alginate hydrogel beads

SA was dissolved in distilled water at a concentration of 1.5 g/100 mL. Then, required amounts of drugs were added to the SA solution and dispersed thoroughly. RFP is a hydrophobic drug, which is difficult to dissolve or disperse in the SA solution. In this study, RFP is uniformly dispersed in the SA solution by ultrasonic dispersion method. The SA solution was added dropwise into a gelation medium containing $CaCl_2$, using a 0.5-mm-diameter syringe needle at room temperature. Then, the drug-loaded hydrogel beads were prepared.

Preparation of microcapsules

Drug-loaded microcapsules were prepared by coating thin PES porous membranes onto the SA hydrogel beads by using a liquid–liquid phase separation technique. PES and the additive (PEG) were dissolved in DMAC to prepare the polymer solution. The drug-loaded hydrogel beads prepared earlier were immersed in the polymer solution for 30 s at room temperature, then the beads were removed from the polymer solution, exposed to air for some seconds, and then the beads were placed into water. After about 5 min in water, the beads were washed with double distilled water and then vacuum-dried for 24 h. Thus, PES–alginate microcapsules were prepared. Table I shows the experimental parameters for the preparation of the microcapsules.

SEM observation

For the SEM observation, the dried microcapsule samples were quenched by liquid nitrogenous gas, cut with a single-edged razor blade, attached to the sample supports, and coated with a gold layer. A scanning electron microscope (JSM-5900LV, JEOL) was used for the morphology observation of the membrane cross section of the microcapsule. (The dried inner alginate beads were removed.)

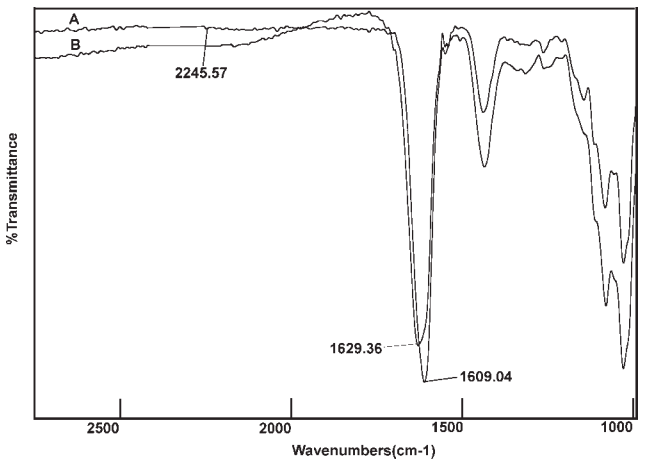

Figure 1 FTIR spectra of the drug-loaded hydrogel beads (A) and the calcium alginate hydrogel beads (B).

Calculation of the porosity of the microcapsule membrane

The porosity of the microcapsule membrane was calculated from the density of the polymer and the weight change before and after drying,[22] using the following formula

$$\text{Porosity(P)} = \frac{(W_B - W_A)/\rho_W}{W_A(1-C\%)/\rho_P + W_A \times C\%/\rho_C + (W_B - W_A)/\rho_W} \times 100\%, \quad (1)$$

Where W_B is the weight of the membrane before drying, g; W_A is the weight of the membrane after drying, g; ρ_w is the density of water, $\rho_w = 1.0$ g/cm^3; and ρ_P is the density of the PES, $\rho_P = 1.43$ g/cm^3; $C\%$ is the additive ratio in the membrane; and ρ_c is the density of the additive (PEG).

Statistical data analyses

Statistical data analyses were performed using the Student's *t*-test with $P < 0.05$ as the minimal level of significance. Calculations were done using the software Origin 7.0.

In vitro release studies

VB_{12} (a hydrophilic model drug), RFP (a hydrophobic model drug), and BSA (a macromolecular weight model drug) were used as the model drugs to test the functional utilization of the microcapsules. The drug-loaded microcapsules were immersed in PBS buffer solution and incubated at room temperature. The concentrations of the released drugs were quantified by the absorption at 361 nm for VB_{12}, 340 nm for RFP, and 280 nm for BSA, respectively. The percentage of the released drug was calculated as the ratio of the mass of the released drug to the mass of the drug in the microcapsules. The drugs used for the preparation of the microcapsules are also listed in Table I.

