Control of Release Characteristics in pH-Sensitive Poly(vinyl alcohol)/Poly(acrylic acid) Microcapsules Containing Chemically Treated Alumina Core

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ABSTRACT: The pH-sensitive poly(vinyl alcohol)/poly (acrylic acid) hydrogel microcapsules containing vitamin B_{12}-loaded Al_2O_3 core were prepared with a three-step emulsion polymerization. Al_2O_3 was chemically treated with HCl or NaOH solutions at room temperature for 24 h to modify the binding properties with vitamin B_{12}. The colon-targeted release characteristics of vitamin B_{12} from the microcapsules were evaluated at different pHs. These microcapsules showed the faster and larger release of vitamin B_{12} due to the high swelling of microcapsule shell as the pH was changed into more basic condition. However, these microcapsules showed the slower and less release of vitamin B_{12} as the acid value of Al_2O_3 increased due to the strong binding interaction between Al_2O_3 core and vitamin B_{12} even though the initial loading of vitamin B_{12} was higher. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 115: 1853–1858, 2010

Key words: microcapsules; pH-sensitive hydrogel; alumina; vitamin B_{12}; controlled release

INTRODUCTION

Hydrogels are defined as the polymeric networks capable of imbibing and retaining large quantities of water in their swollen structures without dissolution or loss of their three-dimensional network structure. Smart hydrogels are able to alter their volume and properties in response to environmental stimuli, such as, pH, temperature, ionic strength, and electric field. Drug delivery systems based on the smart hydrogels have many advantages that overcome the limitation of the conventional polymeric systems.[1–5] Because of their drastic response to environmental stimuli, these hydrogels have been investigated for many biomedical and pharmaceutical applications including controlled drug delivery, molecular separation, tissue culture substrates, enzyme activity controlling systems, and materials for improved biocompatibility.[6–12]

Generally, hydrogels have many different forms including matrices, microparticles, membranes or sheets, and encapsulated particles. Microencapsulation is one of the widespread applications of polymer, protecting specific functional materials or releasing them into an outer phase for a long period. Among various applications of microencapsulation, controlled drug delivery gives many advantages, such as, improved efficacy, reduced toxicity, and better patient compliance compared with conventional drug form.[13] Significant effort has been devoted to develop the microcapsules for drug delivery because it offers suitable means of delivering small molecular weight drugs as well as macromolecules, such as, protein, peptide or genes by either localized or targeted delivery. Self-regulated drug delivery system has also been of great interest because it allows the drug to be released when it is needed.[14,15]

Poly(acrylic acid) (PAAc) is extensively studied as pH-sensitive and mucoadhesive polymer. When the pH is higher than the pKa of PAAc, PAAc hydrogel would swell due to the repulsion among carboxylate anions. Several types of pH-sensitive hydrogels have also been developed.[16,17] Recently, encapsulation of silica or other inorganic materials have attracted more attention because of their specific combining properties and applications in controlled release systems. Encapsulated inorganic materials have been utilized in various fields, such as, adsorption, gelling, and microemulsion.[18–23]

In this study, novel design of microcapsules was investigated in order to control the release of vitamin B_{12} more effectively by combining the pH-sensitive hydrogel shell and the specifically binding inorganic core. The colon-targeted delivery of vitamin B_{12}, the model drug which has the basic functional groups, from the pH-sensitive hydrogel

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microcapsules was studied in terms of the characteristics of both microcapsule shell and inorganic core. Several buffers of different pHs were used as simulating gastric and intestinal fluids.

EXPERIMENTAL

Materials

Poly(vinyl alcohol) (PVA) and acrylic acid (AAc) were purchased from Aldrich. Glutaraldehyde (GA) and ethylene glycol dimethacrylate (EGDMA) were purchased from Sigma and used as the crosslinking agent. Span 80 was obtained from Sigma and used as surfactant. Potassium persulfate (KPS) obtained from Sigma was used as initiator. Extra pure grades of Al_2O_3 and vitamin B_{12} were purchased from Junsei and Samchun, respectively.

