Spray-Dried Lactose Composite Particles Containing an Ion Complex of Alginate-Chitosan for Designing a Dry-Coated Tablet Having a Time-Controlled Releasing Function

Hirofumi Takeuchi,[1] Takehiko Yasuji,[1] Hiromitsu Yamamoto,[1] and Yoshiaki Kawashima[1,2]

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Purpose. The properties of novel spray-dried lactose composite particles suitable for the coating filler of a dry-coated tablet having a long induction period in drug release were investigated.

Methods. To prepare spray-dried composite particles containing alginate-chitosan complex (SD(L/AL-CS)), an aqueous solution of lactose and sodium alginate and the acetic acid solution of chitosan were concomitantly fed into the rotary atomizer of a spray-dryer. The formation of the alginate-chitosan complex was confirmed by measuring the weight of insoluble portion in the mixture of sodium alginate and chitosan solutions. The dissolution properties of the dry-coated tablet were measured with the JP specified paddle method.

Results. The micromeritic properties of SD(L/AL-CS) were compared to those of the SD composite particles of lactose-sodium alginate, having a good compacting property. The drug release profiles of dry-coated tablet with SD(L/AL-CS) contained a long induction period followed by a rapid drug release phase in the artificial intestinal fluid. The induction period for drug release to occur was increased with an increase in the degree of deacetylation of chitosan and in the amount of chitosan in the formulation. The prolongation of induction period was attributed to the formation of an insoluble ion complex between sodium alginate and chitosan in the composite particles, which could form a rigid gel structure on the tablet surface.

Conclusions. A time-controlled release tablet was designed with the composite particles of lactose containing the alginate-chitosan ion complex. The induction period of the dry-coated tablet could be prolonged in order to deliver the drug to the colon by controlling the type and amount of chitosan formulated in the composite particles.

KEY WORDS: spray-drying; alginate-chitosan complex; dry-coated tablet; time-controlled release; colonic delivery.

INTRODUCTION

The delivery of drugs to the colon is useful in the topical treatment of the diseases such as ulcerative colitis, the oral delivery of peptide drugs susceptible to degradation in the upper gastrointestinal tract and the treatment of diseases susceptible to circadian rhythm such as asthma (1,2). A number of approaches have been devised for delivering the drugs to the colon, including: (i) microbial enzymes predominantly in the colon can be exploited in site-specific drug delivery to the colon (3), (ii) a polymeric coating which dissolves at a specific pH can protect the drug release until the system arrives in the colon (4) and (iii) a time-controlled release system which can release the drug from the devices when the dosage form has arrived in the colon (5).

A dry-coated tablet is one of the candidate delivery systems to realize such as a delayed drug release pattern. Gel-forming polymers such as hydroxyethylcellulose have been reported as the suitable materials for the outer layer of the dry-coated tablet (6). The tablet may release the drug formulated in the core tablet after the coating layer is eroded. It is required for the coating layer to have a reliable tolerance to the drug release in the stomach and upper part of the intestinal tube. Compressibility is also an important property for the coating material because the compressibility of dry-coated tablets is highly dependent on that of the coating material.

In a previous paper, we reported on the property of composite particles prepared by spray-drying a mixed solution of lactose and sodium alginate. The spray-dried (SD) composite particles were demonstrated to possess a significantly improved compaction property as compared with sodium alginate particles and commercial directly compressive lactose materials. This spray-dried material also displayed a sustained drug release property when used as a filler of matrix tablets (7). It was also demonstrated that the composite particles could be applied as a coating layer to a dry-coated tablet (8). The drug release pattern of the dry-coated tablet was composed of an induction phase that was followed by a rapid release phase. As the induction period was determined by eroding rates of the coating layer of dry-coated tablet, the induction period could be controlled by changing the thickness of the outer layer of the dry-coated tablets. However, the thickness of the outer layer of the dry-coated tablet was restricted considering the size of resultant tablet. Although the increase in the amount of sodium alginate in the composite particles could prolong the induction period, the excess amount of sodium alginate in the particles led to poor compactibility of the tablet (9).

The aim of this paper is to design and investigate the properties of the novel composite particles suitable for the coating of dry-coated tablets which provide a long induction period suitable for targeting drugs to the colon. The design was based on the formation of an ionic complex in the SD composite particles between sodium alginate and chitosan. The compactibility of the particle and the drug release properties of dry-coated tablets with the particles was investigated as well as the formation of the ionic complex.

