

Studies on Internal Structure of Tablets. VI. Stress Dispersion in Tablets by Excipients

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The aim of this study was to reduce the stress concentration of a medicine by dispersing the stress in tablets at tableting by addition of excipients. The mechanism of the stress dispersion was elucidated.

Phenacetin (PHE) was used as a model of crystalline medicine with a high brittleness, and the degree of stress dispersion was evaluated by the change in the exposed surface area of PHE. To learn the mechanical strength of tablets, the crushing strength and friability were measured, their internal structure was analyzed by the porosity and pore size distribution, and stress relaxation experiments were performed. The results were as follows.

Calcium silicate (Florite® RE, FLR) showed a high stress dispersion effect, adding a high formability and mechanical strength to tablets. It was thought that the high stress dispersion resulted from the rapid stress relaxation caused by the plastic deformation and brittleness fracture of pores in FLR under a low compression pressure. Thus the stress caused locally on PHE particles may disperse.

Key words tablet; stress; excipient; calcium silicate; stress relaxation

It is generally known that a uniform stress is not generated in all parts of a tablet at tableting, but that the stress and density in compressed powder are localized, with the result that the internal structure of a tablet is not necessarily uniform.^{1,2)} Moreover, in practical tablet manufacturing, it is expected that the physicochemical properties of medicines included in tablets are changed by the high stress part in the stress distribution, that is, the stress concentration. For example, in low melting point medicines included in tablets, compressing problems such as sticking or picking by fusion sometimes occur; or there can be a decrease in the number of cells actually living in live bacterial cells; a devitalization of enzyme activities in enzymes; destruction of the wall in microcapsules, or a change in the property of peptides.^{3–6)}

In this paper, excipients were added to tablet formulations and the authors aimed at reducing the stress concentration of medicine by dispersing the stress in tablets during compression; the mechanism of the stress dispersion was then elucidated.

Experimental

Materials and Measurement of the Properties of Powders Phenacetin (PHE, Tsukishima Yakuhin Co., Ltd.) which was used as a model of a highly brittle crystalline medicine was sieved and the particle-size fractions which did not pass through the 355 μm screen were obtained. Porous calcium silicate (Florite® RE, FLR, Eisai Co., Ltd.), crystalline cellulose (Avicel® PH-301, MCC, Asahi Kasei Kogyo Co., Ltd.), lactose (Lact, DMV Co., Ltd.), anhydrous dibasic calcium phosphate (Fujikarin®, ADCP, Fuji Kagaku Kogyo Co., Ltd.) and cornstarch (CS, Nippon Cornstarch Co., Ltd.) used as the excipient were passed through a 75 μm screen. Hydroxy propyl starch (HPS, Freund Industries Co., Ltd.) used as the disintegrator was also passed through a 75 μm screen. The powders were pretreated in a vacuum dryer at 80 °C for 2 h before compression.

The density and angle of repose of each powder were measured using an air comparison pycnometer (Toshiba-Beckman Co., Ltd., Model 930) and a Konishi angle of repose meter (Konishi Seisakusho Co., Ltd., Model FK), respectively. The specific surface area was measured by the air permeability method, employing a specific surface area meter (Shimazu Seisakusho Co., Ltd., Type SS-100), and the particle diameter was determined by the following equation,

$$S_w = 6/\rho \cdot D$$

where S_w is specific surface area, ρ is density and D is particle diameter. Measurement was repeated 3 times for each kind of powder, and the mean value and standard deviation were determined. The obtained values are shown in Table 1. Figure 1 shows the particle size distributions of excipients by the sieve analysis. A scanning electron microscope (SEM, Hitachi Seisakusho Co., Ltd., Type S-2250N) was used to view the surface of various excipients, and Fig. 2 shows these SEM photographs.

