ELSEVIER

International Journal of Pharmaceutics 174 (1998) 91–100

international journal of pharmaceutics

Spray-dried composite particles of lactose and sodium alginate for direct tabletting and controlled releasing

Hirofumi Takeuchi, Takehiko Yasuji, Tomoaki Hino, Hiromitsu Yamamoto, Yoshiaki Kawashima *

Gifu Pharmaceutical University, 5-6-1, Mitahora-higashi, Gifu, 502-8585, Japan

Received 18 May 1998; received in revised form 26 June 1998; accepted 21 July 1998

Abstract

A novel composite particle suitable for the filler of controlled-release matrix tablets was prepared by spray-drying an aqueous solution of α-lactose monohydrate and sodium alginate. The spray-dried (SD) particles had an excellent flowing property due to their spherical shape and sharp particle size distribution. When the SD particles were compressed into a tablet in a compressing pressure range of 100–400 MPa using an Instron-type hydraulic press, the tensile strength of compacts was much higher than that of a commercial lactose for direct tabletting and a physical mixture of lactose and sodium alginate particles with the same formulating ratio as for the SD particles. The improvement in compressibility of the SD particles was attributed to an increased deformability of particles with a decrease in crystallinity of lactose. Thermal stability of amorphous form of lactose in the SD particles determined by differential scanning calorimetry was dramatically enhanced with the presence of sodium alginate in the particles. It was assumed that sodium alginate interacted with lactose molecules in SD particles. The drug release from the matrix tablet prepared with the SD particles and acetaminophen in JPXIII No. 1 medium (pH 1.2) was more prolonged than that of a physically mixed tablet of lactose, sodium alginate and the drug, because of the improved gel forming property of sodium alginate formulated in the SD particles.

Keywords: Direct tabletting; Controlled releasing filler; Lactose; Spray-drying; Amorphous composite particle

1. Introduction

Lactose is one of the most widely used excipients in pharmaceutical manufacturing due to its stable physicochemical properties such as unhygroscopicity. It can form several crystal forms, which are responsible for the different physicochemical properties, including tabletting characteristics (Lerk, 1993). In the various commercial lactoses, a spray-dried lactose, which appeared on the pharmaceutical market in the early 1960s, was

* Corresponding author. Tel.: +81 582 373931; fax: +81 582 375979.

0378-5173/98/$ - see front matter
PII S0378-5173(98)00248-8

the first product specially designed for direct tabletting (Gunsel and Lachman, 1963). The spray-dried lactose had good flowing and binding properties due to the spherical shape of the particles and the amorphous form of lactose in the particles (Gunsel and Lachman, 1963; Vromans et al., 1986). It has been reported that the compactibility of commercial spray-dried lactose was affected by the amount of amorphous lactose in the particles as well as the primary particle size (Vromans et al., 1987). However, the amorphous lactose in the spray-dried particles is physically and thermally unstable (Elamin et al., 1995). Sebhatu et al. (1994) showed that moisture was selectively taken up in an amorphous region of the commercial spray-dried lactose containing 15% amorphous lactose and the moisture sorption resulted in crystallization of the amorphous lactose.

A drug controlled-releasing property is one of the most important functions of oral drug delivery systems, and various dosage forms and preparation methods are available. Among them, a controlled-releasing tablet is a preferable dosage form for patient compliance and for pharmaceutical production. Tablets coated with water-insoluble materials such as waxy materials and acrylic and methacrylic ester copolymer (Ishino et al., 1992; Garacia-Arieta et al., 1996) and matrix tablets composed of a drug and gel-forming water-soluble polymers such as hydroxypropylmethylcellulose (Tahara et al., 1995) are known as typical controlled-releasing tablets. The latter is more desirable from the point of view of manufacturing because the manufacturing process is comparatively simple. However, polymeric materials are poorly compressible in general due to their elastic properties, and their micromeritic properties, such as a flowing property, are generally unsuitable for the manufacturing process unless they are agglomerated. Therefore, some physicochemical modifications of polymeric particles are necessary so as to apply the direct tabletting method.

