Compaction Properties of Composite Particles Consisting of Lactose with Sodium Alginate Prepared by Spray-Drying

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Purpose. Composite particles of lactose with a small amount of sodium alginate were prepared by spray-drying (SD) in an effort to improve the compactibility of the polymer for direct compression. The compaction behavior of the SD composite particles with a range of polymer contents was investigated.

Methods. Composite particles were prepared by spray-drying an aqueous solution of lactose and sodium alginate at various formulating ratios. Improvement in the compactibility of the composite particles was evaluated by measuring the tablet tensile strength, porosity-applied pressure profiles, stress relaxation, elastic recovery of the compressed powder, and surface properties of the tablets by scanning electron microscopy.

Results. The tensile strength of compacts formed from the SD composite particles containing sodium alginate (≦10 wt%) was as high as that of spray-dried amorphous lactose. The improved compaction was attributed to the higher relaxation pressure and lower elastic recovery of the composite particles compared with α-lactose monohydrate. However, increasing the sodium alginate content of the SD composite particles above 10 wt% led to a marked reduction in the tensile strength of the resultant tablets. Scanning electron micrographs revealed that composite particles with a good compactibility fused totally in the tablets while composite particles containing 15% or more sodium alginate retained their shape, even after compression. The presence of sodium alginate layered uniformly on the surface of the particles and the increase in the glass transition temperature of the particles, possibly due to interpolation of sodium alginate are responsible for the reduction in the fusion property of the composite particles on compression.

Conclusions. Although increasing the sodium alginate content of SD composite particles led to an increase in their plastic deformation, fusion on compression was prevented by the presence of sodium alginate. The reduced compactibility of SD composite particles with an excess amount of sodium alginate was attributed to reduced cohesion and fusion of the particles during compression.

KEY WORDS: spray-drying; amorphous composite particle; tablet strength; compaction behavior; glass transition temperature; interparticulate bonding.

INTRODUCTION

The compacting properties of polymeric materials are important in pharmaceutical manufacturing processes, especially in the preparation of sustained release tablets with hydrophilic and gel forming polymers. Various polymeric materials, such as hydroxypropylmethylcellulose, have been investigated in terms of their drug controlled-release (1,2) and compaction properties (3,4). In general, polymeric materials are unsuitable for tabletting unless they are agglomerates because of their elasticity and poor flow and compression properties. Combination of an easily compressed materials with the polymer to give a composite particle is one way to improve the compression properties of the polymeric materials.

Lactose is a suitable candidate for combination with the polymeric materials, because it is widely used in tablet formulations due to its stable physical properties and the fact that it is not hygroscopic. Recently, some modified lactoses have been developed as multipurpose excipients by co-formulating several excipients in an agglomeration procedure. For instance, Cellactose®, which is prepared by co-processing 25 wt% powdered cellulose and 75 wt% α-lactose monohydrate, is an excellent excipient for direct compression compared with the simple mixture of lactose and cellulose (5). Ludipress®, which is composed of 93 wt% α-lactose monohydrate, 3.5 wt% povidone as a binder, and 3.5 wt% crospovidone as a disintegrant, exhibits good compactibility and confers a certain swelling ability on the resultant tablet (6).

We have produced a composite particle of lactose with polymeric matrix materials, such as sodium alginate, by spray-drying an aqueous solution of lactose and polymer at the ratio of 9:1 (7). In the Japanese Pharmacopoeia XIII No.1 medium (pH 1.2), the drug release pattern of a matrix tablet with the spray-dried (SD) composite particles was similar to that of a sodium alginate matrix tablet, although the SD composite particles contain only 10 wt% of sodium alginate. Increasing the sodium alginate content in SD composite particles led to a more sustained release of drug from the matrix tablets. It was also found that the SD composite particles containing 10 wt% sodium alginate had a good compactibility similar to the spray-dried fully amorphous lactose having plastic deforming property (8,9).

The aim of this paper was to investigate the compaction properties of SD composite particles in detail. The compaction behavior and bond-forming properties of the particles were measured using SD composite particles with various polymer contents.