RESULTS AND DISCUSSION

PES–alginate microcapsules

The fabrication of the microcapsules includes two steps. First, preparation of the alginate beads; as Ca^{2+} could crosslink alginate, thus, when the SA solutions containing the model drugs were added dropwise into the $CaCl_2$ solution, alginate beads formed. Monovalent cations and Mg^{2+} ions do not induce gelation, whereas Ba^{2+} and Sr^{2+} ions produce stronger alginate gels than Ca^{2+}. Other divalent cations such as Pb^{2+}, Cu^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, and Mn^{2+} could also induce the crosslink of alginate but their use was limited because of their toxicity.[23] In this study, the good biocompatibility and nontoxicity of the beads are required while high mechanical strength was not required, so $CaCl_2$ was used as the crosslinker.

The drug-loaded microcapsules are characterized by FTIR spectra. Figure 1 shows the FTIR spectra of the drug-loaded hydrogel beads and the calcium alginate hydrogel beads. From the spectrum of the drug-loaded hydrogel beads (VB_{12}), a characteristic absorption peak of —CN groups in VB_{12} can be observed at 2245 cm^{-1}, and the migration of the absorption peak from 1629 to 1609 cm^{-1} attributed to —CONH— stretch was also observed. Moreover, after VB_{12} is dissolved in the solution, the color of the solution changed red. These confirmed that VB_{12} was loaded in the calcium alginate hydrogel beads.

For the second step, it was the preparation of the drug-loaded alginate microcapsules. A liquid–liquid phase separation technique was employed to coat the PES membrane onto the alginate beads. When the drug-loaded alginate beads were added into the PES solution containing the additives (PVP or PEG), a rapid phase inversion took place because of the surface water of the alginate gels. When the beads were coated with a uniform layer of the PES solution, they were removed from the polymer solution and placed into water. Then, the drug-loaded alginate microcapsules were prepared. To reduce the drug loss and eliminate the remnant DMAC, the microcapsules were vacuum-dried.

Figure 2 shows a typical SEM image of the cross-sectional view of the prepared microcapsule membrane. It was clearly observed that dense skin layers existed on both of the internal and the outer surface of the membrane, under the skin layer a finger-like structure was observed. These were the feature of the phase separation.

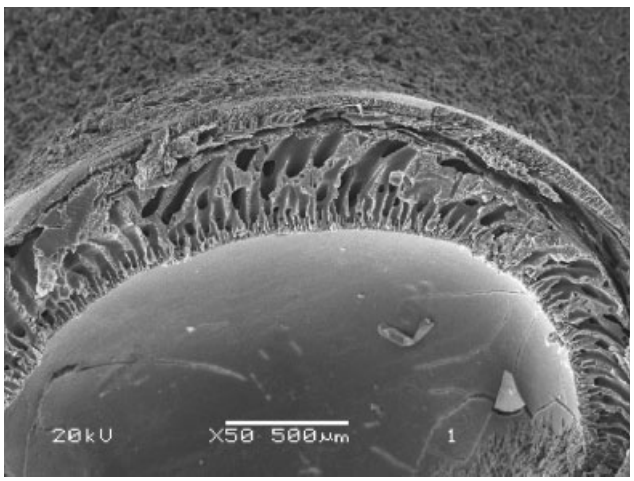

Figure 2 Typical SEM image of the cross section of the prepared microcapsule membrane.