This paper will report preparation of a novel modified lactose particle containing a gel-forming polymer for controlling the drug release rate from the resultant matrix tablets. Sodium alginate was selected as the model polymeric material because it was a biocompatible natural polymer with the pH-sensitive gel-forming ability. The composite particles of lactose and sodium alginate were produced by using a spray-drying method, and the micromeritic and controlled-releasing properties were evaluated.

2. Materials and methods

2.1. Materials

Lactose (Pharmatose 450M, hereinafter called Pharm. 450M) and sodium alginate (NSPLL) were supplied from DMV, Netherlands and Kibun Food Chemifa, Japan, respectively. A spray-dried lactose (DCL11, DMV), which was a mixture of α-lactose monohydrate and amorphous lactose, and roller-dried β-lactose anhydrate (DCL21, DMV) were used as a reference of direct tabletting fillers. The content of amorphous lactose in the commercial spray-dried lactose (DCL11) was approximately 15%. Acetaminophen and ascorbic acid used as a water-soluble and poorly compressible model drug were supplied by Yamamoto Chemical, Japan and Takeda Chemical Industries, Japan, respectively. Light anhydrous silicic acid (Aerosil 200, Nippon Aerosil, Japan) was used as a glidant.

2.2. Preparation of spray-dried composite particles

In preparation of spray-dried composite particles (SD particles), lactose (Pharm. 450M) and sodium alginate were dissolved at various formulating ratios in 3000 ml of distilled water, and the aqueous solution was spray-dried using a rotary atomizing spray-dryer (Type L-12, Ohkawara Kakoki, Japan) under the following conditions; rotational velocity of atomizer: 15000 rpm, spray rate of the solution: 50 ml/min, inlet and outlet air temperatures: 175 and 100°C.

The prepared SD particles were kept in a glass vial and stored in a desiccator with below 30% relative humidity (RH) at room temperature, because 30% RH is lower than the critical RH (50–60% RH) for crystallization of amorphous lactose (Buckton and Darcy, 1995).

2.3. Physicochemical properties of SD particles

The crystallinity of lactose was identified by a powder X-ray diffraction method. The powder samples were placed into a sample holder for the powder X-ray diffraction and the surface was smoothed with a glass slide. The measurement was carried out with the powder X-ray diffraction meter (RAD-1C, Rigaku, Japan) using Cu-Kα radiation and at scan rate of 2° 2θ/min. X-ray diffractograms were recorded between 5 and 40° in 2θ.

The particle size was measured by 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 evaluation was carried out by the 50% particle size (D_{50}) and the 16 and 84% particle sizes (D_{16}, D_{84}) on a volume basis, which represents the average particle size and particle size distribution, respectively.

The true density of lactose particles were determined by an air comparison pycnometer (Model 930, Beckman-Toshiba).

The total moisture content in the particles was determined with a Kirl Fischer moisture meter (MKA-510, Kyoto Electronics, Japan). The Kirl Fischer solution, a standard water-methanol solution and a dehydrating solvent for sugar were used. Additionally, the adsorbed moisture contents of particles were measured by thermogravimetric method (TG-DTA6200, Seiko Instrument, Japan). A weighted sample (7 mg) of each particle was heated from 25 to 80°C at heating rate of 10°C/min and then maintained at 80°C for 2 h. The weight loss of the sample was determined once thermogravimetry (TG) curves showed the steady state.

The flowing properties of particles were evaluated by measuring angle of repose with a powder pouring method. The sample powders were mixed with 0.5% (w/w) light anhydrous silicic acid, because it was difficult to observe a reproducible value of the angle of repose for the original lactose (Pharm. 450M) without adding the glidant. The powders were piled on the specimen table (diameter 40 mm) by an electromotive feeder (PS-10S, Tohnichi Computer, Japan), which was fixed at a height (75.5 mm) to form a stable heaped cone. The heaped cone was photographed with an image processing apparatus (Color video camera DXC-C1, Sony, Japan). The height and diameter of the heaped cone were measured from the projection image, then the angle of repose was calculated.