MATERIALS AND METHODS

Preparation of SD Composite Particles

Mixtures of α-lactose monohydrate (Pharmatose 450M, DMV, Netherlands) and sodium alginate (NSPLL, Kibun Food Chemifa, Japan) were completely dissolved at various formulating ratios (sodium alginate ratio: 0 ~ 30 wt%) in 3000 mL of distilled water. The aqueous solution was spray-dried using a rotary atomizing spray dryer (Type L-12, Ohkawara Kakoki, Japan). The spray-drying conditions were as follows: inlet and outlet temperatures were 175°C and 100°C, respectively; rotational velocity of atomizer was 15,000 rpm; feeding rate of the solution was 50 mL/min.

The resultant spray-dried (SD) particles were spherical in form and contained amorphous lactose. The mean diameter of the SD particles was about 16 μm and the geometric standard deviation of the particle size was about 2.0 regardless of the sodium alginate content (7). The SD composite particles were

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kept in a glass vial and stored in a desiccator with below 30% relative humidity (RH) at room temperature before compaction, because 30% RH is below the critical RH where the crystallization of amorphous lactose can take place (10).

Tensile Strength of Tablet

Compaction of SD composite particles was carried out using an Instron-type hydraulic press (Autograph AG5000D, Simadzu Co., Japan). The weighed sample (200 mg) was compacted at a compression velocity of 10 mm/min under various compression pressures (150, 200, 300, 400 MPa) using a die with an 8.0 mm internal diameter and flat-faced punches. After storing the tablets in sealed vials for more than 24 hours, the compacts were diametrically compressed at a velocity of 0.5 mm/min using an Instron-type hydraulic press (Autograph AG5000D, Simadzu Co., Japan) to measure the tablet crushing strength, which is the force required to fracture the compacts. The tablet tensile strength (Ts) required to split the compressed tablets was calculated from the following equation (11):

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

where F(N) is the crushing force, and D(m) and T(m) are the diameter and thickness of the compact, respectively. The results are presented as the mean of four tablets.

Heckel Plots of SD Composite Particles

The compaction behavior of SD composite particles was evaluated by Heckel analysis (12,13). Compaction was performed as described above, expect that the punches and a die were externally lubricated with a very small amount of magnesium stearate before each compaction. During each compaction of powders, the stroke distance and the compression pressure at the upper punch were recorded in a personal computer once a second. The apparent volume of the compact was determined from the stroke distance to calculate the porosity (ε) of the compact during the compression. Data were analyzed by the following Heckel equation:

$$\ln \frac{1}{\varepsilon} = kP + \ln \frac{1}{\varepsilon_0} \quad (2)$$

where ε and ε_0 are the porosity at applied pressures P and zero, respectively.

The slope k was determined by regression analysis of the linear portion of Heckel profiles (about 75 and 300 MPa) with a correlation coefficient of 0.99. The reciprocal of the slope k was referred to as the mean yield pressure. This reflects the plastic flow of the particles.

Stress Relaxation and Elastic Recovery

Stress relaxation (14) was also measured by an Instron-type hydraulic press (Autograph AG5000D, Simadzu Co., Japan). Powder (200 mg) was directly compacted at a compression velocity of 10 mm/min with flat-faced punches and a die lubricated with a small amount of magnesium stearate, until the required compression pressure of 200 MPa was reached. Then, the upper punch was kept stationary and the decay of the upper punch force was measured during a 900 second holding interval to determine the stress relaxation. In order to compensate for any additional relaxation caused by the tabletting machine itself, a blank relaxation test was carried out under the same compression conditions and this value was subtracted from the apparent values for the samples.

The elastic recovery was measured by a multiple recompression technique with the Instron-type hydraulic press. The punch and die set was the same as that used for the stress relaxation test. The weighed sample (200 mg) was repeatedly compressed (20 times) at a compression velocity of 10 mm/min without ejecting the resultant tablet from the die. The work done during every compression was calculated by integration of each force-displacement curve. When the work done became constant (We), this value was taken as that for elastic deformation during compression (15), and was an indicator of the elasticity of the powder during tabletting. The elastic recovery was calculated using the following equation:

$$\text{Elastic Recovery}(\%) = \frac{\text{elastic energy}}{\text{input energy}} \times 100 \quad (3)$$

where the input energy is the gross compression energy, i.e., the work done during the first compression (W_1).