Tablet Preparation Tablet formulations and compacting conditions are shown in Table 2. For the experiments on the stress dispersion effect

Table 1. Particle Diameters, Densities and Angles of Repose of Powders Used

	Particle diameter (μm)	Density (g/cm^3)	Angle of repose (°)
PHE	119.4 \pm 20.3	1.235 \pm 0.001	—
FLR	0.49 \pm 0.02	2.758 \pm 0.029	46.7 \pm 1.2
MCC	12.66 \pm 0.15	1.539 \pm 0.004	42.4 \pm 1.1
LACT	10.35 \pm 0.11	1.537 \pm 0.001	49.2 \pm 1.1
ADCP	5.23 \pm 0.15	2.943 \pm 0.020	29.6 \pm 0.7
CS	11.40 \pm 0.14	1.476 \pm 0.002	45.2 \pm 0.4
HPS	11.57 \pm 0.05	1.465 \pm 0.001	42.0 \pm 0.8

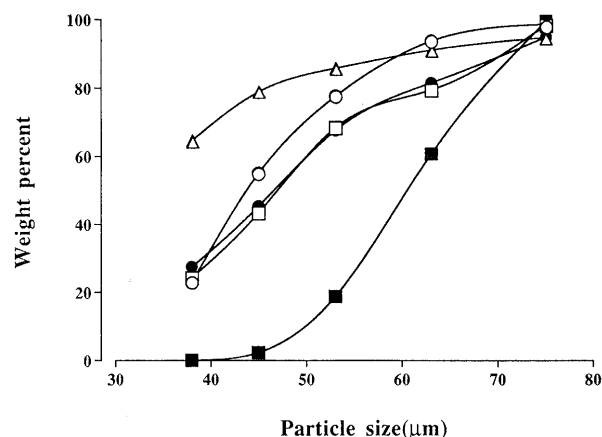


Fig. 1. Cumulative Undersize Distributions of Various Excipients
○: FLR; ●: MCC; □: LACT; ■: ADCP; △: CS.