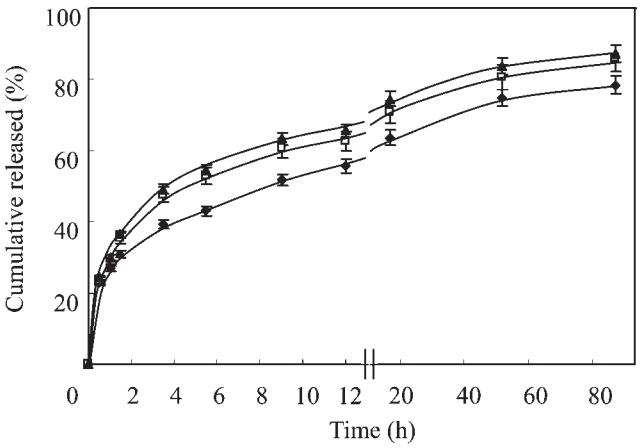

Figure 3 Release of vitamin B_{12} from the microcapsules prepared from different crosslinking degree alginate in PBS buffer solution at 37°C. Crosslinking $CaCl_2$ solutions: (◆, B_1), 3.0 g/100 mL; (□, A_2), 6.0 g/100 mL, and (▲, B_2) 9.0 g/100 mL; PES concentration: 16%.

Effect of crosslinking degree of alginate on drug release

To investigate the effect of the crosslinking degree of the alginate on the drug release, the SA solution was added dropwise into $CaCl_2$ solutions with different concentrations (3.0 g/100 mL, 6.0 g/100 mL, and 9.0 g/100 mL $CaCl_2$ solution) to prepare the microcapsules. The release profile is shown in Figure 3. As shown in the figure, the VB_{12} release maintained for over 80 h; and the release rate increased with the increase of the $CaCl_2$ concentration, which corresponded to the high crosslinking degree. The result is contrary to the usual results. This may due to the fact that the main mechanism of the drug release from the microcapsules is free diffusion because of the membrane wall, so the drug concentration in the microcapsules has great effect on the release behavior, high concentration might lead to the faster release of the drug. Figure 4 shows the encapsulation efficiency of the VB_{12}. The higher efficiency indicated a larger amount of the encapsulated drug and lead to a higher concentration in the microcapsules. As shown in the figure, the drug amount encapsulated in the alginate gel beads with higher crosslinked degree was larger than that with lower degree. The ratio of the drug loaded is not very high. VB_{12} can be easily dissolved in the SA solution; thus, by increasing the concentration of VB_{12} in the SA solution, the ratio of the drug loaded would be increased. These results also suggested that the membrane might play an important role in the drug release from the microcapsules. Thus, further studies were carried out for the effect of the microcapsule membrane on the drug release.

Effect of PES concentration on the release behavior

Polymer PES is the primary material for preparing the microcapsule membranes, and therefore, the variation of PES concentration in the chemical recipe remarkably affects the microstructure of the microcapsule membranes, thus may affect the drug release profile. Figure 5 shows the release curves of the microcapsules prepared from different PES concentrations and of the alginate beads without PES membrane, VB_{12} was used as the model drug. As shown in the figure, when PES membranes were coated onto the alginate beads to prepare the microcapsules, the drug release rate was significantly decreased (Student's t-test, $P < 0.05$). With the increase of the PES concentration, the drug release rate decreased. And, the "burst release" was depressed when high PES concentration was used to prepare the outer wall membrane. However, it is

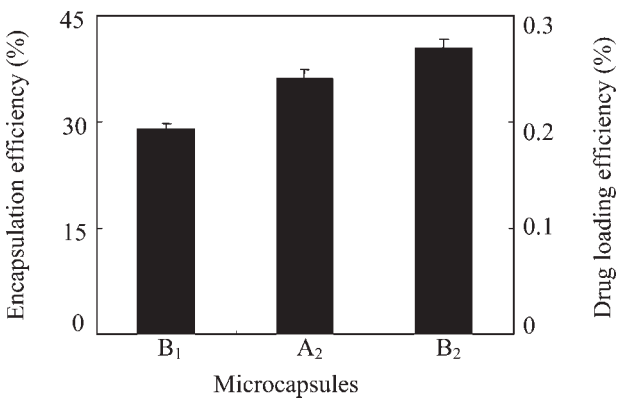

Figure 4 Encapsulation efficiency and drug-loading efficiency of VB_{12} in the microcapsules prepared from different crosslinking degree of alginate. Crosslinking $CaCl_2$ solutions: (B_1), 3.0 g/100 mL; (□, A_2), 6.0 g/100 mL; and (▲, B_2) 9.0 g/100 mL. Each point represents the mean ± SD of three independent measurements.