MATERIALS AND METHODS

Materials

Sodium alginate (NaAlg) with average molecular weight of about 11.5×10^4 was supplied from Kibun Food Chemifa Co., Japan. Chitosans (CS) with different degrees of deacetylation (81 ~ 98%) and molecular weights (ca. 150 kDa ~ 3,000 kDa) were supplied from Katakura Chikkarin Co., Japan. Lactose (Pharmatose 450M, DMV, Netherlands) was obtained from DMV Japan. Acetaminophen used as a water-soluble and poorly compressible model drug was purchased from Yamamoto Chemical, Japan.

[1] Gifu Pharmaceutical University, 5-6-1 Mitahora-Higashi, Gifu 502-8585, Japan.

[2] To whom correspondence should be addressed. (e-mail yoshiaki@gifu-pu.ac.jp)

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Preparation of Spray-Dried Composite Particles

The spray-dried particles were prepared by using a rotary atomizing spray dryer (Type L-12, Ohkawara Kakoki, Japan) and a roller pump (RP-N3, Furue science Co. Ltd.). The solutions to be spray-dried were fed into a rotary atomizer through inlet tubes equipped at the center part of atomizer. To prepare lactose: sodium alginate composite particles (9:1) (hereinafter called SD(L/AL)), an aqueous solution of lactose and sodium alginate was spray-dried. To include the chitosan in the lactose-sodium alginate composite particles, an aqueous solution of lactose and sodium alginate in a ratio of 9:1, and the acetic acid solution of chitosan (2% v/v) were concomitantly fed into a rotary atomizer of a spray dryer from the different inlet tubes, and spray-dried immediately after mixing. As a reference, another composite particle containing alginate-chitosan complex was prepared by spray-drying the suspension of the complex which was prepared by mixing the sodium alginate solution and chitosan acetic acid solution (hereinafter called SD(L/(AL + CS)). The spray-dried conditions were as follows: inlet and outlet temperatures were 175°C and 100°C, respectively; rotational velocity of the atomizer was 15,000 rpm and the feed rate for the total solution was 50 mL/min. The SD(L/AL) and chitosan powders were physically mixed (hereinafter called PM(SD(L/AL) + CS)). The chitosan powders were ground in a ball mill and subsequently sieved with a 200 mesh sieve.

Confirmation of Alginate-Chitosan Complex

To prepare the alginate-chitosan complex, an appropriate amount of the acetic acid solution of chitosan (2% v/v) was mixed with the aqueous solution of sodium alginate (0.1 g in 15 mL) in a test tube. The sample solution was then incubated at 37°C for 2 days to complete the complex formation. The alginate-chitosan complex precipitated in the solution was collected by centrifuging the solution at 43,400×g for 10 minutes with a Kubota 7800 centrifuge (Kubota, Japan). Following the removal of the supernatant, the pellets were dried at 80°C under vacuum for 3 days.

Fourier-transform infrared (FT-IR) spectra of the alginate-chitosan complex was compared with those of sodium alginate and a physical mixture of sodium alginate and chitosan powder to confirm the formulation of the complex using a Jasco model FT/IR-230 spectrophotometer (KBr disk method).

Physicochemical Properties of Spray-Dried Composite Particles

The crystallinity of lactose in the composite particles was identified with a powder X-ray diffraction method. The measurements were carried out using the Powder X-ray Diffraction Meter (RAD-1C, Rigaku, Japan) with Cu-Kα radiation and a scan rate of 2° 2θ/min. The X-ray diffractograms were recorded between 5 and 40° in 2 θ. The particle size of the composite particles was measured with a laser scattering light analysis system (LDSA-2400A, Tohnichi Computer, Japan) using a dispersing-in-air method (air pressure: 3.0 kg/cm^2). The true density of the composite particles was determined with an air comparison pycnometer (Model 930, Beckman-Toshiba). The flow properties of the composite particles were determined by measuring the angle of repose with a powder pouring method. A small amount of light anhydrous silicic acid (0.5 wt %) was added to each sample powder, because it was difficult to observe a reproducible value of the angle of repose for the original lactose (Pharmatose 450M) without adding the glidant.