Imaging of Tablet Surface

Micrographs of the upper surface of tablets with SD composite particles were taken using a scanning electron microscope (JSM-T330, Nihon Denshi, Japan) at an accelerating voltage of 15 kV to observe the change in shape of the SD composite particles after tabletting. Tablets prepared with 100 mg of particles at a compression pressure of 400 MPa were attached directly on the stage of the scanning electron microscope using double-sided adhesive tape. They were then coated with a thin layer of gold using an ion sputter (JCPD-3, Nihon Denshi, Japan).

Glass Transition Temperature

A differential scanning calorimeter (DSC6200, Seiko Instrument Inc., Japan) was used to identify the glass transition temperature of amorphous lactose in SD composite particles. Indium and zinc were used as calibrants, also α-alumina was used as a reference. Each sample (10 mg) was placed in the sealed aluminum sample pans and scanned at heating rate of 20°C/min between 5 to 175°C in the calorimeter.

Sodium Alginate Distribution in SD Composite Particles

The distribution of sodium alginate in the SD composite particles was evaluated by measuring quantitatively the distribution of sodium on the surface of tablets with an electric probe microanalyzer (JMA-8800, Nihon Denshi, Japan). To determine the elemental sodium on the surface of the SD composite particles, acetic thallium with the inherent wavelength of sodium (ca. 12 Å) was used. The conditions for the electric probe microanalysis were as follows: Accelerating voltage was 15 kV; Magnification of photographs was 5000× and 1000× for qualitative and surface analysis, respectively; Absorption current of samples were 5×10^{-5} A.

RESULTS AND DISCUSSION

Compactibility of SD Composite Particles

The tensile strength of tablets with amorphous lactose particles was significantly higher than that of commercial lactose as far as direct tabletting was concerned (DCL21) (1.26 ± 0.01, 1.70 ± 0.01, 2.55 ± 0.06 and 3.70 ± 0.08 MPa at compression pressure of 150, 200, 300 and 400 MPa, respectively), as described earlier (7). The compactibility of SD composite particles of lactose with sodium alginate was as good as that of amorphous lactose particles when the sodium alginate content was less than 10 wt% (Fig. 1). However, the tensile strength of tablets with SD composite particles was markedly lower at a sodium alginate content higher than 15 wt% in SD composite particles. The SD composite particles containing 30 wt% of sodium alginate could not be compacted at a compression pressure of 200 MPa. These results suggested that the amount of sodium alginate in the formulation of SD composite particles is limited by the compactibility, although sodium alginate is needed in the formulation to confer sustained release behavior on the resultant tablets of the SD composite particles.

To clarify the change in the tabletting properties of the SD composite particles, the compaction behavior was analyzed by measuring the relationship between the compression pressure and porosity of the powder compact (Heckel plot). The Heckel plots obtained are illustrated in Fig. 2. The correlation coefficients (r^2) describing the linearity of the Heckel plots and the mean yield pressure (P_y) from these Heckel profiles are listed in Table 1. Duberg and Nyström have used the correlation coefficient for the Heckel plot as an indication of particle fragmentation (16). A correlation coefficient of the amorphous lactose particles (SD-L) higher than that of α-lactose monohydrate suggested less densification of the powder bed of the amorphous lactose caused by particle fragmentation. Considering the much higher correlation coefficient of the SD composite particles containing sodium alginate compared with that of SD-L, the fragmentation of the particles was reduced more by incorporating sodium alginate into the composite particles. The lower mean yield pressure of SD composite particles indicated a higher degree of particle deformation of SD composite particles than that of α-lactose monohydrate. The increase in plastic deformation of particles leads to an increase in the tensile strength of the resultant compact, because plastic deformation of particles increases the contact area between the particles under load (17). Based on the Heckel analysis, the SD composite particles tended to be consolidated by particle deformation rather than particle fragmentation. To confirm the plastic deformation of SD composite particles containing sodium alginate, we measured the stress relaxation of compacted powders (Table 1), which is one of the most direct methods for measuring the plastic deformation of particles (14). As the relaxation pressure increased with the increasing amount of sodium alginate in the SD composite particles, this confirmed that the plastic deformation of the SD composite particles increased on incorporating sodium alginate into the particles. However, a higher plastic deformation was observed for SD8:2 and SD7:3 which exhibited poor compression properties. In other words, the higher plastic deformation of SD composite particles was ineffective in compacting the composite particles containing more than 10 wt% sodium alginate. The values for the elastic recovery of SD composite particles are also listed in Table 1. Although the elastic recovery of SD composite particles was lower than that of α-lactose monohydrate, the values for the SD composite particles remained almost onchanged, regardless of the sodium alginate content.