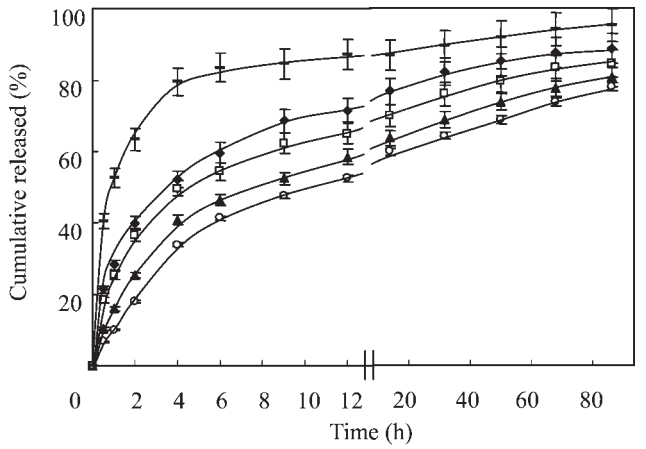

Figure 5 Effect of PES concentration used to prepare the microcapsule membrane on the release profile. The concentration of PES in the polymer solution are 12% (◆, A_1); 16% (□, A_2); 20% (▲, A_3); and 24% (○, A_4), respectively. Alginate gel bead without PES membrane (–, F_1). Each point represents the mean ± SD of three independent measurements.

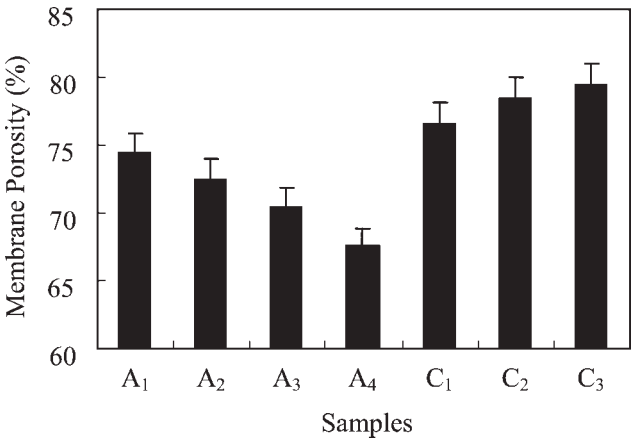

Figure 6 Porosities of the microcapsule membrane. The chemical components of these microcapsules were PES 12% (A_1), PES 16% (A_2), PES20% (A_3), PES24% (A_4), PES16% + PEG2% (C_1), PES16% + PEG6% (C_2), and PES16% + PEG10% (C_3). Each point represents the mean ± SD of three independent measurements.

difficult to prepare uniform microcapsules when the PES and PEG concentrations were high because of the high viscosity of the polymer solution.

To understand the effect of the PES concentration, we investigated the porosity and the morphology of the microcapsule membrane. Figure 6 shows the membrane porosities of the microcapsules. As shown in the figure, with the increase of the PES concentration in the chemical recipe, the porosity of the microcapsule membranes decreased. The membrane porosity for the microcapsule A_1 (PES 12%) was about 74.4%; whereas that for the microcapsule A_4 (PES 24%) was about 67.5%. When the PES concentration increased, the polymer-rich phase increased and the polymer-lean phase decreased in the process of the phase separation. The higher the polymer concentration is, the larger the viscosity of the polymer solution. The larger viscosity hampers the diffusion exchange between solvent and nonsolvent and leads to a higher polymer concentration at the interphase between the polymer solution and the nonsolvent, and hence leads to a lower porosity of the membrane.[24] Figure 7 shows the cross-sectional views of the microcapsule membranes. As shown in the figure, with increasing the PES concentration, the number of the finger-like pores decreased. Because of the small porosity and the microstructure, the drug release rate decreased.

