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Note

Influence of load on particle size distribution of lactose–crystalline cellulose mixed powder

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Abstract

Effects of loads applied to a powdery layer of a mixture of lactose and crystalline cellulose (granules) on the microparticle formation were evaluated. In a 1:1 mixture, the number of particles size, 20 μm or smaller in diameter, was reduced under loading compared with the standard value. It tended to increase with increasing ratio of lactose. In samples with a particle size of 350 μm or less, the shear friction coefficient increased with increase in the load, reached a peak at a mixing ratio of 50%, and decreased with increase in the mixing ratio. These changes were similar to those of the number of particles 20 μm or smaller. These results suggest that particle formation and aggregation under loads are dependent on the mixing rate and that there is a range of mixing rates in which no changes in the particle size distribution are observed.

Keywords: Load; Crystalline cellulose; Lactose; Internal friction coefficient; Particle size distribution

1. Introduction

In manufacturing of solid pharmaceutical preparations, mixing of powders requires careful quality control of such parameters as content homogeneity, distribution of additives, and compression. Preparations are composed of many constituents different in physicochemical properties. Particle sizes of constituents are related to properties of the particle mixture such as the flowability, compressibility, porosity, and bulk density. Moreover, as the particle size affects the plasticity of the mixture and tablet hardness, evaluation of effects of constituents mixed under loading with lactose powder on the particle size distribution and powder properties of lactose is considered to be useful for the clarification of changes in the properties of the final powdery product obtained by mixing of constituents in large quantities (Kanaba et al., 1988; Tsunakawa, 1990, 1993; Yamamoto and Shioji, 1990; Eitoku et al., 1994; Juppo et al., 1995; Mackaplow et al., 1997; Matsumoto et al., 1997; Millan et al., 1998; Tatsumi et al., 2000). We have previously clarified changes in the particle size distribution of lactose powder during flowing under loads and the presence of a critical particle size at which properties of the powder layer show significant changes (Tsunakawa and Aoki, 1974).

This study was carried out to clarify effects of crystalline cellulose particles mixed with lactose powder on the particle size distribution and powder characteristics of microparticles in lactose–crystalline cellulose mixtures and to evaluate the effects of loading on such mixtures.

Materials. JP lactose (Lac) (DMV Japan, Co. Ltd.; stored in an air-tight container at a room temperature of 22 °C and a relative humidity of 50%) was used. Celphere® with a particle size range of 500–700 μm (CP-507, Asahi Kasei Co.) and Celphere® with a particle size range of 300–500 μm (CP-305, Asahi Kasei Co.) were used as crystalline cellulose (CC). The materials were graded in advance by sieving them with an ultrasonic sieve (SW-20, Seishin Enterprise Co. Ltd.) for 10 min. JP corn starch (Nihon Shokuhin Kako Co. Ltd., mean particle

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size about 20 μm) was used as a standard for focusing of light microscopes.

Mixing of powders. After obtaining a standard state by mixing Lac and CC for 10 min without loading, mixing was continues with a load of 10, 20, or 40 g/cm^2 in a powder stress stirrer. About 750 g the materials were placed in a powder stress stirrer (Murata Kogyo Co. Ltd.) and stirred for 60 min by applying a load of 10–40 g/cm^2 to the powder layer. The stirrer was rotated at 60 rpm. Samples for measurement of the particle size were collected by stopping the stirrer at a fixed interval and thrusting a glass tube of 5 mm diameter at the same point on the margin of the powder layer. The samples, each weighing about 2 g, were stored under the same conditions as the constituent materials. Lactose and crystalline cellulose (granules) were mixed at 1:2 (Lac33), 1:1 (Lac50), or 2:1 (Lac67).

Measurement of the particle size and particle size distribution. Specimens were prepared by sprinkling about 50 mg of each sample through a sieve from a height of 20 cm over a glass slide 7 cm × 7 cm. A 350-μm sieve was used for CP-507, and a 300-μm sieve was used for CP-305. The particle size was measured using a light microscope and image-analysis software (Win Roof®, Mitsuya Co. Ltd.). Three specimens were prepared with each sample, each specimen was photographed at 5 sites (15 photographs in total), and about 2000 particles were measured in each sample. The specimens were prepared and particle size distribution was measured in a climatic chamber at a room temperature of 22 °C and a relative humidity of 50%.

