Effect of Granule Strength on Compressed Tablet Strength[1)]

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Received May 31, 1995; accepted August 14, 1995

The effect of granule strength on the strength of a tablet compressed under a certain force was examined. Crushing strength and diametral compression tests were carried out to assess granule and tablet strength, respectively. When granules were weak, tablet strength increased with granule strength. In some powder/polymer binder systems, a further increase in granule strength led to tablets with maximal strength, which then decreased. It was apparent that hard granules were difficult to deform by compression, and the resulting tablets fractured at the boundary between granules.

Key words granulation; granule strength; polymer binder; compressed tablet strength; radial tensile strength

Pharmaceutical powders are often granulated with binders to improve adhesiveness and cohesiveness in tableting. Tablet strength is affected by the mechanical characteristics of the granules to be compressed. Mechanically weak granules are considered to make weak tablets when compressed at a certain force. When granules were prepared by the agitation method, however, the strength of a tablet obtained by compression of the granules decreased with increasing granular strength.[2)] A number of powder/binder systems should thus be studied in detail. In previous studies,[3,4)] it was shown that granule strength was affected by the polarity of powdered materials and polymer binders. Since then, granules with a wide variety of strength could be prepared in a particular powder/polymer binder system. These granules were compressed at a given force to obtain model tablets. Tablet strengths were then determined by the diametral compression method.

Experimental

Materials The sample powders used were a mixture of lactose (#200, DMV Co., Ltd. Heywood diameter d_p: 94.8 μm) and corn starch (Nichidenkagaku Co., Ltd. d_p: 36.5 μm) for typical hydrophilic powder (the mixing ratio is 70 : 30),[4)] aspirin (Mitsui-Toatsu Chemical Co., Ltd. d_p: 26.7 μm), which is intermediate in surface polarity, and M-5011 (*d*-2-[4-(3-metyl-2-thienyl)phenyl]propionic acid: $C_{14}H_{14}O_2S$, Maruho Co., Ltd. d_p: 11.1 μm) as a typical hydrophobic powder, which was developed as a nonsteroidal anti-inflammatory antipyretic analgesic. The polymer binders used were polyvinylpyrrolidone (PVP K-30, K-90: BASF Co., Ltd.), hydroxypropylcellulose (HPC-EFP, HPC-LFP: Shin-Etsu Chemical Co., Ltd.; contents of functional group, $-OC_3H_6OH$: 62—64%) and hydroxypropylmethylcellulose (HPMC TC-5E, TC-5S: Shin-Etsu Chemical Co., Ltd.; contents of functional group, $-OC_3H_6OH$: 9%, $-OCH_3$: 29%).

Determination of Physicochemical Properties of Binders The apparent viscosity η of aqueous solutions of each binder was measured at 20 °C with a rotation viscometer (B8H, Tokimec Inc.). The surface tension γ_L of an aqueous binder solution was measured by the capillary rise method at 20 °C. Table 1 shows the physicochemical properties of the binders used.

Granulation All the granule formulations are listed in Table 2. 800 g of sample powders were kneaded with a given volume (40—720 g) of 10—30% (w/w) binder solution. The mixture was kneaded at 200 rpm for 10 min using a kneader (Erweka AR400), and the moist mass was forced by hand through a 1.00 mm screen (JP#16). The extruded granules were dried at 60 °C for 3 h, and sifted through two screens to obtain granules ranging in size from 0.71 (JP#24) to 1.00 mm (JP#16).

Granule Crushing Test The crushing load P_g (N) for more than 30 granules was determined as previously reported.[3)] The strength of granule T_g (MN m^{-2}) was calculated from Eq.1, proposed by Kuno *et al.*,[5)] assuming that granules were spherical:

$$T_g = P_g/A \quad (1)$$

where A is the cross-sectional area of a granule. A is given by $\pi D_g^2/4$, where D_g is the granule diameter (m).