Because the additives PVP and PEG can increase the viscosity of the polymer solution markedly, and make the fabrication difficult, 16 wt % was selected as the PES concentration for the preparation of the porous microcapsule membranes in the following studies.

Effect of PEG on the release behavior

PEG is always used to increase the hydrophilicity of hydrophobic membranes. Here, the effect of PEG concentration used to fabricate the microcapsule membrane on the drug release was studied, and the

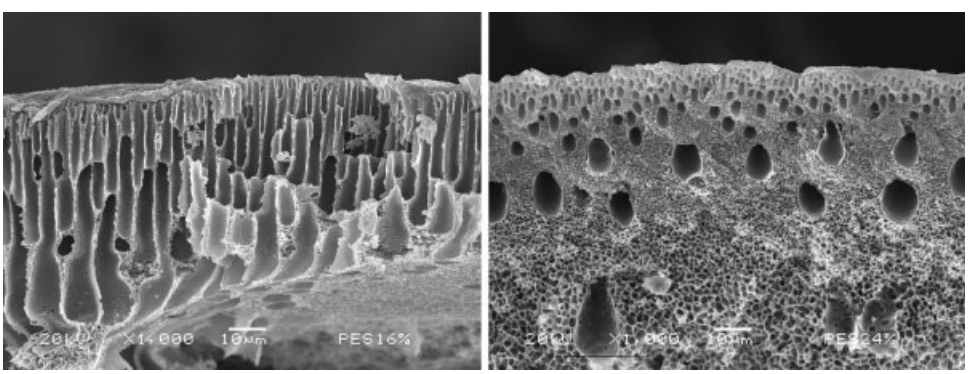

Figure 7 SEM micrographs of the cross-sectional views of the microcapsule membranes prepared with different PES concentration. The left picture is for A_2 (PES16%); the right one is for A_4 (PES24%).

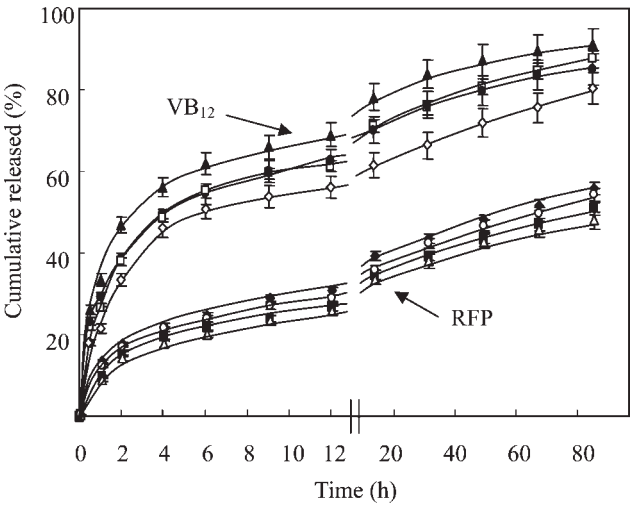

Figure 8 Effect of PEG in the outer wall membrane on the release profile. For the hydrophilic drug VB_{12}: PEG 0% (●, A_2); PEG 2% (◇, C_1); PEG 6% (□, C_2); and PEG 10% (▲, C_3). For the hydrophobic drug RFP: PEG 0% (○, D_1); PEG 2% (◆, D_2); PEG 6% (■, D_3); and PEG 10% (△, D_4). Each point represents the mean ± SD of three independent measurements.

data are shown in Figure 8. As shown in the figure, the RFP release maintained a longer time than VB_{12}. Furthermore, with the increase of the PEG concentration used to fabricate the membrane, the release rate for the hydrophilic drug VB_{12} increased (Student's *t*-test, $P < 0.05$); however, for the hydrophobic drug RFP, with the increase of the PEG concentration, the drug release rate decreased (Student's *t*-test, $P < 0.05$).