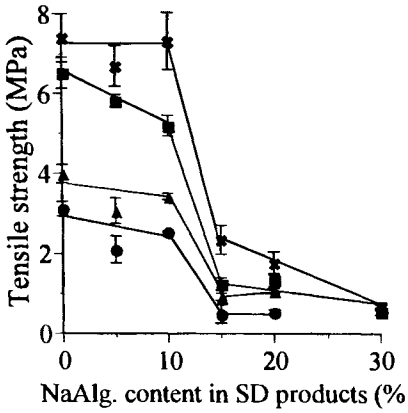


Fig. 1. Tensile strength of tablets composed of SD composite particles at different compression pressures: (●) 150 MPa, (▲) 200 MPa, (■) 300 MPa, and (×) 400 MPa. Data are expressed as the mean ± S.D. of four runs.

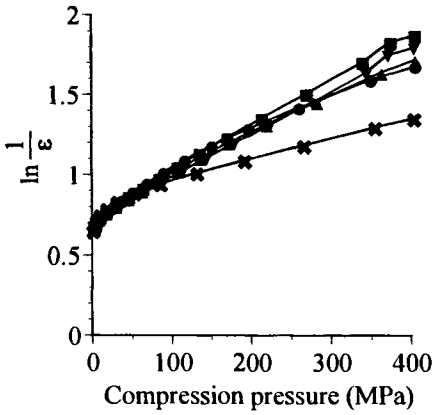


Fig. 2. Compression behavior (obtained from the Heckel equation) of SD composite particles: (●) SD-L, (▲) SD9:1, (■) SD8:2, (▼) SD7:3, and (×) original lactose (α-lactose monohydrate).

Microstructure in Tablet with SD Composite Particles

To clarify the effect of the sodium alginate content in SD composite particles on the tablet tensile strength, the microstructure of tablets prepared with SD composite particles was investigated by obtaining scanning electron micrographs. The micrographs of the upper surface of tablets with SD composite particles are shown in Fig. 3. When there was 10 wt% or less sodium alginate in SD composite particle, a smooth surface of tablet was observed, suggesting fusion and cohesion of the SD composite particles during compression. On the other hand, the particle shape was clearly observed on the surface of tablets of composite particles with 15 wt% or more sodium alginate, although the particles were closely packed and slightly deformed. These photographic observations fully explain the difference in tensile strength of these tablets. The higher tensile strength of SD composite particles containing less than 10 wt%

Table 1. Effect of Sodium Alginate Content in SD Composite Particles on the Compression Behavior of the Tablets.

Sample	Heckel analysis		Relaxation pressure (MPa)	Elastic recovery (%)
	r^2	Py		
α-lactose monohydrate	0.958 ± 0.007	812.9 ± 26.3	27.0 ± 0.5	30.5 ± 2.1
SD-L	0.983 ± 0.004	496.3 ± 19.0	32.9 ± 0.2	23.2 ± 0.5
SD9:1	0.993 ± 0.001	426.5 ± 37.5	41.3 ± 0.3	23.7 ± 0.3
SD8:2	0.997 ± 0.001	355.0 ± 34.0	50.7 ± 0.2	23.1 ± 1.3
SD7:3	0.999 ± 0.000	372.1 ± 10.9	53.6 ± 0.2	24.3 ± 0.2

Note: Data are expressed as the mean ± S.D. of three runs.

of sodium alginate was concluded to be due to fusion and cohesion of the particles with a strong bonding force. Since no fusion and cohesion of particles was observed for SD8:2 and SD7:3, which had higher plastic deformation characteristics, this suggested that other properties besides plastic deformation control the fusion and cohesion of the particles.