Tablet Preparation One gram of granules was compressed using a universal tester (Shimadzu Autograph AG-5000E) with 16 mm flat-faced punches at a compression force of 10 kN. For lactose–corn starch granules, compressions at 5 and 15 kN were added. Compression was carried out at a rate of 1 mm/min. After standing for 30 s at a given force, the force was removed.

Tablet Tensile Strength The diametral compression test for tablets was done at least 12 h after compression. The method of measurement of tablet tensile strength T_t has been described elsewhere.[6)] T_t (MN m^{-2}) was calculated using the following equation:

$$T_t = 2P_t/\pi \cdot D \cdot L \quad (2)$$

where, P_t is the maximum load (N) when the tablet fractured, D is tablet diameter (m) and L, tablet thickness (m), as measured by a micrometer (IDC-1012M; Mitutoyo Co., Ltd.). The mean value of 5 tablets was determined.

Stereo-Microscopic Observation The fracturing of tablets was examined by a stereo-microscope (SMZ-2T, Nicon Co., Ltd.) and photographs were taken.

Results and Discussion

Figures 1—3 show the relationship between granule strength T_g and compressed tablet strength T_t. In all cases, T_t increased with T_g when T_g was low, regardless of the binders used. This result was expected.

For the lactose–corn starch mixture (70 : 30), which

Table 1. Physicochemical Properties of Binding Agents

Polymer binder	Apparent viscosity of aq. soln., η (10^{-1} Pa s)		Surface tension of aq. soln., γ_L[a)] (mN m^{-1})
PVP K-30	10%	0.080	68
PVP K-90	10%	3.0	69
	20%	41	70
	30%	390	69
HPC-EFP	10%	1.9	42
HPC-LFP	10%	9.5	42
HPMC TC-5E	10%	1.1	45
	20%	11	45
	30%	87	45
HPMC TC-5S	10%	22	46

a) Determined by the capillary rising method at 20 °C.

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Table 2. Granulation Formulation

Powdered material	Binding agent	Concentration of aqueous binder solution (% w/w)	Proportion of binder solution added (g/g powder)				
Lactose–corn starch mixture (70:30)	PVP K-30	10	0.05	0.10	0.20	0.30	0.40
	PVP K-90	10, 20, 30	0.05	0.10	0.20	0.30	0.40
	HPC-EFP	10	0.05	0.10	0.20	0.30	0.40
	HPC-LFP	10	0.05	0.10	0.20	0.30	0.40
	HPMC TC-5E	10, 20	0.05	0.10	0.20	0.30	0.40
	HPMC TC-5S	10	0.05	0.10	0.20	0.30	0.40
	Water	—	0.05	0.10	0.20	0.30	0.40
Aspirin	PVP K-30	10	0.05	0.10	0.20	0.30	0.40
	PVP K-90	10, 20, 30	0.05	0.10	0.20	0.30	0.40
	HPC-EFP	10	0.05	0.10	0.20	0.30	0.40
	HPC-LFP	10	0.05	0.10	0.20	0.30	0.40
	HPMC TC-5E	10, 20	0.05	0.10	0.20	0.30	0.40
	HPMC TC-5S	10	0.05	0.10	0.20	0.30	0.40
	Water	—	0.05	0.10	0.20	0.30	0.40
M-5011	PVP K-30	10		0.10	0.30	0.60	0.90
	PVP K-90	10, 20		0.10	0.30	0.60	0.90
	HPC-EFP	10		0.10	0.30	0.60	0.90
	HPC-LFP	10		0.10	0.30	0.60	0.90
	HPMC TC-5E	10, 20, 30		0.10	0.30	0.60	0.90
	HPMC TC-5S	10		0.10	0.30	0.60	0.90
	Water	—		0.10	0.30	0.60	0.90