Chemical treatment of Al_2O_3

Al_2O_3 was chemically treated with 35 wt % hydrochloric acid or 35 wt % sodium hydroxide solution at room temperature for 24 h to modify the surface. The treated Al_2O_3 was washed several times with distilled water and dried in a vacuum oven. About 0.5 g of dried Al_2O_3 was stirred in 20 mL of distilled water for 24 h and was filtered. The pH of the filtrate was determined by pH meter F-54BW (Horiba). The various kinds of Al_2O_3 treatment and vitamin B_{12} loading are listed in Table I. Acid and base values of various Al_2O_3 species were measured by Boehm's titration method.[24] To measure the base value, 1.0 g of dried Al_2O_3 specimen was added to 100 mL of 0.1*N* HCl solution, and was stirred for 48 h, and was filtered. The filtrate was titrated with 0.1*N* NaOH solution. The base value was calculated from the amount of NaOH reacted with HCl. The acid value was measured by similar procedure.

Preparation of microcapsules

The microcapsules consisting of hydrophilic interpenetrating polymer network shell of PVA and pH-sensitive PAAc were prepared by a three-step emulsion polymerization technique. (1) Emulsion 1 was prepared by adding 20 mL of 10 wt % PVA solution, 10 mL of 20 wt % AAc solution, and 6 mL of span 80 as emulsifier into 100 mL of *n*-hexane. Emulsion 2 was made by adding 1 mL of 25 wt % GA solution and 1 mL of EGDMA as crosslinking agents, 6 mL of span 80 as emulsifier into 100 mL of *n*-hexane. (2) Emulsion 1 and Emulsion 2 were mixed for 10 min. (3) 20 mL of 1 wt % KPS solution as initiator and 1 g of vitamin B_{12}-loaded Al_2O_3 (150 mg vitamin B_{12}/g Al_2O_3) were added and stirred vigorously for 2 h under 1000 rpm at 65°C. The microcapsules were filtered by suction and washed several times with petroleum ether. The microcapsules were

TABLE I
Classifications of Chemical Treatment of Al_2O_3 and Microcapsules Containing Vitamin B_{12}-Loaded Al_2O_3

Sample name	Acid-treated Al_2O_3	Base-treated Al_2O_3	Vitamin B_{12} loading	Encapsulation
AL-A	O	–	–	–
AL-B	–	O	–	–
AL-AV	O	–	O	O
AL-BV	–	O	O	O

O, correspondence to treatment or loading.

TABLE II
Variations in pH, Acid Value, and Base Value of Al_2O_3 Depending on Chemical Treatments

	pH	Acid value (mequiv g^{-1})	Base value (mequiv g^{-1})
AL-A	6.2	1.9	1.0
AL-B	9.0	1.2	2.0