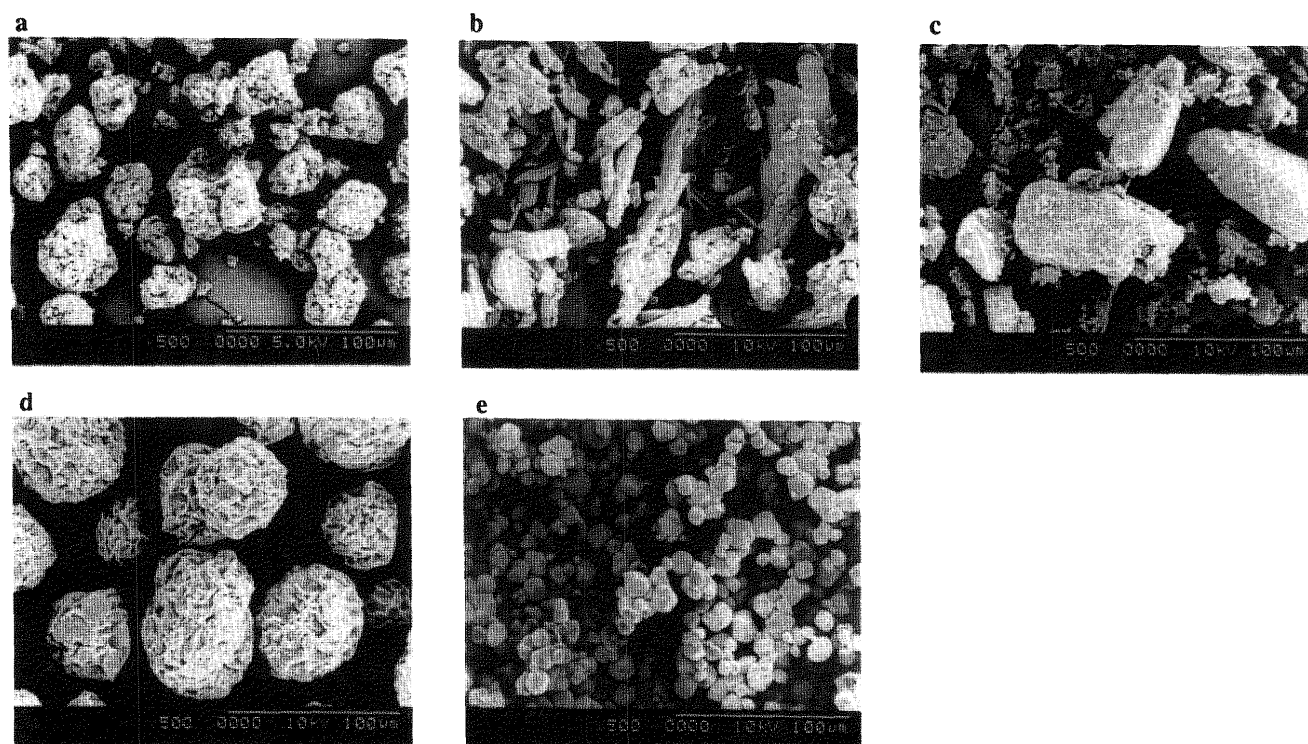


Fig. 2. Scanning Electron Micrographs of Particles of Various Excipients

a: FLR; b: MCC; c: LACT; d: ADCP; e: CS.

Table 2. Tablet Formulations and Experimental Conditions

	PHE (mg)	FLR (mg)	MCC (mg)	LACT (mg)	ADCP (mg)	CS (mg)	HPS (mg)	Compression pressure (kg/cm ²)
Formulation A	100	100	—	—	—	—	50	1000
	100	—	100	—	—	—	50	1000
	100	—	—	100	—	—	50	1000
	100	—	—	—	100	—	50	1000
	100	—	—	—	—	100	50	1000
Formulation B	180—60	20—140	—	—	—	—	50	1000
Formulation C	100	100	—	—	—	—	50	100—2000
	200	—	—	—	—	—	50	100—2000

of various excipients, formulation A was used, for those of FLR percent in tablets, formulation B was used, and for those of the compression pressure, the formulation C was used. Powder mixtures were compressed into tablets by the direct compression method, using a universal testing machine (Minebea Co., Ltd., Model TCM-5000C) with a die of 8.9 mm internal diameter and flat-faced punches. The compression speed was 50 mm/min.

Evaluation of Stress Dispersion Effect A uniform stress is not always established in a powder bed at compression, so the stress dispersion effect for tablets containing PHE with a slight solubility was evaluated according to our previous paper^{4,7,8}; considering that as the local stress applied to PHE particles increases, the degree of crush increases and thus the exposed surface area of PHE increases, accelerating the dissolution rate of PHE from the tablets. The degree of stress dispersion effect was evaluated by the change in the rate of dissolution of PHE from tablets; this rate was determined by the paddle method (JPXII). The dissolution test was carried out for 5 tablets by the flow method and absorbance at 243 nm was measured with a UV spectrophotometer (Hitachi Co., Ltd., U-3200). The medium was 1000 ml of distilled water. It was observed that the tablets containing 20% of HPS disintegrated within 1 min and there was not believed to be any effect of disintegration, so the slope of absorbance from 1 min after the start of the dissolution test up to 5 min was determined as the dissolution rate.

Measurement of Tablet Porosity The porosity of 10 tablets of each kind was determined a day after compression by measuring the diameter, thickness and weight and using the density of each powder included in

the tablets (Table 1).

Measurement of Tablet Strength The tablet strength of 5 tablets of each kind was measured with a hardness tester (Kiya Seisakusho, Ltd.).

Measurement of Tablet Friability The friability was determined by the method of Funakoshi *et al.* using 20 tablets of each kind.⁹

Measurement of Pore Size Distribution The pore size distribution of each tablet was measured by mercury intrusion porosimetry, employing a mercury porosimeter (Quanta Chrome Co., Autoscan-33). The contact angle of mercury with the samples and the surface tension of mercury were regarded as 140° and 480 dyn/cm, respectively.¹⁰

Measurement of Stress Relaxation Stress relaxation experiments were performed during compaction of materials, using the universal testing machine described above. To determine the residual stress at virtually constant strain, powder was compressed until the required peak force was reached, and then the punches were held at this fixed position.¹¹ The compacting conditions were as follows: 500 mg of powder of each excipient, 50 mm/min compression speed, and 100—2000 kg/cm² peak compression force. The time required to decrease stress to 90% of initial stress was determined as the 10% stress relaxation time.