The compaction of the composite particles was evaluated by means of tensile strength of the compacts. The weighed sample (200 mg) was placed into a die of diameter 8.0 mm, and directly compacted with edged-faced punches using an Instron-type hydraulic press (Autograph AG5000D, Shimadzu Co., Japan) at a compaction velocity of 10 mm/min, until the compaction pressure of 200 MPa was reached. The tablet crushing strength, which is the force required to fracture the compacts by diametrical compression, was measured with the Instron-type hydraulic press (Autograph AG5000D, Shimadzu Co., Japan) at a speed of 0.5 mm/min. The tensile strength (Ts) was calculated from the following equation (10):

$$Ts = \frac{2F}{\pi DT}$$

where F (N) is the crushing strength, and D (m) and T (m) are the diameter and thickness of the tablet, respectively.

Preparation of Dry-Coated Tablets

All tablets for the dissolution tests were prepared using an Instron-type hydraulic press (Autograph AG5000D, Shimadzu Co., Japan) at a compaction velocity of 2 mm/min with flat-faced punches and a die. Core tablets (7 mm) of 50 mg of acetaminophen and 50 mg of commercial lactose for direct tabletting (DCL21) were compacted at the compaction pressure of 100 MPa, unless otherwise stated. To prepare the dry-coated tablets, the amount of the coating filler for the lower, upper and side coating layers in the resultant dry-coated tablet (400 mg) was calculated by considering the volumetric ratios. The powder for the lower layer was filled into a die of a diameter 10 mm, and then lightly compacted at the compression pressure of 20 kPa for 30 seconds to make a flat surface powder bed. The core tablet was manually placed on the center of the powder bed. After filling the space of die with the remainder of the powder, the powder bed containing the core tablet was compacted at the compaction pressure of 200 MPa to make the dry-coated tablet (total weight: 500 mg).

To determine the drug release mechanism of the dry-coated tablets, a model double layered tablet was used, which has all been previously described (10).

Dissolution Tests

The dissolution tests of the dry-coated tablets and the model tablet were carried out with the paddle method specified in the Japanese Pharmacopoeia XIII (JPXIII). The dry-coated tablet placed in a sinker for dissolution test specified in JP XIII or the model tablet weighted down by a lead weight was sunk in 900 mL of JPXIII disintegration No. 1 fluid (pH 1.2) or No. 2 fluid (pH 6.8) thermally controlled at 37°C and rotated at 100 rpm. The sinker and the lead were used to ensure the constant dissolution conditions for the tablets without floating and adhering the tablet in the dissolution vessel. McIlvaine's buffer solutions (pH 3, 4, 5), consisting of 0.2 M sodium hydrogen phosphate and 0.1 M citric acid, were also used in the dissolution test to determine the acid-resistance of the dry-coated tablet. The concentration of acetaminophen dissolved

in the medium was spectrophotometrically measured at a wavelength of 243 nm (UV-160A, Shimadzu, Japan).

Measurement of the Eroding Rate of Controlled-Releasing Filler

The weight of compacts composed of the coating filler with a diameter of 10 mm was periodically measured to investigate the erosion rate. The compact (400 mg) was prepared at compacting pressure of 200 MPa by using the Instron-type hydraulic press (Autograph AG5000D, Shimadzu Co., Japan). The compacts placed in a sinker was sunk in 900 mL of JPXIII disintegration No. 2 fluid (pH 6.8) thermally controlled at 37°C and rotated at 100 rpm. The compacts were taken out of the dissolution medium at an appropriate time interval, and then put on the glass dish whose weight was previously measured. The samples were dried in an oven at 80°C for 2 days and in a vacuum for longer than 3 days. The dried samples were weighed, and the change in the weight fraction of each compact was calculated.

RESULTS AND DISCUSSION

Formation of Alginate-Chitosan Complex

Chitosan, which is a partially N-deacetylated product of chitin, has been used in the preparation of granules (11) and tablets (12) for controlled-release of the active drug substance. In a previous paper, we reported on the properties of controlled-release theophylline granules coated with polyelectronic complex of sodium tripolyphosphate and chitosan (13). It was also reported that chitosan formed a complex with sodium hyaluronate by interpolymeric and intrapolymeric cross-linking mechanisms (14).