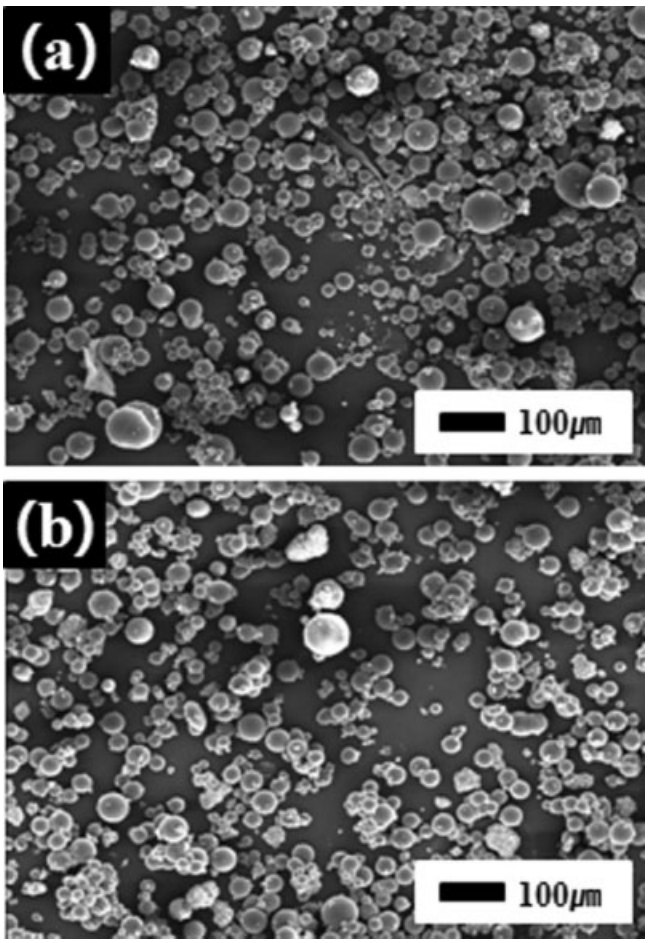

Figure 1 SEM microphotographs of the PVA/PAAc microcapsules containing vitamin B_{12}-loaded Al_2O_3; (a) AL-AV and (b) AL-BV.

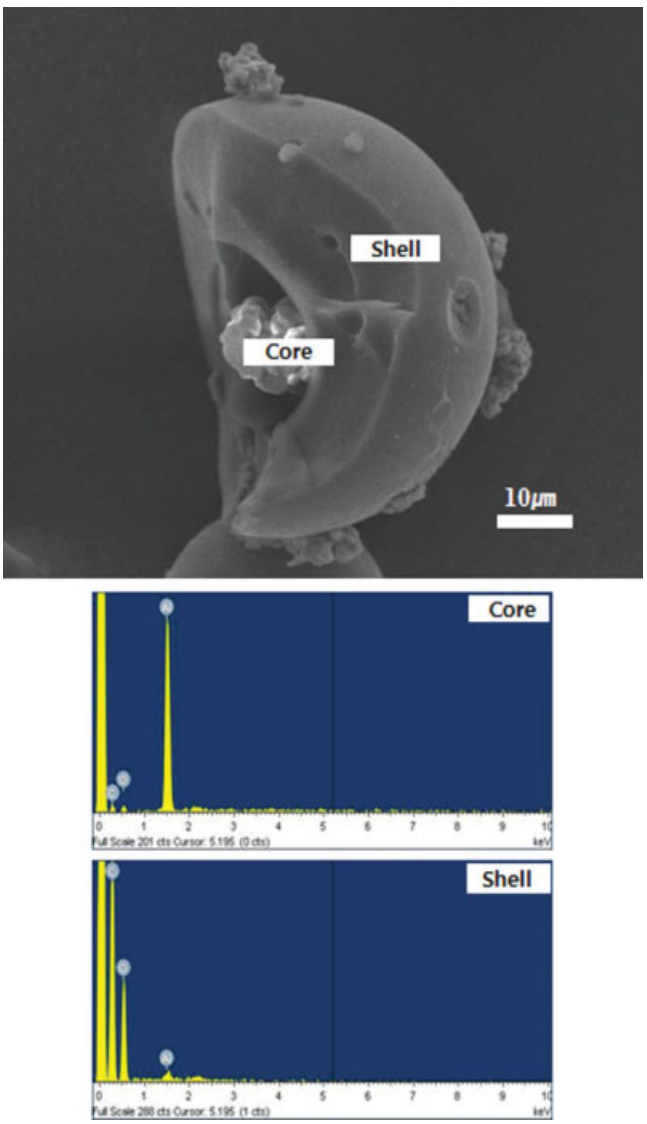

Figure 2 EDX spectra of AL-BV shell and AL-BV core. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

obtained after solvent evaporation under vacuum at 50°C. Various kinds of Al_2O_3 cores and microcapsules are classified in Table I.