Photographs of SD particles were taken with a scanning electron microscope (JSM-T330A, Nihon Denshi, Japan) at accelerating voltage of 5 kV. Samples were coated with a thin layer of gold by using an ion sputter (JCPD-3, Nihon Denshi, Japan).

A differential scanning calorimeter (DSC6200, Seiko Instrument, Japan) was used to detect the melting temperature of the crystalline lactose and the crystallization of amorphous lactose. Indium and zinc were used as calibrants. Each sample (7 mg) was placed in the sealed aluminum sample pan and scanned at heating rate of 10°C/min.

2.4. Evaluation of compactibility

The compactibility of lactose particles was evaluated by means of tensile strength of the compacts. The weighed sample (200 mg) was placed into a die with a diameter of 8.0 mm, and compressed with edged-faced punches using an Instron-type hydraulic press (Autograph AG5000D, Shimadzu, Japan) at 10 mm/min under various compression pressures. The tablets were stored in a sealed vial for more than 24 h to complete the stress relaxation of the tablets before the crushing strength tests. The crushing strength, which is the force required to fracture the tablet by diametrical compression at speed of 0.5 mm/min, was measured with the Instron-type hydraulic press (Autograph AG5000D, Shimadzu, Japan). Tensile strength (T_s) was calculated by the following equation (Fell and Newton, 1970):

$$T_s = \frac{2F}{\pi DT} \quad (1)$$

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

2.5. Dissolution test of matrix tablets containing acetaminophen

Acetaminophen and SD particles (or physical mixtures (PM) of Pharm. 450M and sodium alginate as a reference) were mixed in the ratio of 1:1, and the mixture (200 mg) was compressed by the Instron-type hydraulic press (Autograph AG5000D, Shimadzu, Japan) under a compression pressure of 400 MPa, using flat-faced punches and a die with a diameter of 8.0 mm.

The dissolution test of the matrix tablet was carried out according to the paddle method specified in the Japanese Pharmacopoeia XIII (JPXIII). The sample tablet placed in a sinker was sunk in 900 ml of JPXIII No. 1 disintegration medium (pH 1.2) or No. 2 medium (pH 6.8) thermally controlled at 37°C and rotated at 100 rpm. The sinker was used to ensure the constant dissolution conditions for the tablets without adhering to the bottom of the dissolution vessel. The concentration of acetaminophen dissolved in the medium was spectrophotometrically measured at 243 nm with a spectrophotometer (UV-160A, Shimadzu, Japan).

3. Results and discussion

3.1. Physicochemical properties of SD particles

The physicochemical properties of SD particles and commercial lactose are listed in Table 1. The mean diameters and particle size distributions of SD particles were almost the same regardless of sodium alginate content and the range of distribution was narrower geometric standard deviations than the original lactose particles (Pharm. 450M) used in preparation of SD particles and the commercial lactose for direct tabletting (DCL11, DCL21) as shown in their lowered geometric standard deviations. The true density of spray-dried lactose (SD-L) was a little bit smaller than that of the commercial crystalline lactose. The SD composite particles containing sodium alginate also showed lower values than those for the corresponding physical mixtures, which were calculated with the true density of sodium alginate (1.73) and lactose (1.54). These differences in true density of samples suggested the transformation of crystalline form. The amorphous form of lactose in SD particles was confirmed by halo pattern in powder X-ray diffraction analysis. Scanning electron microphotographs of the SD particles are shown in Fig. 1. Regardless of sodium alginate content, SD particles were more spherical with smoother surface than DCL11, DCL21 and Pharm. 450M. Owing to the change in the particle shape and surface property, the angle of repose of SD particles was lower than that of the commercial lactose for direct tabletting (Table 1). These results suggested that the SD particles had a preferable micromeritic property for direct tabletting.