The magnification of the light microscope was 40×, starch with a particle size of about 20 μm was used as a standard material, and the measurement was performed under the same image processing conditions with all samples.

Powder property test. After mixed samples stirred under various loading conditions were graded, the angle of repose, loose bulk density, tight bulk density, and angle of spatula were determined with a general-purpose powder property tester (Powder Tester®, Hosokawa Micron), the compressibility and cohesiveness were calculated from these values, and the flowability of the powder was evaluated according to the flowability index of the CARR. The measurements were carried out at a room temperature of 21–23 °C and a relative humidity of 65 ± 3%.

Measurement of the powder flowability by the direct single-plane shear test. The direct single-plane shear test was carried out with samples stirred under various loading conditions, and the internal friction coefficient and shear adhesiveness were measured in the powder layer. A powder shear tester (Tsutui Rikagaku Kikai Co.) was used, and each powder sample was packed in the cell with compression at about 140 g/cm^2. Normal stress was measured in a range of about 30–70 g/cm^2. The measurements were performed three times, and an effective yield locus was determined from the relationship between normal stress and shear stress.

Effects of loads on Lac microparticles alone. Effects of particles 74 μm or smaller in a powder of Lac alone were studied by stirring LacA, from which particles 74 μm or smaller were eliminated, and LacB, which contained particles 74 μm or smaller at about 5%, under loads of 10 and 30 g/cm^2 for 60 min. Fig. 1 shows serial changes in the number of particles 20 μm or smaller (20p) during stirring.

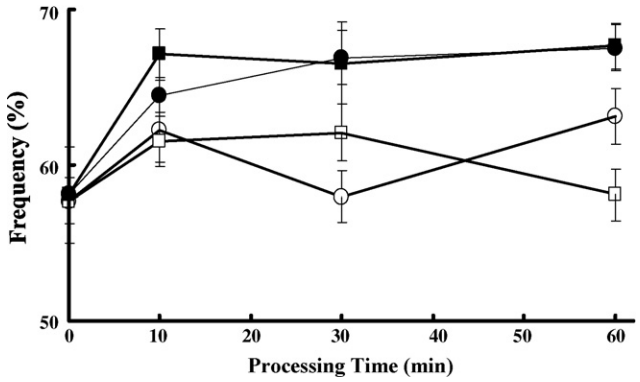

Fig. 1. Relationship between proportion of 20 μm particles (%) and processing time (min) during loading: (◯) 10 g/cm^2 LacA; (●) 10 g/cm^2 LacB; (□) 30 g/cm^2 LacA; (■) 30 g/cm^2 LacB.

The number of 20p increased serially in LacA under a load of 10 g/cm^2. In LacB, it increased during the first 10 min but became stable thereafter.

Under a load of 30 g/cm^2, the number of 20p increased during the first 10 min but decreased serially thereafter in LacA. In LacB, the changes in the number of 20p were similar to those under loading at 10 g/cm^2. Thus, changes in the number of 20p were greater when particles 74 μm or smaller were eliminated compared with those when they were not eliminated.

Effects of stirring under a load on the particle size distribution of Cel. Table 1 shows changes in the number of particles 350 μm or smaller generated during stirring of CP-507 on a 350-μm sieve at 40 g/cm^2 for 60 min. The number of particles 350 μm or smaller increased serially, but it was markedly smaller than the number of Lac particles 350 μm or smaller generated during stirring under the same load (about 2000). Therefore, the effect of load on the generation of microparticles of CP-507 was judged to be small.

Effect of crystalline cellulose particles (CP-507) on the particle size distribution of lactose. Fig. 2(A)–(C) shows changes in the number of 20p relative to the standard value when CP-507 was mixed with Lac at various ratios. The standard value was the number of 20p after a Lac-Cell mixture was treated for 10 min in a powder stress stirrer.