Results and Discussion

Comparison of Stress Dispersion Effect of Tablets Containing Various Excipients at Compression Figure 3 shows the dissolution rate of PHE from tablets containing various excipients, which were prepared according to the

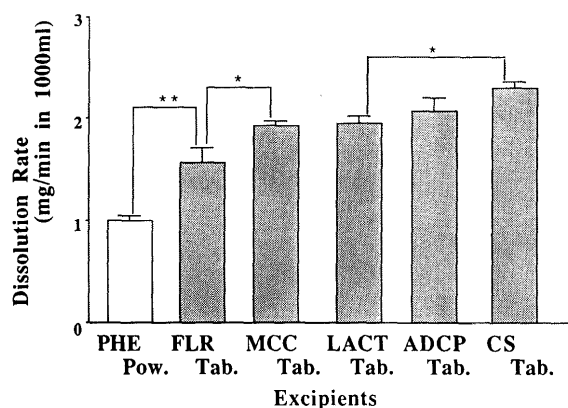


Fig. 3. Dissolution Rate of Phenacetin from Phenacetin Powder and Tablets Containing Various Excipients

*: $p < 0.05$; **: $p < 0.01$.

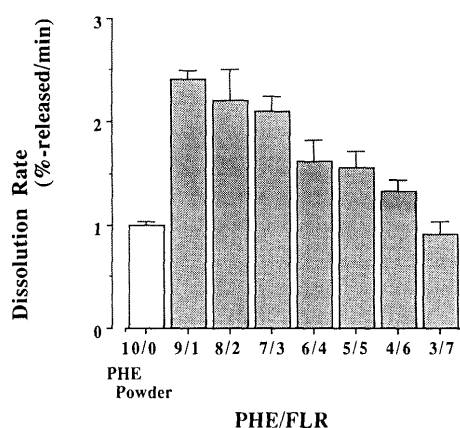


Fig. 4. Effect of FLR Percent in Tablets on Dissolution Rate

formulations and conditions shown in Table 2A, and that of PHE powder. The dissolution rate was in the rank order of $FLR < MCC < LACT < ADCP < CS$, hence stress dispersion effect within the tablet became larger in the rank order of $FLR > MCC > LACT > ADCP > CS$.

Figure 4 shows the dissolution rate of PHE from tablets containing FLR which had the largest stress dispersion effect of the excipients used. The tablets were prepared according to the formulations and conditions shown in Table 2B. In a tablet with a small FLR content, the dissolution rate of PHE remarkably increased, while when FLR content increased, the dissolution rate of PHE decreased, so the stress dispersion effect increased. In a tablet whose ratio of PHE and FLR was 3:7, the dissolution rate of PHE was almost the same as the original PHE powder. These results suggest that when a small quantity of FLR was added to PHE powder (ex. PHE:FLR=9:1), the degree of crushed PHE increased because most of the highly brittle PHE particles were in contact with the other PHE particles in a powder bed at compression, so the dissolution rate of PHE from the tablet increased. When a relatively large quantity of FLR was added to PHE powder (ex. PHE:FLR=3:7), PHE particles were dispersed in the FLR powder, so stress dispersion caused by the FLR addition occurred at compression, and the dissolution rate of PHE from the tablet was almost the same as the original PHE powder.

In relation to the effects of the compression pressure

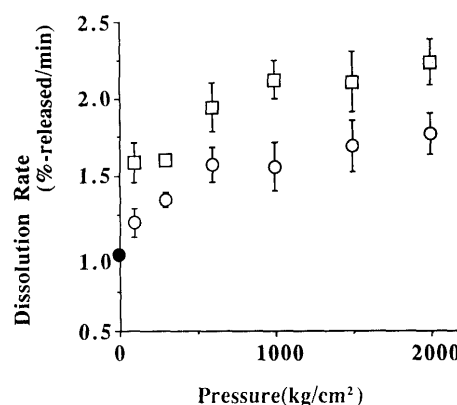


Fig. 5. Effect of Compression Pressure on Dissolution Rate

●: PHE powder; ○: FLR tablet; □: non-FLR tablet.