Water content in the SD particles was measured by Karl Fischer (KF) and TG methods. KF method was used to measure the total water content in SD particles, while water content measured with TG method represented the amount of adsorbed water in the particles. The results showed that almost all the water molecules in SD-L particles are classified as adsorbed water. On the other hand, the total water content exceeded the adsorbed content in the case of SD composite particles containing sodium alginate. This result suggested that the SD composite particles contain non-adsorbed water molecules.

Differential scanning calorimetry (DSC) curves of SD particles and Pharm. 450M are shown in Fig. 2. An amorphous form of lactose in the SD-L particle was identified by the presence of an exothermic peak at 170°C which represented the transformation of amorphous to crystalline form of lactose (Sebhatu et al., 1994). The two endothermic peaks at ≈ 215 and ≈ 230°C correspond to the melting points of α-lactose monohydrate and α- or β-lactose anhydrate, respectively, which confirmed the transformation of the amorphous form of lactose to the two types of crystalline form by heating. On the other hand, lactose in the SD composite particles containing 10% sodium alginate (SD9:1) showed no exothermic or endothermic peaks in the same heating range as for SD-L, although the presence of amorphous form was confirmed by powder X-ray diffraction analysis. This result suggested that the

Table 1
Physicochemical properties of SD particles and commercial lactose

Excipient	Particle size (μm)			Geometric standard deviation of particle size	True density (g/cm^3)	Form	Angle of repose (°)	Moisture content (%)	
	D_{16}	D_{50}	D_{84}					KF method	TG method
DCL11	51.6	104.4	176.4	1.9	1.55 ± 0.03	α-Lactose +amorphous	40 ± 1	5.10 ± 0.09	0.58 ± 0.02
DCL21	19.7	126.8	256.3	4.2	1.58 ± 0.02	β-Lactose	42 ± 1	0.21 ± 0.02	0.04 ± 0.01
Pharm. 450M	9.1	24.6	71.1	2.8	1.54 ± 0.01	α-Lactose	47 ± 1	5.04 ± 0.10	0.02 ± 0.01
SD-L	9.7	15.7	23.1	1.5	1.50 ± 0.02	Amorphous	37 ± 1	2.48 ± 0.08	2.39 ± 0.18
SD9:1	8.6	15.3	25.0	1.7	1.51 ± 0.01	Amorphous	34 ± 2	4.52 ± 0.16	3.75 ± 0.10
SD8:2	8.7	16.4	28.8	1.8	1.51 ± 0.02	Amorphous	38 ± 1	4.90 ± 0.06	2.89 ± 0.02
SD7:3	8.4	16.1	29.5	1.9	1.52 ± 0.02	Amorphous	37 ± 1	5.02 ± 0.17	2.69 ± 0.04

The data are the average values of four runs.