Characterization of microcapsules

Particle size and surface morphology of microcapsules were examined by scanning electron microscope (SEM, Jeol JSD 6300). The microcapsules containing Al_2O_3 in core were confirmed by EDX spectra. The pH-sensitive properties were examined by the optical microscope (Olympus CH-2). Release experiments of the microcapsules containing vitamin B_{12}-loaded Al_2O_3 were carried out at room temperature in each of the buffer solution (pH 2, 7, and 10). The released amounts of vitamin B_{12} were measured at various time periods by UV/VIS spectrophotometer (Shimadzu UV-1201). The buffer was refreshed after sampling. All experiments were carried out in triplicate.

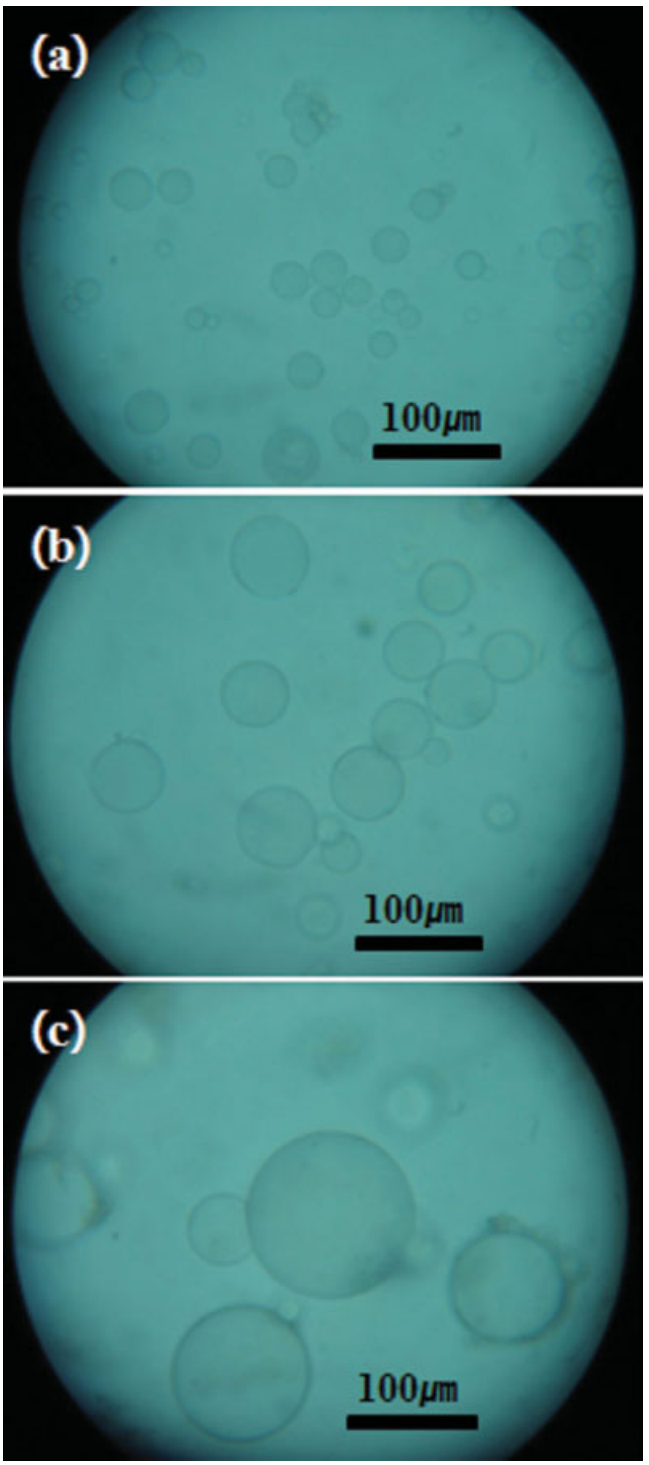

Figure 3 Optical microscope photographs of AL-BV swollen in the various buffer solutions for 48 h; (a) pH 2, (b) pH 7, and (c) pH 10. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