In the present study, our goal was to confirm the formation of an ionic complex of chitosan with sodium alginate in order to formulate the complex into spray-dried (SD) composite particles of sodium alginate and lactose. The amount of precipitate obtained from the mixing of an aqueous solution of sodium alginate with various amounts of an acetic acid solution of chitosan (2% v/v), was measured after drying up the precipitate. The amount of precipitate was increased proportionally with the weight fraction of chitosan in the mixture (Fig. 1). The increase in the degree of deacetylation in chitosan led to an increase in the amount of precipitate at the same weight fraction, while the molecular weight of the chitosan resulted in minimal changes in the amount of precipitate formed. These results suggested that the formation of the complex was attributed to an ionic interaction between the positively charged chitosan and the alginate anion in the solution.

To clarify the interaction between the alginate and chitosan, Fourier-transform infrared (FT-IR) spectra of the complex and the corresponding physical mixture of sodium alginate and chitosan were measured. Although a typical peak in the spectra was observed at 1620 cm^{-1} for both the sodium alginate powder and the physical mixture, new peaks appeared at 1670 cm^{-1} and 1560 cm^{-1} in the spectra of the alginate-chitosan complex. The strength of these peaks was decreased with a decrease in the weight fraction of chitosan, and they disappeared in the spectra of the complex when the weight fraction of chitosan was 0.001. These peaks at 1670 cm^{-1} and 1560 cm^{-1} were assigned to the carboxyl groups of the alginate interacted with the chitosan and the amino groups of the chitosan interacted with alginate, respectively. Takayama *et al.* have previously reported the similar FT-IR spectra to demonstrate the interaction of the amino groups of the chitosan with the carboxyl groups of polyacrylate, alginate and hyaluronate (14, 15). These results strongly supported our findings that the cationic groups of the chitosan had interacted with the anionic groups of the sodium alginate through electrical interaction.

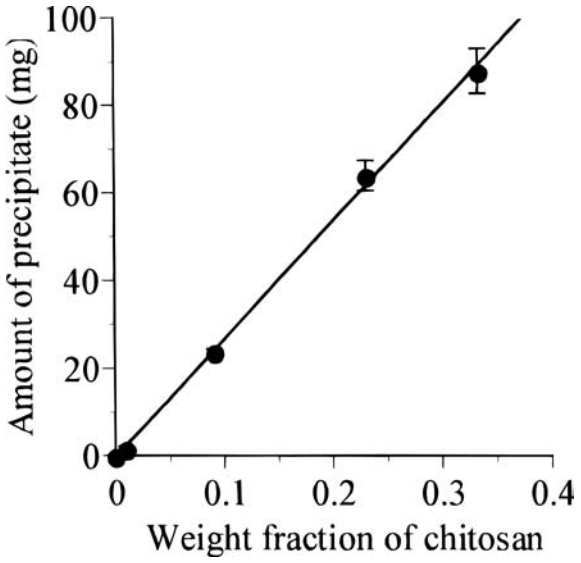

Fig. 1. Formation of the alginate-chitosan complex as a function of the amount of chitosan with degree of deacetylation of 84% (Mw.: 580,000). Data are expressed as the mean ± S.D. of three runs.

Physicochemical Properties of the Composite Particles Containing Alginate-Chitosan Complex

The lactose-sodium alginate composite particles that were added to the chitosan (SD(L/AL-CS)) were prepared by use of a spray-drying technique. The physicochemical properties of the composite particles (SD(L/AL-CS)), as well as other spray-dried particles and the original α-lactose monohydrate particles are listed in Table 1. The tensile strength of compacts of SD(L/AL-CS) was much higher than that of the original α-lactose monohydrate as well as that of the spray-dried lactose (SD-L) or lactose-sodium alginate composite particles (SD (L/AL)). The good compacting properties of the composite particles were attributed to the increase in the plastic deformation and easily fusing property of the spray-dried particles containing the amorphous lactose (9). The addition of chitosan, which could not be compacted at compression pressure of 100 MPa, into the composite particles did not affect the compactibility of the resultant composite particles. In measuring the angle of repose of these particles, the flow properties of these spray-dried particles were confirmed, and the reduction in the angle of repose measurement was ascribed to the spherical shape and the narrow particle size distribution of the particles. The physicochemical properties of the composite particles containing alginate-chitosan complex (SD(L/AL-CS)) were preferable for direct tabletting as well as the composite particles of lactose and sodium alginate (SD(L/AL)).