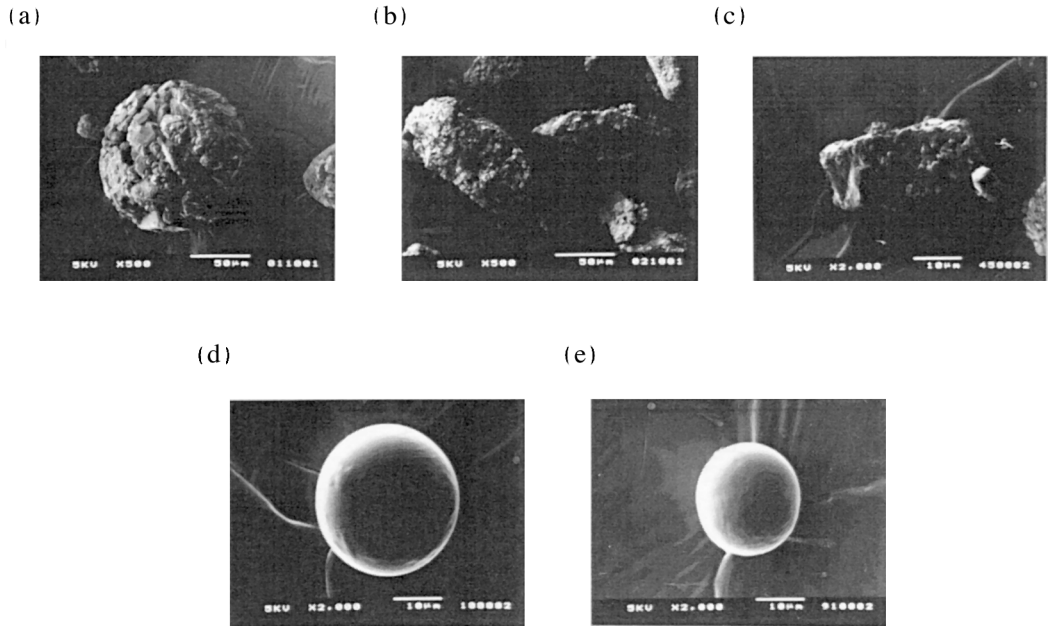

Fig. 1. Scanning electron microphotographs of SD particles and commercial lactose: (a) DCL11, (b) DCL21, (c) Pharm. 450M, (d) SD-L, (e) SD9:1.

crystallization of amorphous lactose in SD9:1 during heating was prevented probably because of the presence of sodium alginate. As this stabilizing effect of sodium alginate for amorphous lactose could not be observed in a physical mixture of amorphous lactose (SD-L) and sodium alginate particles at the same formulating ratio of 9:1 (PM9:1(SD-L)), it was assumed that sodium alginate molecularly dispersed in amorphous lactose of SD9:1 particles could stabilize the amorphous lactose by interacting with the lactose molecules through hydrogen bonding network formed intermolecularly.

3.2. Compactibility of SD particles

Compactibility of SD particles was evaluated by comparing the tensile strength of tablets prepared with the SD particles or commercial lactose (Fig. 3). The tensile strength of SD-L tablet was significantly higher than that of Pharm. 450M and a commercial lactose for direct tabletting (DCL21) compared at the same compression conditions. It has been reported that the fully amorphous lactose particles have good compacting properties owing to their plastically deforming properties (Vromans et al., 1986). The plastically deformation of particles increases the contact area between the particles under load, which is responsible for the increase in the tensile strength of the resultant tablets (Sebhatu et al., 1997).

The compactibility of SD composite particles containing sodium alginate was found to be com-

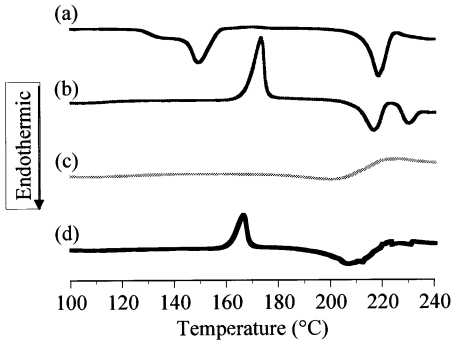

Fig. 2. Differential scanning calorimetry of original lactose and SD particles: (a) Pharm. 450M, (b) SD-L, (C) SD9:1, (d) PM9:1(SD-L).

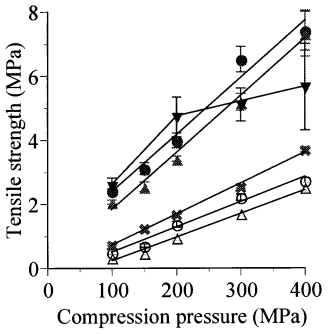

Fig. 3. Tensile strength of tablet with (●) SD-L, (▲) SD9:1, (○) Pharm. 450M, (△) PM9:1, (▼) PM9:1(SD-L), and (×) DCL21. The data are the average values of four runs.