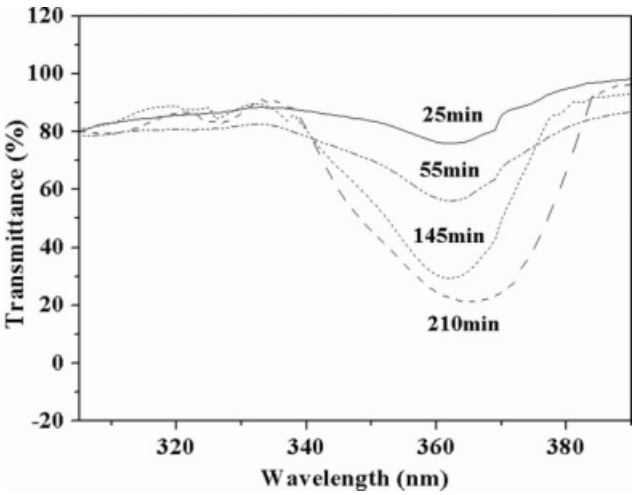

Figure 4 Variation of UV transmittance for the release of vitamin B_{12} from AL-BV depending on the release period in the buffer solution of pH 10.

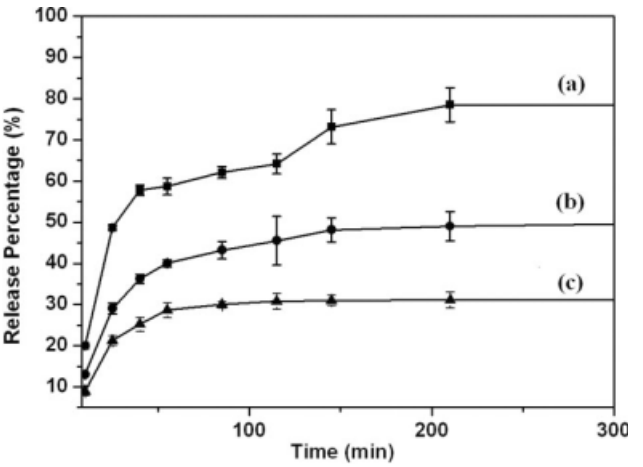

Figure 5 Release of vitamin B_{12} from AL-BV in the various buffer solutions; (a) pH 10, (b) pH 7, and (c) pH 2.

RESULTS AND DISCUSSION

Chemical treatment of Al_2O_3

The adsorption properties of Al_2O_3 are greatly affected by the surface functional groups. The presence of various functional groups on the surface of adsorbent depends on the nature of the activation technique used in the manufacturing process and the post-treatments.[24] The chemical treatment of Al_2O_3 with acidic or basic solution was performed to give functional groups on the surface. Such chemical treatment of surface is very important because of the improved adsorption and selectivity of the active ingredients, such as, protein, peptide or genes.[25] As shown in Table II, the acid value of Al_2O_3 increased by HCl treatment and the base value of Al_2O_3 increased by NaOH treatment, respectively. It was sure that the surface of Al_2O_3 was modified successfully to give a noticeable difference in the binding properties with model drug by acid or base treatment.

Characterization of microcapsules

Figure 1 shows the SEM images of PVA/PAAc hydrogel microcapsules containing vitamin B_{12}-loaded Al_2O_3 core. The size of microcapsules is in the range of 10–100 μm. All the microcapsules had similar shape and size distribution regardless of the chemical treatments on Al_2O_3 core. As shown in Figure 2, core-shell morphology was clearly observed. As confirmed by EDX, the peaks of carbon and oxygen were mostly detected at the shell of microcapsule but Al peak was detected noticeably only at the core of microcapsule. These results showed that the main elements of shell were the organic polymers and the main element of core was Al_2O_3. Vitamin B_{12}-loaded Al_2O_3 seemed to be located successfully inside of the PVA/PAAc microcapsule.

pH-sensitive behavior of microcapsules

The pH-sensitive polymers usually contain pendant acidic or basic groups that either release or accept protons in response to the changes in pH. PAAc, the