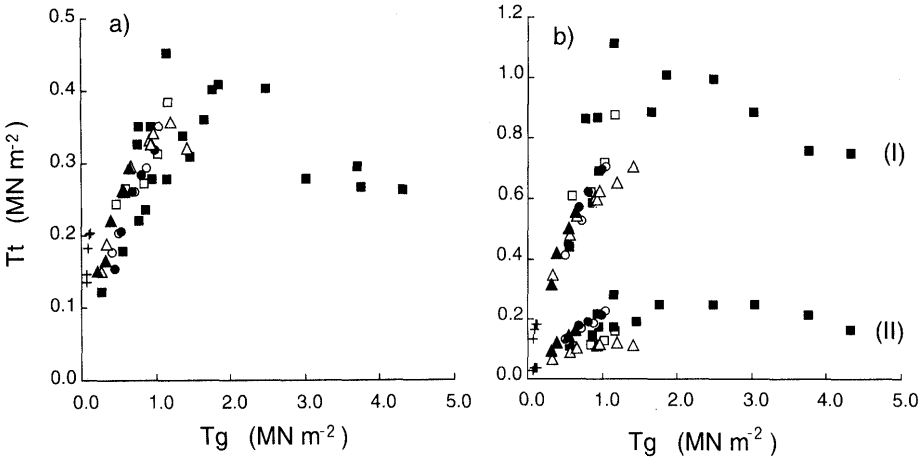

Fig. 1. Relationship between Granule Strength, T_g, and Tablet Strength, T_t, of Lactose–Corn Starch Tablet

a) Tablet compressed at 10 kN. b) Tablet compressed at 5 kN (I) and 15 kN (II). Key: □, PVP K-30; ■, PVP K-90; ○, HPC-EFP; ●, HPC-LFP; △, HPMC TC-5E; ▲, HPMC TC-5S; +, without polymer binder.

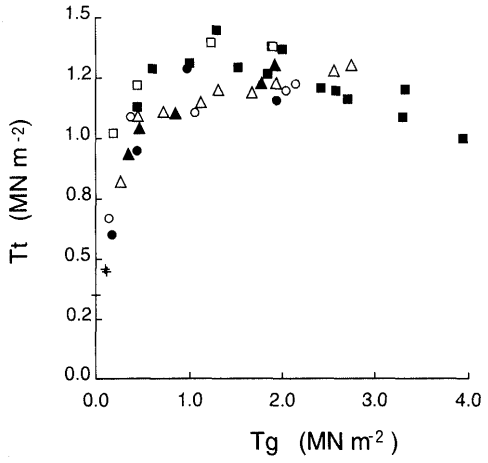

Fig. 2. Relationship between Granule Strength, T_g, and Tablet Strength, T_t, of Aspirin Tablet Compressed at 10 kN

Key as in Fig. 1.

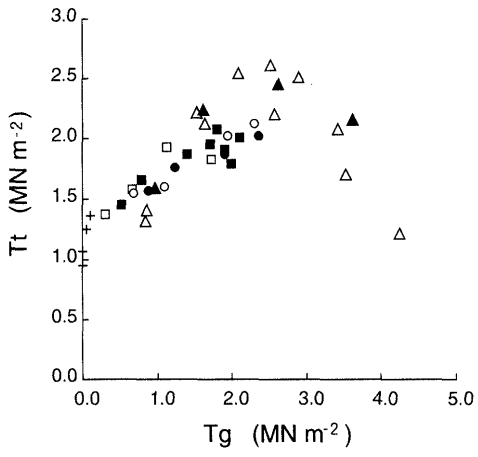

Fig. 3. Relationship between Granule Strength, T_g, and Tablet Strength, T_t, of M-5011 Tablet Compressed at 10 kN

Key as in Fig. 1.