parable to that of the spray dried amorphous lactose (SD-L) as shown in Fig. 3. Considering the lower tensile strength of sodium alginate tablet (1.14 ± 0.09 MPa at compression pressure of 200 MPa) and tabletted physical mixtures of Pharm. 450M and sodium alginate (PM9:1) shown in Fig. 3, the higher compactibility of amorphous lactose was effective in compacting the SD composite particles containing sodium alginate. The plastic deforming property of amorphous lactose particle might be retained even when the sodium alginate was formulated in the particle. The tensile strength of tabletted physical mixtures of amorphous lactose (SD-L) and sodium alginate at the ratio of 9:1 (PM9:1(SD-L)) was almost similar to that of SD-L or SD9:1 tablet at the compression pressure range of 100–200 MPa, but it became lower at compression pressures higher than 300 MPa. It was concluded that the molecular dispersion of sodium alginate in the particle is important in conferring a good compacting property to the lactose-sodium alginate mixture.

When poorly compressible drug particles, such as acetaminophen or ascorbic acid, were formulated to the tablet at the mixing ratio of 50%, the tensile strength of the matrix tablet prepared with SD9:1 was higher than that with commercial lactose for direct tabletting (DCL11 and DCL21) (Fig. 4). When the compression was increased up to 400 MPa, the tensile strength of the matrix tablet with SD composite particles increased to 5.71 ± 0.56 MPa for acetaminophen tablet and 5.88 ± 0.90 MPa for ascorbic acid tablet. On the other hand, physical mixture of the drug and commercial lactose (DCL11, DCL21) could not be compacted at a compression pressure higher than 300 MPa owing to occurrence of lamination. These results confirmed that the SD composite particle was suitable for the filler of the matrix tablet with regard to compactibility.

3.3. Controlled-releasing properties of SD particles as a matrix filler

The controlled-releasing properties of the SD composite particles in matrix tablets were evaluated with the matrix tablets containing acetaminophen or ascorbic acid. The drug releasing profiles of the matrix tablets of sodium alginate and the SD composite particle (SD9:1) are shown in Fig. 5. The drug dissolution from the matrix tablet of sodium alginate depends on the pH of the dissolution medium, because sodium alginate is water soluble but can be easily transformed into a water insoluble and swellable acid form at lower pH (Hodsdon et al., 1995). Thus, the matrix tablets show a sustained release of drug in an acidic solution by forming a gel-like structure. In the case of the matrix tablet containing ascorbic acid, similar dissolution properties were observed (data not shown). Hereafter, the acetaminophen was used as a model drug.

The drug release pattern of matrix tablet with the SD composite particles was similar to that of sodium alginate matrix tablet in No. 1 medium

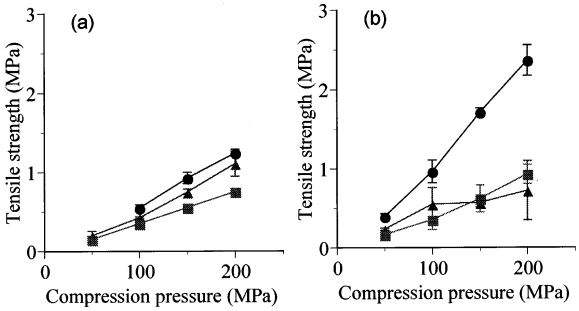

Fig. 4. Tensile strength of the matrix tablet prepared with the drug (50%) and filler (50%): (●) SD9:1, (▲) DCL11, and (■) DCL21. Model drug: (a) acetaminophen, (b) ascorbic acid. The data are the average values of four runs.

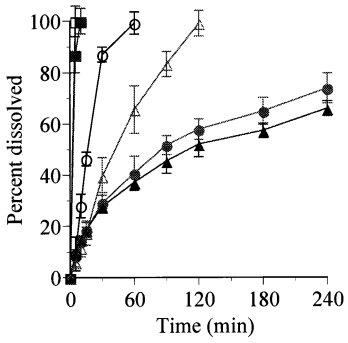

Fig. 5. Dissolution profiles of acetaminophen from the matrix tablet with (●, ○) SD9:1, (■, □) PM9:1 or (▲, △) sodium alginate. Closed symbols: in No. 1 medium; open symbols: in No. 2 medium. The data are the average values of three runs.