When the load was 10 g/cm^2, the number of 20p increased relative to the standard value in Lac67, increased continuously but was always smaller than the standard value in Lac50, and decreased continuously but was always greater than the standard value in Lac33. Under a load of 20 g/cm^2, it was greater than the

Table 1
Mean particle size of spherical crystalline cellulose in number frequency distribution on 40 g/cm^2

	Time (min)			
	0	10	30	60
Samples (number)	58	94	92	181
S.D.	10.0	12.2	14.2	12.3
Mean particle size	14.9	13.5	11.6	12.0

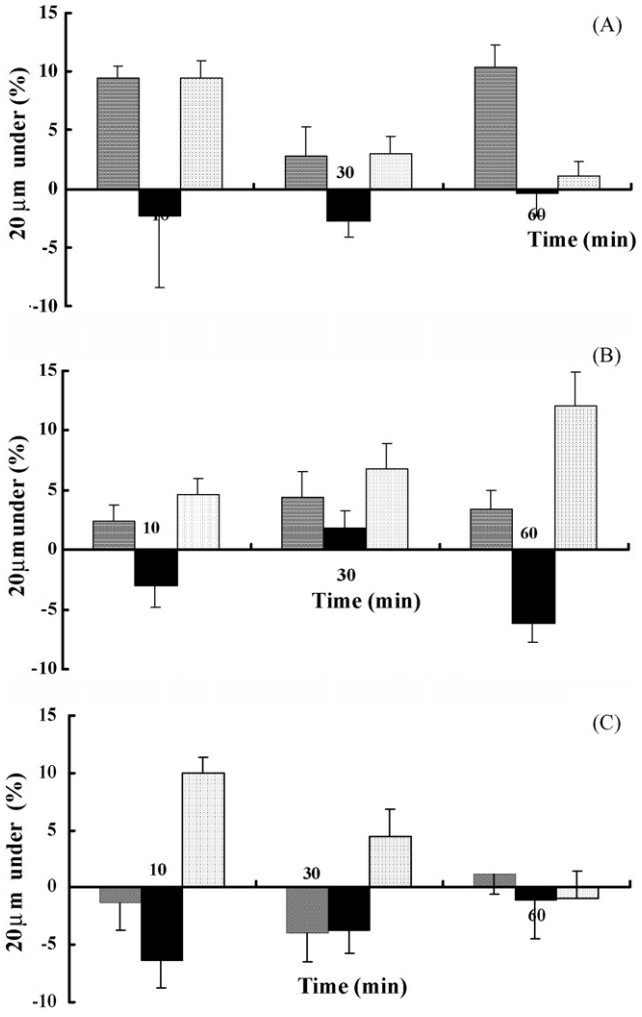

Fig. 2. (A) Relationship between proportion of under 20 μm particles (%) and processing time (min) during loading at 10 g/cm^2. Lactose content (%, w/w): (▨) 67%; (■) 50%; (⁙) 33%. (B) Relationship between proportion of under 20 μm particles (%) and processing time (min) during loading at 20 g/cm^2. Lactose content (%, w/w): (▨) 67%; (■) 50%; (⁙) 33%. (C) Relationship between proportion of under 20 μm particles (%) and processing time (min) during loading at 40 g/cm^2. Lactose content (%, w/w): (▨) 67%; (■) 50%; (⁙) 33%.

standard value and showed small changes in Lac67, increased above the standard value after 30 min but decreased below the standard value after 60 min in Lac50, and increased continuously and was always greater than the standard value in Lac33. Under a load of 40 g/cm^2, it increased continuously but was smaller than the standard value in Lac67 and Lac50, and it decreased continuously but remained greater than the standard value until after 30 min and decreased below the standard value after 60 min in Lac33. Under a load of 10–40 g/cm^2, the number of 20p was smaller in Lac50 than in Lac67 or Lac33.

The number of particles 20 μm in diameter did not change after mixing Cel and Lac without loading. With loading, it changed with the mixing ratio and was smallest when the mixing ratio was 50%. The shear friction coefficient also changed with the mixing ratio and showed a maximum value at a mixing ratio of 50% under loading at 20 and 40 g/cm^2. The results were similar with CP-305 with a different particle size. Also, the effect of loading on the generation of Lac microparticles increased with increases in the particle size of the material mixed with Lac.