Table 1. Physicochemical Properties of Lactose-Sodium Alginate Particles Modified with Chitosan (SD(L/AL-CS))[a]

Properties	Excipient			
	Pharm.450M	SD-L	SD (L/AL)	SD (L/AL-CS)
Tensile strength (MPa)	0.5 ± 0.1	2.4 ± 0.1	2.1 ± 0.1	1.9 ± 0.1
Angle of repose (degree)	47 ± 1	37 ± 1	34 ± 2	38 ± 2
Form	α-lactose	amorphous	amorphous	amorphous
Particle size (μm) D_{16}	9.1 ± 2.0	9.7 ± 0.2	8.6 ± 0.2	8.7 ± 0.3
Particle size (μm) D_{50}	24.6 ± 4.8	15.7 ± 0.3	15.3 ± 0.4	15.3 ± 0.3
Particle size (μm) D_{84}	71.1 ± 12.5	23.1 ± 0.8	25.0 ± 1.0	22.6 ± 0.9
True density (g/cm^3)	1.54 ± 0.01	1.50 ± 0.02	1.51 ± 0.01	1.50 ± 0.02

[a] Data are expressed as the mean ± S.D. of four runs.

Drug Release Profiles of Dry-Coated Tablet with the Composite Particles

The controlled-released properties of the lactose-sodium alginate composite particles modified with chitosan (SD(L/AL-CS)) as the coating filler of dry-coated tablet were evaluated with a model tablet containing acetaminophen in the core tablet. The drug release was tested for both composite particles of SD(L/AL) and SD(L/AL-CS) in the various dissolution media with different pH (Fig. 2(A) and (B)).

In No. 2 disintegration fluid specified in the JP, the drug release pattern of the dry-coated tablet with SD(L/AL-CS), as well as in the case of SD(L/AL), was composed of an induction period which was followed by the rapid drug release phase. The induction period of the drug release from the dry-coated tablet with SD(L/AL-CS) was more retarded than that with SD(L/AL). It was also characteristic in the drug release profile for the tablet with SD(L/AL-CS) to show the acid-resistance at the pH of dissolution media of 1.2–5, while the tablet with SD(L/AL) showed a rapid drug release in the pH range of 4–5. These results confirmed that the addition of the chitosan to the SD(L/AL) particles is an effective step in prolonging the induction period in the drug release process.

Control of the Induction Period of the Dry-Coated Tablet

The difference in the drug release profiles of the dry-coated tablets with SD (L/AL- CS) or SD(L/AL) may be explained by the presence of alginate-chitosan complex in the composite particles. The alginate-chitosan complex in the composite particles might form a stronger gel structure on the surface of the tablet in contact with the dissolution medium, resulting in the retardation of drug release from the tablet. In this case, the induction period of the dry-coated tablet may be controlled by the type and formulating ratio of chitosan. The induction period in the drug release from the dry-coated tablet was evaluated by using a model tablet with SD(L/AL-CS) particles prepared with the various types and amount of chitosan (Table 2). The induction period was increased in increasing the degree of deacetylation of chitosan, and the amount of chitosan formulated in SD(L/AL-CS), probably owing to the increase in the amount of the alginate-chitosan complex in the particles (Fig. 1). When the molecular weight of chitosan formulated in SD(L/AL-CS) was increased from 580,000 to 3,000,000, the induction period of the drug release was not prolonged. A possible explanation for the unexpected result is the decreased solubility of chitosan with the molecular weight of 3,000,000. The decreased