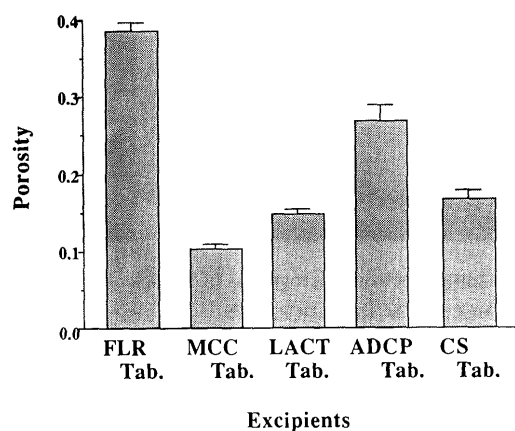


Fig. 6. Porosity in Tablets Containing Various Excipients

and addition of FLR on the dissolution rate, Fig. 5 shows the dissolution rate of PHE from samples which were prepared according to the formulations and conditions shown in Table 2C. In the powder mixtures consisting of PHE and HPS, but not containing FLR, tablets were not formed because of the poor formability. In all compression pressures, the tablets containing FLR had a smaller dissolution rate of PHE than the compacted powders consisting of PHE and HPS. With larger compression pressure, the difference in the dissolution rate of PHE between the addition and non-addition of FLR increased slightly up to about 600 kg/cm² of pressure, but above this, the difference remained almost the same. This suggests that most of the stress dispersion due to the addition of FLR occurred up to about 600 kg/cm² of compression pressure.

Mechanical Strength and Porosity of Tablets Containing Various Excipients Figures 6 and 7, respectively, show the porosity, and the crushing strength and friability of tablets prepared according to the formulations and conditions shown in Table 2A. The porosity of tablets containing FLR was much larger than that of tablets containing other excipients. It is generally thought that as the porosity of tablets increases, the contact points and the contact area among particles which compose the tablets decrease and the interparticle adhesion decreases, lowering the mechanical strength of the tablet. Tablets containing FLR, however, had a considerably stronger crushing strength and a smaller friability, meaning that they had a

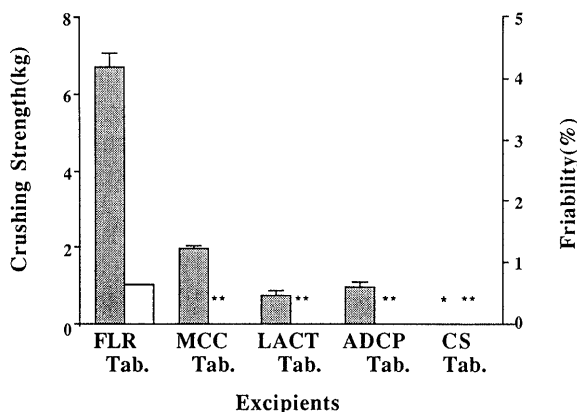


Fig. 7. Crushing Strength and Friability in Tablets Containing Various Excipients

■: Crushing strength; □: Friability. (*: less than 0.5 kg; **: more than 5%).

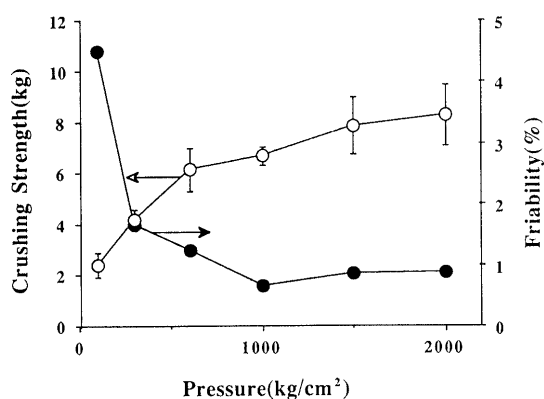


Fig. 8. Effect of Compression Pressure on Crushing Strength and Friability

○: Crushing strength; ●: Friability.

higher mechanical strength than tablets containing other excipients. This result suggests that FLR particles appeared as a petal structure because of the scaly crystals of calcium silicate and formed many pores,¹²⁾ and that the structure fractured brittly and deformed plastically under the compression; the result was that the contact points and the contact area among particles increased, and a twined structure was formed.