Effects on the particle size of Cel on changes in the particle size distribution of Cel–Lac mixtures. Fig. 3(A) and (B) shows changes in the number of 20p relative to the initial number after mixing of CP-305 and CP-507 with Lac under various loads at various mixing ratios for 60 min. In CP-507 (1), the number of 20p was large in Lac33, decreased to a minimum level in Lac50, and increased in Lac67 under loads of 10 and 20 g/cm^2. Under loading at 40 g/cm^2, the changes in the number of 20p with the mixing ratio were less notable. In CP-305 (2), the number of 20p changed with the load and was large in Lac 33, smallest in Lac50, and increased again in Lac67.

Direct single-plane shear test of Cel–Lac mixtures. Fig. 4 shows changes in the internal friction coefficient on the shear test of particles 350 μm or smaller (primarily Lac) after mixing CP-507 and Lac under various loads at various mixing ratios for 60 min. The internal friction coefficient gently increased at 10 g/cm^2, increased with the mixing ratio. But the internal friction coefficient at 20 and 40 g/cm^2 decreased with increase in the mixing ratio after reaching a peak at a mixing ratio of 50%.

In particles 350 μm or greater, no marked changes in the internal friction coefficient were observed regardless of the mixing ratio or the load.

Flowability testing. Table 2 shows the flowability of powders with a particle size of 350 μm as determined by a powder tester. No changes in the angle of repose, angle of spatula, bulk

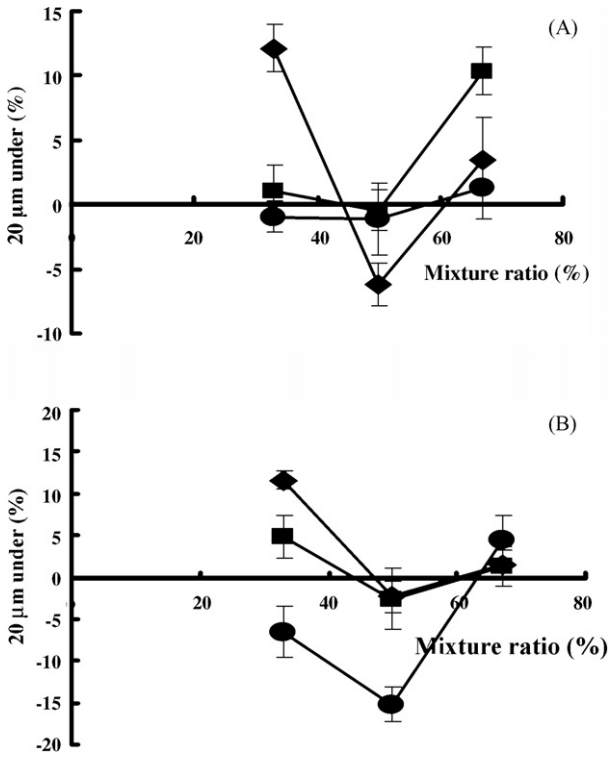

Fig. 3. (A) Relationship between proportion of under 20 μm particles (%) and lactose mixture (%) with CP-507: (■) 10 g/cm^2; (♦) 20 g/cm^2; (●) 40 g/cm^2. (B) Relationship between proportion of under 20 μm particles (%) and lactose mixture (%) with CP-305: (■) 10 g/cm^2; (♦) 20 g/cm^2; (●) 40 g/cm^2.

Table 2
Microchemical properties of lactose in lactose–cellulose mixture at different mixing ratio and load

Load (g/cm^2)	Angle of repose (°)	Compressibility (%)	Cohesiveness (%)	Angle of supatula (°)	Flowability index of CARR
Lac 75					
10	44.4	22.4	27.9	65.5	56.0
20	45.1	22.0	30.9	63.0	52.5
40	43.9	21.7	28.3	60.4	59.0
Lac 50					
10	47.0	22.4	29.6	63.2	50.0
20	46.6	24.6	29.7	64.7	50.0
40	46.6	25.2	31.0	63.5	48.0
Lac 25					
10	44.8	23.2	30.9	62.9	52.5
20	46.2	25.0	30.4	64.6	51.5
40	46.0	23.1	30.6	65.4	55.0

density, compressibility, or cohesiveness were observed after mixing with loading, and the flowability index of the CARR was not good in any mixture.

Changes were observed in the particle size distribution and shear friction coefficient of microparticles in mixed powders as well as in powders of a single material. However, no effect of mixing with loading was observed in powder properties on the macrolevel such as the angle of repose, compressibility, cohesiveness, or angle of spatula, which are important pharmaceutical parameters.