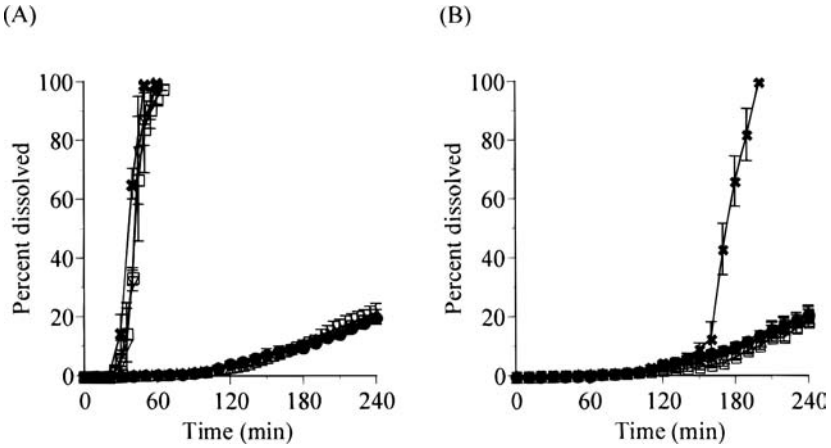

Fig. 2. Dissolution profiles of acetaminophen from dry-coated tablets composed of (A) SD(L/AL) and (B) SD(L/AL-CS). Effect of medium pH on the dissolution profile of the drug. Medium pH: (●) artificial gastric fluid (pH1.2), (△) pH 3, (□) pH 4, (▽) pH 5 and (×) artificial intestinal fluid (pH6.8). Data are expressed as the mean ± S.D. of three runs.

Table 2. Effect of the Type and Amount of Chitosan in the SD(L/AL-CS) on the Induction Period in Artificial Intestinal Fluid Thickness of Coating Layer: 1.0 mm[a]

Sample	Chitosan			Induction period (min) in intestinal fluid
	Deacetylation (%)	Mw	Weight fraction	
SD(L/AL)				32 ± 3
SD(L/AL-CS)	81	570,000	0.001	87 ± 5
	84	580,000	↓	120 ± 6
	98	500,000	↓	146 ± 6
	83	150,000	↓	75 ± 6
	84	580,000	↓	120 ± 6
	85	3,000,000	↓	65 ± 7
	84	580,000	0.001	120 ± 6
	↓	↓	0.048	167 ± 8
	↓	↓	0.091	420 ± 9

[a] Data are expressed as the mean ± S.D. of three runs.

solubility might lead to decrease in the formation of the alginate-chitosan complex.

To clarify the difference in the mechanical strength of the coating layer of the dry-coated tablet consisting of the composite particles, the eroding rate of the tablet prepared with the composite particles was studied in the No. 2 disintegration fluid by measuring the weight of the compact at an appropriate interval (Fig. 3). The change in weight of the compacts with SD(L/AL-CS) was significantly slower than that of SD(L/AL). This result revealed that the induction period of drug release depends on the eroding rate of the coating layer of the dry-coated tablet.

One may expect that the physical mixing of chitosan particles with the SD(L/AL) particles cause a similar prolongation in the induction period in drug release from the resultant dry-coated tablet. However, no significant difference in the induction period was observed for the two tablets prepared with SD(L/AL) and PM(SD(L/AL) + CS) which was the physical mixture of SD(L/AL) and chitosan particles with the same formulating ratio as for SD(L/AL-CS) (Table 3). Even when the physical mixtures were prepared with the excess amount of chitosan particles, the resultant induction period was much shorter than that in the case of SD(L/AL-CS). Moreover, the drug release rate was more retarded than in the case of SD(L/AL-CS), because of the insolubility of the chitosan in the dissolution medium (Fig. 4).

When the composite particles were prepared with lactose and the pre-formed alginate-chitosan complex (SD(L/AL + CS)) (see experimental section), the induction period was almost the same as in the case of SD (L/AL) (Table 3). This result suggested that the distribution of alginate-chitosan complexes in the composite particles play an important role in forming the rigid gel structure when in contact with the dissolution medium. These results suggested that the good dispersion of the alginate-chitosan complex in the controlling filler was necessary in order to achieve the objective drug release pattern. Concomitant complex formation during spray-drying was a suitable method for the preparation of the composite particles.