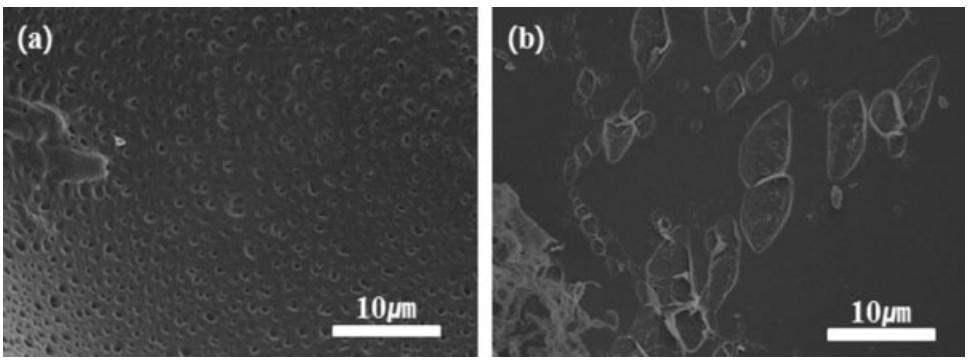

Figure 6 SEM microphotographs of the freeze-dried microcapsule shell swollen in the buffer solutions of (a) pH 2 and (b) pH 10.

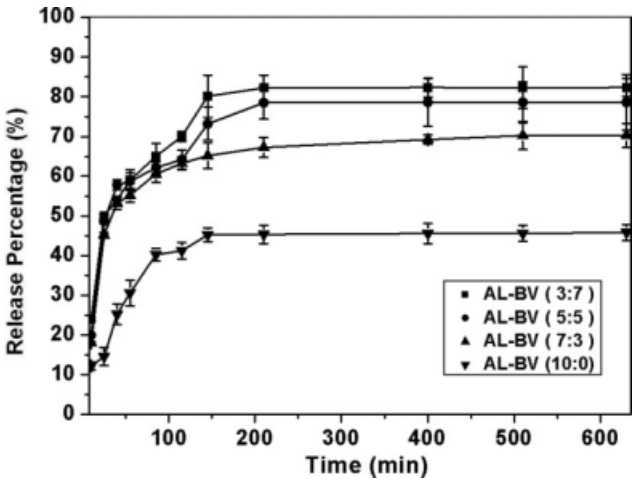

Figure 7 Release of vitamin B_{12} from the microcapsules containing NaOH-treated Al_2O_3 core depending on the compositions of PVA/PAAc microcapsules from 3 : 7 to 10 : 0.

pH-sensitive component in the microcapsule shell, has pendant carboxylic acid groups which can be ionized into carboxylate anion above its pKa of 4.7. The carboxylate anions cause more electrostatic repulsion and hydrophilicity to the polymer chains. Therefore, PVA/PAAc hydrogel microcapsules are expected to show pH-sensitive swelling behavior depending on pH. To confirm the pH-sensitive change of microcapsules, the hydrodynamic size changes of the PVA/PAAc microcapsules were evaluated at several different pHs by optical microscope. Figure 3 shows the images of swollen PVA/PAAc hydrogel microcapsules which were placed in pH 2, 7, and 10 buffer solutions, respectively. As shown in Figure 3, the swelling of microcapsules depended sensitively on pH. The PVA/PAAc hydrogel microcapsules swelled and de-swelled rapidly in the basic and acidic conditions, respectively. These swelling and de-swelling of PVA/PAAc hydrogel microcapsules upon pH variation were reversible.

Controlled release behavior of microcapsules

The release behavior was studied for the PVA/PAAc hydrogel microcapsules containing vitamin B_{12}-loaded Al_2O_3 core in several buffer solutions at room temperature. The released amount of vitamin B_{12} from the microcapsules was measured at 361 nm by using UV/VIS spectrophotometer. The concentration of vitamin B_{12} in buffers increased with increasing release period as shown in Figure 4. The pH-sensitive release behavior of microcapsules is well presented in Figure 5. Both the release rate and the release amount of vitamin B_{12} increased in a basic buffer solution due to the higher swelling of microcapsule shell. The surface morphology of the freeze-dried microcapsule shell was observed by SEM as shown in Figure 6. The expanded surface texture was detected for the microcapsule swollen in the buffer solution of pH 10 due to the extensive swelling of microcapsule shell. These morphological changes are believed to result in the variation of both release rate and release amount of vitamin B_{12} from the microcapsules. Figure 7 shows the release behavior of vitamin B_{12} from PVA/PAAc hydrogel microcapsules of various compositions. The cumulative release increased generally as the PAAc content of microcapsules increased. However, there was not significant change in release behavior above 50 wt % of PAAc in microcapsules.