Figure 8 shows the crushing strength and friability of tablets prepared according to the formulations and experimental conditions shown in Table 2B. Up to about 600 kg/cm² of compression pressure, the crushing strength markedly increased and the friability decreased. Above this pressure, the crushing strength slightly increased and the friability slightly decreased with the compression pressure. Thus a significant change in the internal structure of tablets apparently occurred up to about 600 kg/cm² of compression pressure.

Mechanism of Stress Dispersion by FLR To study the effect of the compression pressure on the internal structure of tablets, Fig. 9 shows the relationship between the cumulative pore volume and porosity of tablets, prepared according to the formulations and conditions shown in Table 2C, and the compression pressure. Both the porosity and cumulative pore volume remarkably decreased up to about 600 kg/cm² of compression pressure. This suggests

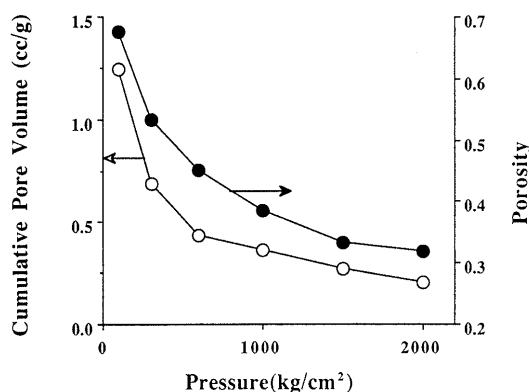


Fig. 9. Effect of Compression Pressure on Cumulative Pore Volume and Porosity

○: Cumulative pore volume; ●: Porosity.

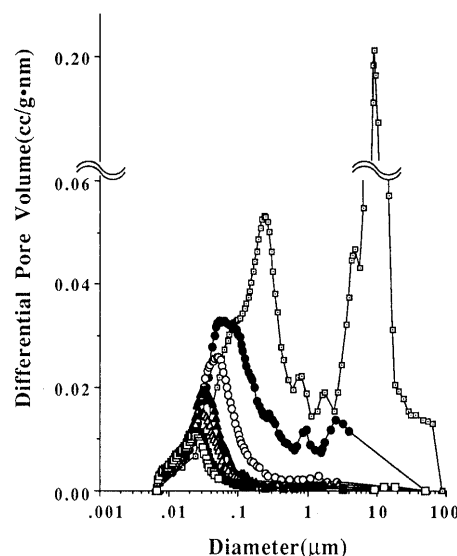


Fig. 10. Effect of Compression Pressure on Pore Size Distributions in Tablets

□: Powder; ●: 100 kg/cm²; ○: 300 kg/cm²; ▲: 600 kg/cm²; △: 1000 kg/cm²; ■: 1500 kg/cm²; □: 2000 kg/cm².

that a significant change in the internal structure of tablets occurred up to about 600 kg/cm² of compression pressure in the same way as previously stated.

The effect of compression pressure on the pore size distribution in tablets is shown in Fig. 10. Powder mixtures showed many pores with diameters of about 8 and 0.2 μ m, which were considered to be interparticle pores of FLR and intraparticle pores, respectively. It was considered that the pores deformed and broke in the order from large to small pores of FLR particles under the compression, so that most of the pores with diameters of more than about 0.1 μ m which were numerously present in the powder mixtures disappeared by the time the compression pressure reached about 600 kg/cm². This result shows that the deformation and breakage of most of the pores present in FLR particles were almost completed by the stress which occurred in the powder bed up to about this compression pressure.