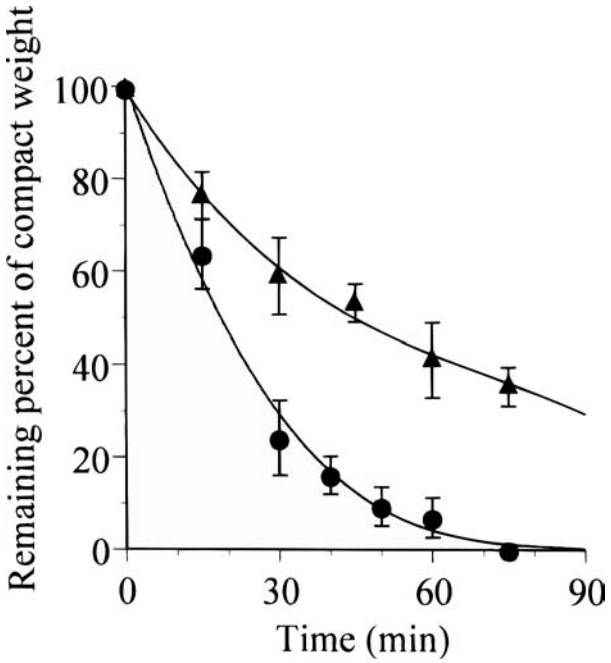

Fig. 3. Change in the weight of compacts prepared with spray-dried composite particles: (●) SD(L/AL), (▲) SD(L/AL-CS) in artificial intestinal fluid (pH6.8). Data are expressed as the mean ± S.D. of three runs.

Table 3. Effect of Preparation Method of Alginate-Chitosan Complex with Spray-Drying Technique on the Induction Period in Artificial Intestinal Fluid (pH6.8). Thickness of Coating Layer: 1.0 mm[a]

Controlling filler	Induction period in artificial intestinal fluid (min)
SD(L/AL)	32 ± 3
PM(SD(L/AL) + CS)	31 ± 6
SD(L/(AL + CS))	38 ± 5
SD(L/AL − CS)	120 ± 6

[a] Data are expressed as the mean ± S.D. of three runs.
Note: PM(SD(L/AL) + CS): physical mixture of SD(L/AL) and chitosan, SD(L/(AL + CS)): spray-drying the suspension containing pre-formed alginate-chitosan complex, SD(L/(AL − CS)): spray-drying the solution of lactose/NaAlg and the acetic acid solution of chitosan.

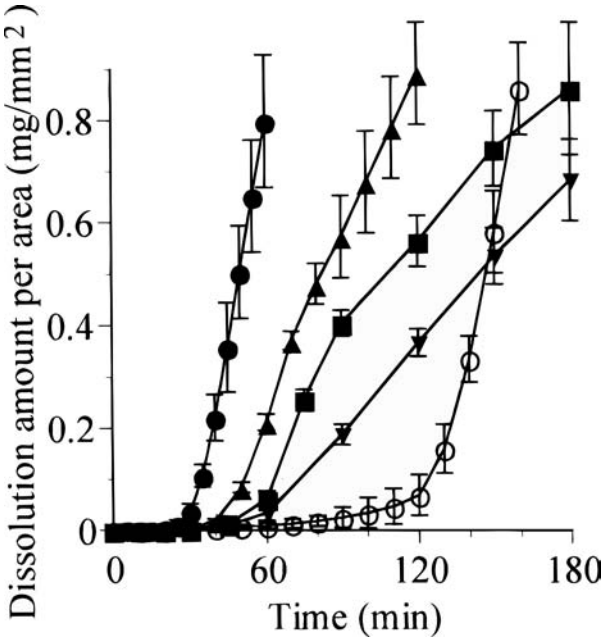

Fig. 4. Dissolution profiles of acetaminophen from the model tablet in artificial intestinal fluid (pH6.8): (●) SD(L/AL), (○) SD(L/AL-CS) and physical mixture of SD(L/AL) and chitosan at various formulating ratios (SD(L/AL): chitosan): (▲) 4:1, (■) 1:1, (▼)1:4. Thickness of coating layer: 1.0 mm. Data are expressed as the mean ± S.D. of three runs.

CONCLUSIONS

The lactose-sodium alginate-chitosan composite particles having good compaction and flow properties were successfully applied to the coating layer of dry-coated tablet. The dry-coated tablets showed excellent acid-resistance and prolonged induction periods in drug release owing to the rigid gel structure formed on the surface of the tablet. When the composite particles were prepared with lactose and the pre-formed alginate-chitosan complex, the prolonged induction period was not obtained, suggesting that the good dispersion of the alginate-chitosan complex in the controlling filler was necessary in order to achieve the objective drug release pattern. Concomitant complex formation during spray-drying was a suitable method for the preparation of the composite particles. The induction period could be controlled by changing the degree of deacetylation and the amount of chitosan formulated in the composite particles. When the composite particles were prepared with a suitable type and level of chitosan and applied to the coating layer, the resultant dry-coated tablet were shown to effectively deliver the drug to the colon.

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