(pH 1.2), although the SD composite particles contain only 10 wt% of sodium alginate. Considering the sustained release mechanism of sodium alginate matrix tablets, the uniformly dispersed sodium alginate molecules in the SD composite particles could form the gel network through the tablet, which was responsible for the sustained release of the drug. As the Higuchi plot (Higuchi, 1963) of the drug release profiles showed a straight line, the drug diffusion through the gel matrix was confirmed to be the rate determining step in the drug release. When the sodium alginate content in the SD composite particles was increased, the resultant drug release was more retarded and became slower than that of the sodium

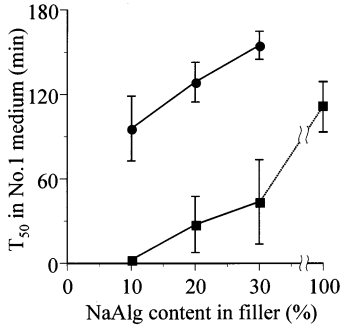

Fig. 6. Effects of a modification of spray-drying procedure and sodium alginate content on the drug release rate (T_{50}) in No. 1 medium. (●) Spray-dried particles, (■) physical mixtures. The data are the average values of three runs.

alginate matrix tablet (Fig. 6). This unusual result may be explained by the difference in the particle size of the fillers. The particle size of SD composite particles ($D_{50} = \approx 16$ μm) was much smaller than the sodium alginate particle ($D_{50} = \approx 150$ μm). The smaller particle size may be preferable to form an effective gel network in the tablet for sustained release of drug, because the homogeneous water penetration onto the surface of tablet is necessary to form an effective gel layer on the surface of tablet.

In No. 2 medium (pH 6.8), the drug was rapidly released from the matrix tablets because sodium alginate was freely soluble in the solution (Fig. 5). The drug release rate of the sodium alginate tablet was lower than that of matrix tablet of SD composite particle, probably because lactose formulated in the matrix tablets was much more rapidly dissolved than sodium alginate. In measuring the dissolution properties, the more rapid erosion on the surface of the tablet was observed for the matrix tablet of SD composite particles. Thus, the drug releasing property of the matrix tablet with the SD composite particle was characterized as slower in an acidic solution and more rapid in a neutral solution than a sodium alginate matrix tablet.

To consider the drug release characteristics of the SD composite particles in the matrix tablet, the drug release of matrix tablet of the physical mixture of lactose and sodium alginate particles was examined. When the physical mixture of lactose and sodium alginate particles (PM) was used for the filler of the matrix tablet at the same formulating ratio of 9:1, the resultant drug release rate from the matrix tablet became very rapid (Fig. 5). The increase in sodium alginate content in the tablet of the physical mixture did not lead to the dramatic sustained release of drug as in the case of SD composite particles (Fig. 6).

The drug release rate was found to depend on the particle size of sodium alginate formulated in the matrix tablets (Fig. 7). The tablet consisting of coarse particles of sodium alginate (>125 μm) showed a rapid disintegration of the tablet and a rapid dissolution of the drug, probably because the gel network could not be formed effectively. When the smaller size of sodium alginate particles

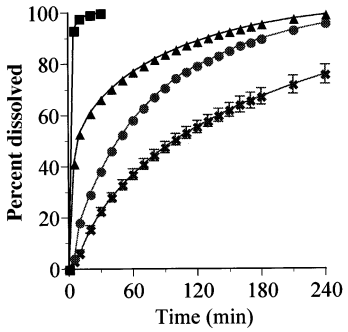

Fig. 7. Effects of particle size of sodium alginate in physical mixtures (PM9:1) on the drug release profiles in No. 1 medium. Particle size of sodium alginate: (●) <75 μm, (▲) 75–125 μm, (■) >125 μm, and ($\times$) SD9:1. Acetaminophen content in matrix tablet: 20%. The data are the average values of three runs.

were formulated into the matrix tablet, the resultant drug release was retarded more as shown in Fig. 7. However, the release rate was still faster than that of the SD composite particles. These results suggested that the even dispersal of sodium alginate particles in the matrix tablet was necessary for the sustained release of drug, and that SD composite particle, in which sodium alginate was molecularly dispersed, was the most suitable form for the filler of the sustained released matrix tablet.