Sebhatu *et al.* (18,19) have pointed out that the good compression of particles could be attributed to their fusing as well as plastic deformation during compression when they examined the effect of moisture content of amorphous lactose on its compaction. They found that the higher moisture content of the lactose particles confers good compression behavior c the particles with a reduction in the glass transition temperatur It was considered that a lower glass transition temperature mig be preferable for particles to form a continuous phase at tl particle-particle interface during compression, partly becau the increased local temperature around the interface promot the fusion of particles with a glassy-to-rubbery transition. A alternative explanation is that the particles with a lower gla transition temperature can easily form a continuous phase, eve in the glassy state. It was found that the incorporation of sodiu alginate into the SD composite particles also caused a chan

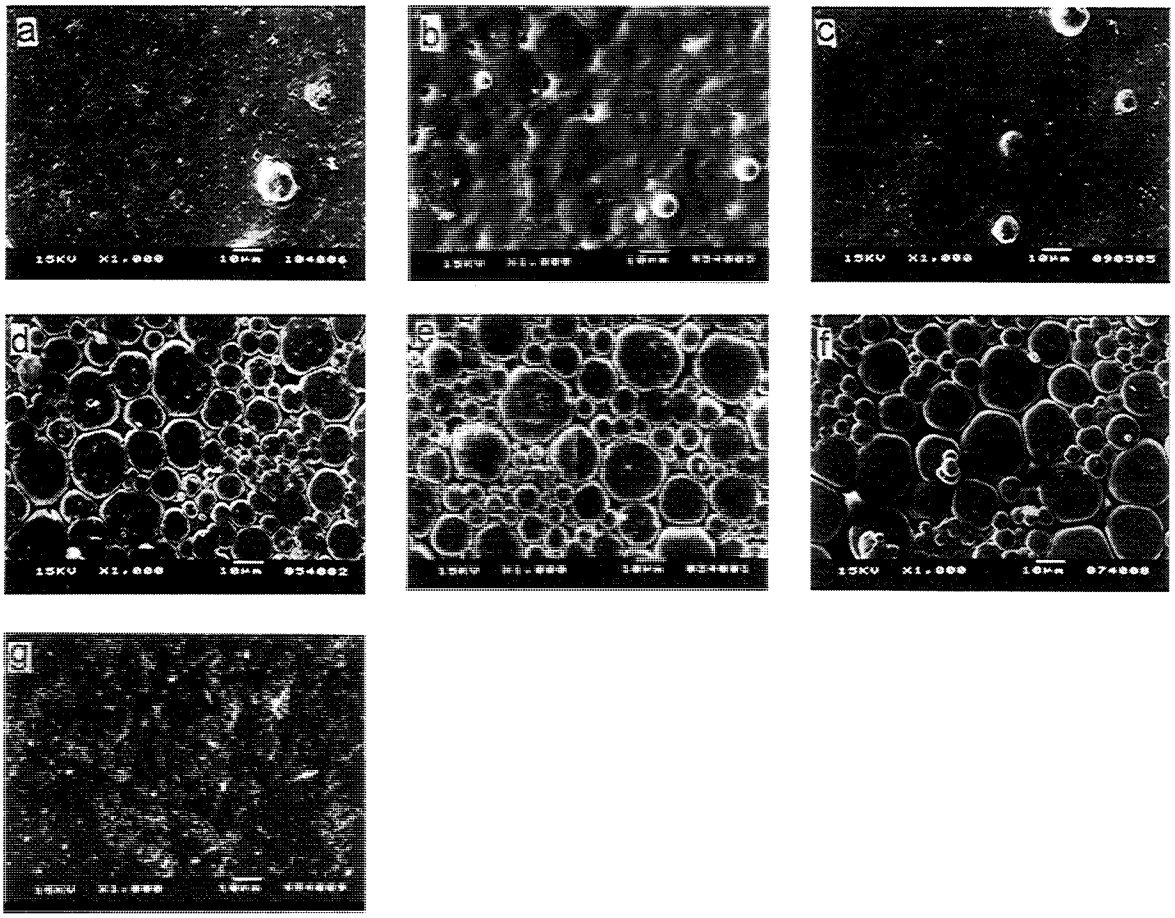
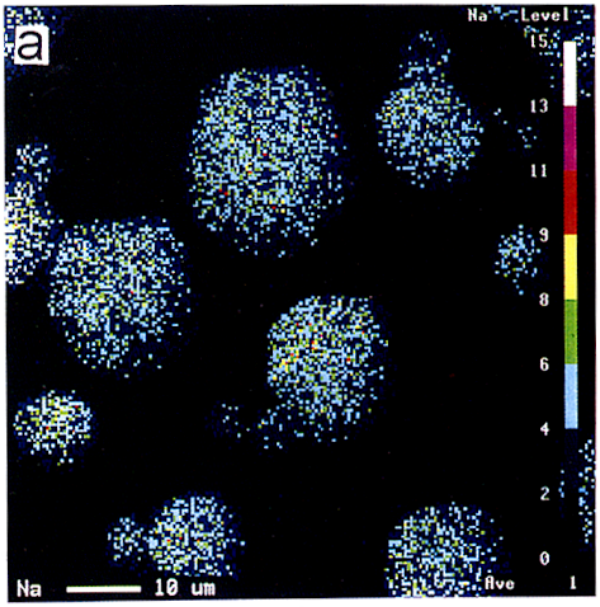