It has been reported that the stress relaxation phenomenon was caused by the flow and deformation of particles in a compact after compression at peak force.^{13,14)} The stress dispersion in this paper was believed to be caused

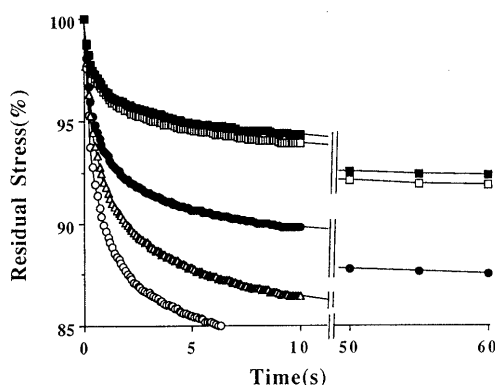


Fig. 11. Stress Relaxation in Various Excipient Powder Beds

○: FLR; ●: MCC; □: LACT; ■: ADCP; ▲: CS.

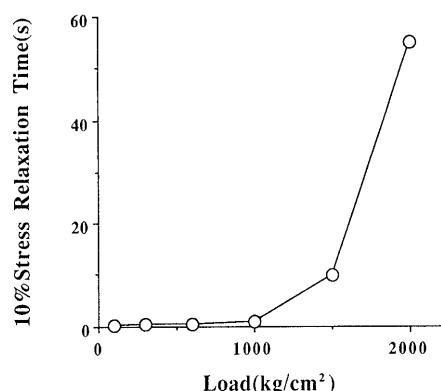


Fig. 12. Effect of Loading Conditions on Stress Relaxation

by the flow and deformation of particles in the powder bed during compaction of materials; stress relaxation experiments were performed, and the degree of stress relaxation was compared with the stress dispersion effect. Figure 11 shows the stress relaxation curves of various excipients at peak force of 1000 kg/cm^2 . The 10% stress relaxation time of FLR was 0.9 s, shorter than those of other excipients. The stress relaxation caused by the flow of FLR particles was thought to be small, because FLR particles have a petal structure and a large angle of repose of 46.7° . Taking this into consideration, the very high rate of stress relaxation of FLR was believed caused by a large plastic deformation and brittleness fracture of FLR particles under low compression pressure. The mechanism of stress dispersion by FLR is therefore probably that stress relaxation is rapidly caused by the plastic deformation and brittleness fracture of FLR particles under a low compression pressure, so that the stress locally caused is dispersed.

Figure 12 shows the 10% stress relaxation time of FLR at various peak forces. The time increased when the peak force was more than about 600 kg/cm^2 . The results of this and of Fig. 10 indicate that the change in the internal structure caused primarily by the plastic deformation and brittleness fracture of FLR particles in the powder bed

was almost completed by the time the compression pressure reached about 600 kg/cm^2 ; a structure similar to the elastic body was formed when the pressure was more than this, thus increasing the 10% relaxation time. From this theorized stress dispersion mechanism by FLR, the change in the stress dispersion effect due to the compression pressure shown in Fig. 5 would be explained as follows: for the tablets containing FLR, the stress relaxation was caused rapidly by the plastic deformation and brittleness fracture of pores in FLR particles up to about 600 kg/cm^2 of compression pressure; the stress caused locally on PHE particles was also dispersed rapidly, and thus the increase in the dissolution rate of PHE was slight compared with that of tablets not containing FLR. When the compression pressure exceeded 600 kg/cm^2 tablets containing FLR showed an increase in the dissolution rate of PHE in the same way as those not containing FLR because almost no stress relaxation by FLR particles occurred.

Conclusion

The authors used PHE as a model of crystalline medicine with high brittleness, and attempted to disperse stress in tablets containing various excipients. Compared with other excipients, FLR showed a high stress dispersion effect and added a high formability and mechanical strength to tablets. The stress dispersion mechanism was believed based on rapid stress relaxation caused by the plastic deformation and brittleness fracture of many pores originating from the structure of FLR under low compression pressure. Thus, the stress caused locally on PHE particles may be dispersed.

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