The number of particles 20 μm or smaller in mixtures of lactose and crystalline cellulose particles changed in a complex manner during stirring with loading with the mixing ratio due to aggregation and pulverization of particles. It decreased during mixing compared with the initial value in a 1:1 mixture. When microcrystalline cellulose and lactose were mixed, the mixing properties of the two-component mixture based on the particle size and surface area were reported to be the best when the two materials were mixed at 1:1 (Vachon and Chulia, 1992). When lactose and crystalline cellulose (granules) were mixed at 1:2 under a high load, particles 20 μm or smaller in mixtures tended to decrease largely due to the strong effect of large particles of crystalline cellulose. In highly breakable crystalline materials, crystalline particles are less likely to be deformed as the crystalline hardness is higher because of the presence of larger spaces in the powder layer. In mixing of large particles under high pressure, energy is considered to be consumed for pulverization of particles and is not considered to increase the strength of the molded bodies (Tatsumi et al., 2000). The internal friction angle of a powder layer is affected by the particle material and materials adsorbed on the surface of the particles, as well as by the particle shape and size. In a 1:2 mixture of crystalline cellulose (granules) and lactose, the properties of lactose powder were observed more clearly because adhesion and aggregation between crystalline cellulose and lactose particles were saturated due to the high lactose content.

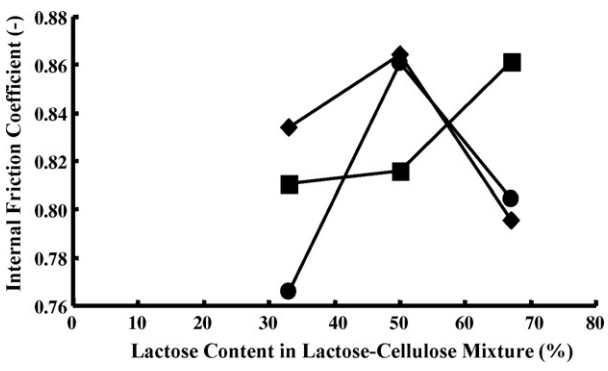

Fig. 4. Relationship between internal friction coefficient and content of lactose in lactose–cellulose mixtures (%): (■) 10 g/cm^2; (♦) 20 g/cm^2; (●) 40 g/cm^2.

The shear strength as determined by the shear test is greatly affected by the packing structure such as the distribution of space in the powder layer, distribution of contact points, and state of contact. As the space decreases with rearrangement, pulverization, and plastic deformation of particles, contact points of particles increase (Juppo et al., 1995), particles are more strongly bound by the surrounding particles, and the internal friction coefficient increases (Danish and Parrott, 1971; Tsunakawa and Aoki, 1974; Aoki et al., 1982; Vachon and Chulia, 1992). As the percentage of small particles 74 μm or smaller in diameter increases, the spaces among large particles are reduced as they are filled by small particles, resulting in an increase in the internal friction coefficient. Moreover, as the percentage of microparticles increases, these microparticles begin to act as aggregates (Tsubaki et al., 1981; Naito et al., 1987). Although there was no correlation between friction characteristics and the particle size, the friction characteristics of a particle layer have been reported to be closely related to the particle shape if the material and size of the particles are the same (Kanaoka et al., 1979; Kanda et al., 1988).

In this study, the effects of loading on mixed powders could be evaluated according to the particle size distribution and friction among particles, which are not reflected by indices commonly used for evaluation of macropowder properties such as the angle of repose. As the variation of the particle size of crystalline cellulose (granules) becomes greater than that of lactose, the particles are displaced more markedly under the same load, and effects of partial breakage appear. Energy needed to obtain the same pulverization efficiency increases with the mass of the material.

Pulverization resistance has been reported to decrease in a certain load range, suggesting the presence of an optimal range in the sample mass (Hirota et al., 1986). Under loading, also, particles are generated and aggregated depending on the mixing ratio, suggesting the presence of a range of mixing ratios in which changes in the particle size distribution disappear. This mixing ratio was found to be more dependent on the crystallinity and hardness of the powder than on the particle size of the materials mixed.

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