Fig. 3. Scanning electron micrographs of the upper surface of tablets: (a) SD-L, (b) SD95:5, (c) SD9:1, (d) SD85:15, (e) SD8:2, (f) SD7:3, (g) original lactose (α-lactose monohydrate).

in the glass transition temperature of amorphous lactose in the particles, as shown in Fig. 4. The increased glass transition temperature of the SD composite particles with the higher content of sodium alginate corresponded well to the reduced fusion during compression.

The distribution of sodium alginate in the SD composite particles may also be an important factor in controlling the compression of particles, i.e., the formation of a continuous phase of lactose between the particles. Fig. 5 presents the distribution of sodium alginate on the surface of the SD composite particles observed using an electric probe microanalyzer. The picture shows that the distribution of sodium alginate on the surface of particles was homogeneous and the sodium intensity (concentration) increased with an increasing amount of sodium alginate in the SD formulation. It was suggested that a continuous phase of amorphous lactose formed on the surface of the SD composite particles might be converted into a discontinuous one by increasing the amount of sodium alginate in the formulation. There might be a threshold for the phase conversion based on the percolation theory (20). The threshold value could be presumed to be around 10%, supposing that sodium alginate was uniformly dispersed in the amorphous lactose-sodium system. Therefore, the SD composite particles containing more than 10% sodium alginate led to a markedly lower tensile strength for the resultant tablet.

To confirm the role of amorphous lactose in forming a tight tablet structure, a model experiment was carried out using a sodium alginate powder (mean diameter: ca. 150 μm) and amorphous lactose (mean diameter: ca. 16 μm) or α-lactose monohydrate (mean diameter: ca. 25 μm) as shown in Fig. 6. The tensile strength of tablets prepared with a physical mixture of amorphous lactose and sodium alginate depends on the sodium alginate content as expected. On the other hand, the tensile strength of tablets with crystalline α-lactose monohydrate was extremely low, regardless of the lactose content. These results suggest that amorphous lactose plays an important role in determining the compaction properties of the binary system of lactose-sodium alginate. In tabletting the amorphous lactose-sodium alginate system, the amorphous lactose particles on the surface of sodium alginate particle may fuse together, resulting in tight bonding between the particles. As shown in Fig.6, the tensile strength of tablets with the physical mixture started to decrease at the formulating ratio of 50:50. Applying the ordered mixing theory reported by Hersey (21) to the amorphous lactose-sodium alginate binary system, the theoretical mixing ratio of the binary system for forming the ordered mixing structure was calculated to be 70:30 (sodium alginate: amorphous lactose) with the particle size and true density of powders. This calculation suggests that a continuous amorphous phase may be formed throughout the tablet when the mixing ratio of amorphous lactose is more than 30%. The difference between the observed critical values 50:50 in measuring the tensile strength of resultant tablets and the theoretical ordered mixing ratio calculated