TABLE III
Initial Loading of Vitamin B_{12} for the Various Al_2O_3 Cores

	Acid-treated	Non-treated	Base-treated
Drug loading (pmm/g Al_2O_3)	370	325	295

The initial drug loading for the various kinds of Al_2O_3 is presented in Table III. The acid-treated Al_2O_3 showed the highest drug loading due to the attractive interaction with the basic vitamin B_{12}. Figure 8 shows the release behaviors of vitamin B_{12} from PVA/PAAc hydrogel microcapsules containing three different types of chemically treated Al_2O_3 core in the buffer solution of pH 10. The release of vitamin B_{12} depended not only on the swelling of microcapsule shell but also the type of chemical treatment of Al_2O_3 core. As the acid value of Al_2O_3 increased, the release rate was getting slower and the release amount was getting lesser even though the initial loading became higher as shown in

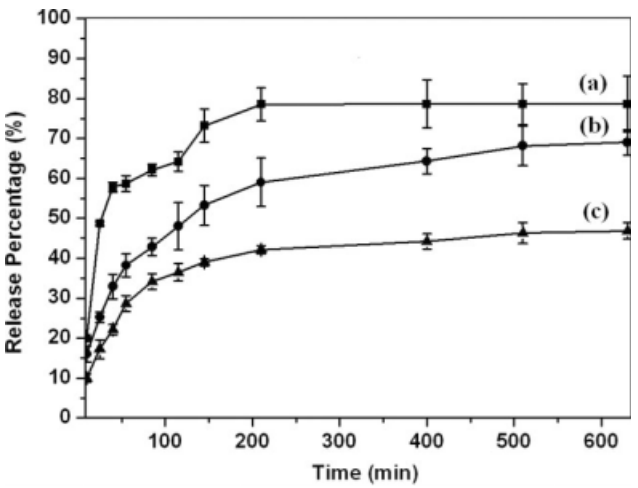

Figure 8 Release of vitamin B_{12} from the PVA/PAAc (5/5) microcapsules in the buffer solution of pH 10; (a) with NaOH-treated Al_2O_3 core, (b) with nontreated Al_2O_3 core, and (c) with HCl-treated Al_2O_3 core.

Table III. This was due to the increased acid-base attractive interactions between acid-treated Al_2O_3 and basic vitamin B_{12}. The modification of Al_2O_3, which was used as a binding support material for the drug loaded, was successfully applied to control the release behavior easily in addition to the general swelling properties of microcapsule shell.

CONCLUSIONS

The hydrogel microcapsules, having interpenetrating network shell of hydrophilic PVA and pH-sensitive PAAc and Al_2O_3 core, were prepared by a three-step emulsion polymerization. The binding properties of Al_2O_3 with vitamin B_{12} were modified by chemical treatment with HCl or NaOH. PVA/PAAc hydrogel microcapsules showed the reversible swelling behavior depending on the pH variations. The shell of PVA/PAAc hydrogel microcapsules swelled rapidly in the basic buffer solution. The extensively swollen shell was responsible for the faster release rate and the larger release amount of vitamin B_{12} in the basic condition. Release behavior was also controlled by chemical treatment of Al_2O_3 core. Acid-treated Al_2O_3 showed the lesser release rate and release amount of vitamin B_{12} due to the strong binding with vitamin B_{12}. The release behavior of vitamin B_{12} could be controlled easily by both the microcapsule shell and the chemically treated Al_2O_3 core.

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