4. Conclusions

The spherical composite particles consisting of amorphous lactose and sodium alginate were prepared by using a spray-drying method. The SD composite particles had good compactibility and excellent micrometric properties as a filler for direct tabletting. The compressed tablet with the composite particles and drug powders showed a more retarded release of drug in an acidic solution and rapid dissolution of drug in a neutral solution compared with that of the physically mixed lactose and sodium alginate particles at the same formulating ratio. These drug release controlling properties were found to be due to the dispersal state of sodium alginate in the particles. It was also found that the thermal stability of amorphous lactose in SD composite particles was dramatically enhanced by the presence of sodium alginate because of its interaction with the amorphous lactose molecules. These results suggested that inclusion of some widely used pharmaceutical materials, such as lactose, in a particle could confer more favorable characteristics as an excipient to the resultant composite particle.

References

Buckton, G., Darcy, P., 1995. The use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powders. Int. J. Pharm. 123, 265–271.

Elamin, A.A., Sebhatu, T., Ahlneck, C., 1995. The use of amorphous model substances to study mechanically activated materials in the solid state. Int. J. Pharm. 119, 25–36.

Fell, J.T., Newton, J.M., 1970. Determination of tablet strength by the diametral-compression tests. J. Pharm. Sci. 59, 688–691.

Garacia-Arieta, A., Torrrado-Santiago, D., Torrado, J.J., 1996. Comparative study of aqueous and organic enteric coatings of chlorpheniramine maleate tablets. Drug Dev. Ind. Pharm. 22, 579–585.

Gunsel, W.C., Lachman, L., 1963. Comparative evaluation of tablet formulations prepared from conventionally-processed and spray-dried lactose. J. Pharm. Sci. 52, 178–182.

Higuchi, T., 1963. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52, 1145–1149.

Hodsdon, A.C., Mitchell, J.R., Davies, M.C., Melia, C.D., 1995. Structure and behaviour in hydrophillic matrix sustained release dosage forms: 3. The influence of pH on the sustained-release performance and internal gel structure of sodium alginate matrices. J. Control. Release 33, 143–152.

Ishino, R., Yoshino, H., Hirakawa, Y., Noda, K., 1992. Design and preparation of pulsatile release tablet as a new oral drug delivery system. Chem. Pharm. Bull. 40, 3036–3041.

Lerk, C.F., 1993. Consolidation and compaction of lactose. Drug Dev. Ind. Pharm. 19, 2359–2398.

Sebhatu, T., Elamin, A.A., Ahlneck, C., 1994. Effect of sorption on tabletting characteristics of spray dried (15% amorphous) lactose. Pharm. Res. 11, 1233–1238.

Sebhatu, T., Ahlneck, C., Alderborn, G., 1997. The effect of moisture content on the compression and bond-formation properties of amorphous lactose particles. Int. J. Pharm. 146, 101–114.

Tahara, K., Yamamoto, K., Nishihata, T., 1995. Overall mechanism behind matrix sustained release (SR) tablets

prepared with hydroxypropyl methylcellulose 2910. J. Control. Release 35, 59–66.

Vromans, H., Boluhuis, G.K., Lerk, C.F., Kussendrager, K.D., Bosch, H., 1986. Studies on tableting properties of lactose. VI. Consolidation on tableting properties of spray dried lactose. Acta Pharm. Suec. 23, 231–240.

Vromans, H., Boluhuis, G.K., Lerk, C.F., Biggelaar, V.D., Bosch, H., 1987. Studies on tableting properties of lactose. VII. The effect of variations in primary particle size and percentage of amorphous lactose in spray dried lactose products. Int. J. Pharm. 35, 29–37.