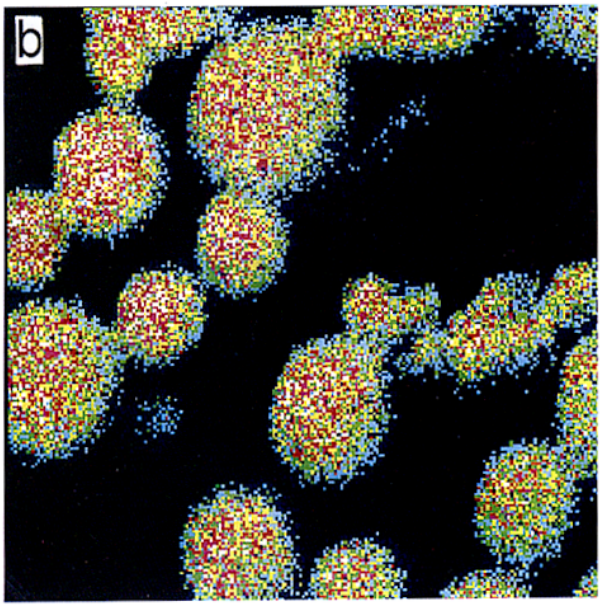


Fig. 5. Distribution of sodium alginate on the surface of SD composite particle: (a) SD 9:1, (b) SD 7:3.

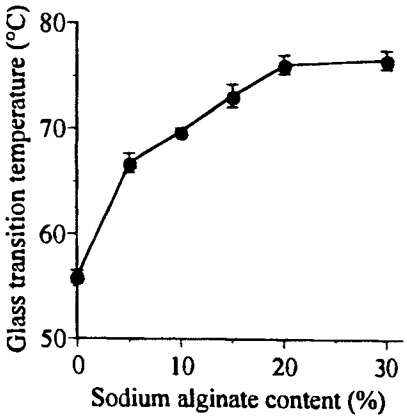


Fig. 4. Effect of sodium alginate content on the glass transition temperature of amorphous lactose in SD composite particles. Data are expressed as the mean ± S.D. of four runs.

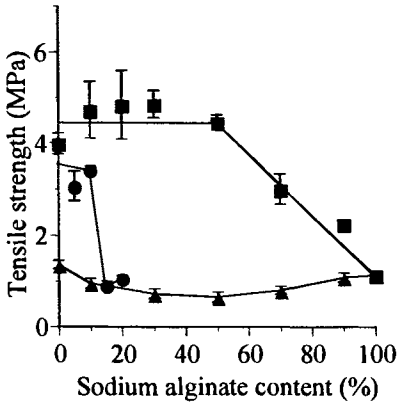


Fig. 6. Comparison of the tensile strength of SD composite particles with that of physical mixtures and the effect of amorphous lactose in filler on the tensile strength of tablets prepared at 200 MPa: (●) SD composite particles, (■) Physical mixtures of sodium alginate powder and 100% amorphous lactose (SD-L), and (▲) Physical mixtures of sodium alginate powder and original lactose (α-lactose monohydrate).

can be explained by the irregular shape of the particles or incomplete mixing.

CONCLUSIONS

The compaction properties of the composite particles with sodium alginate were found to be dependent on the sodium alginate content of the particles. Although the Heckel analysis, stress relaxation and elastic recovery tests on commercial and spray-dried lactose and SD composite particles suggested a higher compactibility of the SD composite particles, their dependence on the sodium alginate content could not be explained. Surface observation of the resultant tablet with scanning electron micrography clearly showed the different compression properties of the SD composite particles with different contents of sodium alginate. Fusion of particles in the resultant tablets was observed when the sodium alginate content in the particles was less than 10 wt%, and this might be responsible for the higher tensile strength of these tablets. As the glass transition temperature of the SD composite particles increases with an increase in the sodium alginate content of the particles, there seems to be a close relationship between the glass transition temperature and the fusion properties of the SD composite particles. The presence of sodium alginate molecule on the surface of the SD composite particles may be also responsible for the low fusion of SD composite particles having a high sodium alginate content.

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