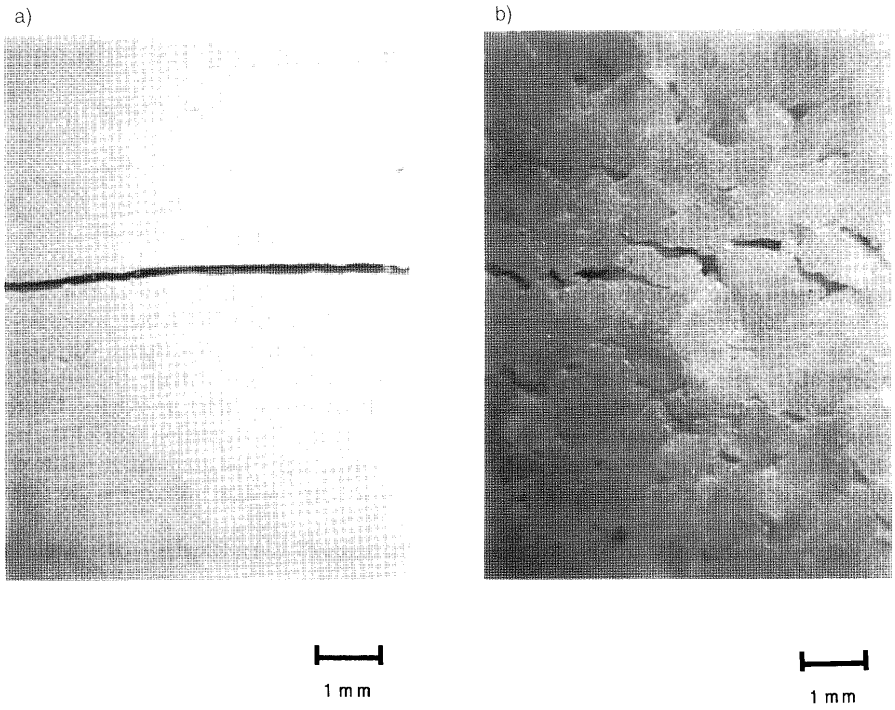

Fig. 4. Stereo-Microscopic Photographs of the Fracture-Face of the M-5011 Tablet

Condition of the granulation. a) Polymer binder, HPMC TC-5E; concentration of binder solution, 10% (w/w); proportion of binder solution added, 0.3 g/g powder. b) Polymer binder, HPMC TC-5E; concentration of binder solution, 30% (w/w); proportion of binder solution added, 0.6 g/g powder.

possesses high surface polarity, hard granules could be prepared using a large quantity of PVP K-90 as a binder. For tablets compressed at different forces (5, 10, and 15 kN), the relationship between T_g and T_t was examined (Figs. 1a, b). In granules with the same T_g, T_t increased as compression force increased. For tablets compressed at a certain force, T_t reached maxima within the range of T_g of about 1 to 2 $MN\,m^{-2}$. Further increases in T_g led to a lowering of T_t.

In aspirin, hard granules were also prepared by the use of PVP K-90 as a binder. Tablet strength T_t showed an approximately constant value in the T_g region of 1 to 3 $MN\,m^{-2}$, and then gradually decreased with T_g (Fig. 2).

In M-5011, which is a hydrophobic powder, HPMC (TC-5E) is suited in the preparation of hard granules. In the T_g–T_t curve (Fig. 3), an obvious maximum could be observed.

Figures 4a and b show stereo-microscopic photographs of the M-5011 tablets after fracture. When T_g was low (Fig. 4a), the fracture was essentially straight and granules appeared to be plastically deformed, and then crushed, indicating that intragranular failures occured by compression of the granules. Tablet strength is thus governed by granule strength. At high T_g (Fig. 4b), an angular or irregular fracture was observed, suggesting that the granules were too rigid to allow complete crushing by compression. Tablet fracturing may have occured at the granule boundaries. Since effective intergranular contact diminished, tablet strength decreased with binder quantity.

Acknowledgment The authors are grateful to Ms. Satoko Kawazoe for assistance with the experimental work. We also acknowledge the encouragement of Dr. Yu Imazato, director of Maruho R & D Laboratories.

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