As mentioned earlier in Figure 6, with the increase of the PEG concentration, the membrane porosity increased. This is easy to be understood, because PEG is also a pore-forming agent here. On the other hand, the membrane hydrophilicity increased, for which had been widely reported elsewhere. Thus, the release rate of the hydrophilic drug VB_{12} increased. However, for the hydrophobic drug RFP, the release rate decreased though the porosity increased. These results indicated that the hydrophilicity had great effect on the drug release rate. The hydrophilic membrane is in favor of the release for hydrophilic drugs, but makes against to the release for hydrophobic drugs.

The influence of PVP dosages on the release profiles of the model drugs has also been investigated. PVP is also a kind of hydrophilic macromolecules as PEG; therefore, the effect of PVP on the microstructure of the porous microcapsule membranes was similar to that of the PEG.[25] BSA was used as a macromolecular model drug in this study, and the cumulative BSA release was only about 20% even after 80 h because of the large molecular weight.

Model of the release behavior

For a deeper understanding of the release profile, the release data were characterized by applying to the Higuchi's model,[26] which is given as follows:

$$M_t/M_\infty = \frac{S}{V}\left[\frac{2DC_s}{A}\right]^{1/2} \times \sqrt{t}, \qquad (2)$$

where M_t/M_∞ is the fraction of the released VB_{12} at time, t; S is the surface area of the particle and V is the volume of the particle; A is the total amount of VB_{12} in the unit volume of the particle; D is the diffusion coefficient of VB_{12} in the particle; k is a kinetic constant; and C_s is the VB_{12} solubility.

Equation (2) indicates that the percentage of the released drug is proportional to the square root of time. The plots for the release data according to the Higuchi's model are shown in Figure 9. The percentage of the released drug as a function of square root of time is linear, which indicated that the VB_{12} release was a diffusion-controlled manner and was in agreement with that discussed in section "Effect of crosslinking degree of alginate on drug release." Because the diffusion coefficient, D, is only correlated with the properties of the membrane; therefore, the diffusion coefficient varied with the PES concentration because of the different membrane structure, as shown in the Figure 7. These results suggested that the release rate could be modulated by changing the structure of the microcapsule membranes.

CONCLUSIONS

The goal of this study is to develop a new method for the preparation of PES–alginate microcapsules

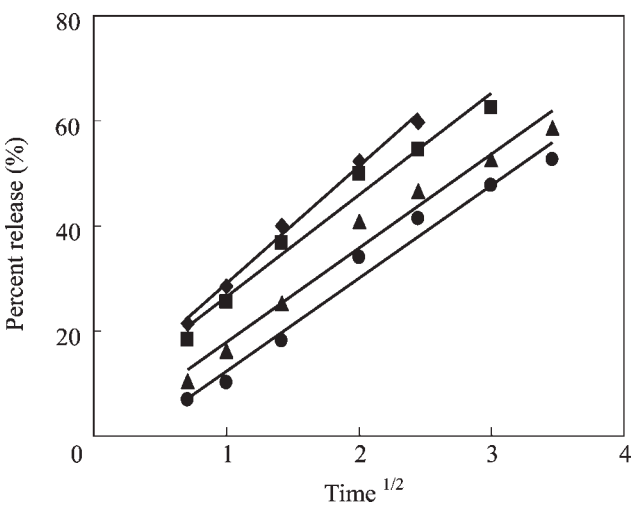

Figure 9 Plot of square root of time versus percent released drug based on eq. (2). PES 12% (◆, A_1); PES 16% (■, A_2); PES 20% (▲, A_3); and PES 24% (●, A_4). Each point represents the mean ± SD of three independent measurements.

for drug-controlled release. This has been successfully accomplished by coating a PES membrane onto the drug-loaded alginate beads. The release profiles of VB_{12} as the hydrophilic model drug loaded in the calcium alginate were studied. It was found that with increasing the crosslinked degree of the alginate, the drug release rate increased; and with increasing the PES concentration used to prepare the membrane, the drug release rate decreased. The hydrophilicity of the microcapsule membrane was in favor of the release for hydrophilic drugs, but went against to the release for hydrophobic drugs. These results indicated that the release rate of the model drugs from the microcapsules could be modulated with the variation of the chemical recipe of the membrane.

The authors thank their laboratory members for their generous help.

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