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Effect of Binder Characteristics on the Strength of Agglomerates Prepared by the Wet Method

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The effect of the physicochemical properties of binders on the strength of agglomerates prepared by the wet method was investigated using untreated and surface trimethylsilylated glass beads as model powders. The crushing test of granules and the bending test of molded tablets were carried out in order to estimate the strength of the agglomerates. A quantitative approach based on the work of Rumpf *et al.* was attempted to obtain the strengths between two contacting particles. The calculated values were in fair agreement with those obtained by the separation test using two big balls. In all the systems, the agglomerates prepared from surface treated glass were weaker in strength than those from untreated glass. In conclusion, it was apparent that the strength of an agglomerate was related both to the wetting of a particle by a binder solution and to the binder cohesion.

Keywords granulation; binder solution; glass beads/binder system; surface treated glass beads; granule strength; wettability

Due to recent remarkable technical advances, various granulation methods are being utilized for drug production. The conventional extruding granulation method, however, is still one of the most popular granulation methods because of its reliability based on many years' experience. Moreover, since this method is relatively simple in operation, it is useful for basic studies of wet granulation.

In our previous study,[1] a lactose/cornstarch mixture was granulated using various binder solutions. It was found that the size and strength of dried granules correlated to the mechanical properties of the moist mass. It was also elucidated that these properties were greatly influenced by the type of binder solution used.

The effect of type of the binder solution on the strength of granules has been studied by several investigators. Krycer *et al.*[2] carried out a friability test on paracetamol granules prepared by the wet method using various binder solutions, and reported a granule strength in the order of HPMC > acasia > PVP > starch > PEG6000 > sucrose. The extruding granulation of sand was conducted by Reading and Spring.[3] The friability of the granules decreased in the order of MC > PVP > gelatin > starch. Cutt *et al.*[4] measured the friability and crushing load of granules of glass beads both untreated and treated with dimethylsilane using three kinds of polymers as binders. They found a rank order of HPMC > gelatin > PVP for friability and gelatin > PVP > HPMC for resistance to crushing. In these previous studies, however, the role of the binder is not clear because the testing powder varies with the researcher.

In order to examine the effect of the physical properties of binders on the strength of granules in detail, spherical glass beads with and without trimethylsilylated surface were used in the present work. From measurements of the crushing load of the granules and the breaking load of molded tablets by the bending test, the adhesive or cohesive strength σ at a contact point between particles was calculated.

A model experiment for evaluating the binder strength or binder/particle adhesive strength was performed using two big glass balls of equal size adhered with a binder. The strength obtained from the force required to separate the balls was compared with the σ value of agglomerated glass beads.

Experimental

Materials Glass beads (#100, Gakunankoki, Ltd., a mean Heywood's diameter of 152 μm) washed with acetone and water, and then surface-treated, were used as the model powder. The surface treatment was carried out as follows. Glass beads were shaken with a solution of 20% (v/v) trimethylchlorosilane in hexane at 25 °C for 7 d and filtered off. After being washed with acetone, the samples were dried at 110 °C for 4 d. The surface treatment of a glass plate was performed according to that of the glass beads. The binders used were polyvinylpyrrolidone (PVP K-30, K-90: BASF Ltd.), hydroxypropylcellulose (HPC-EFP, HPC-LFP: Shin-Etsu Chemical Co., Ltd.), hydroxypropylmethylcellulose (HPMC TC-5S, TC-5E: Shin-Etsu Chemical Co., Ltd.), and carmellose sodium (Na-CMC: Gotokuyakuhin Ltd.).

Table I shows the molecular characteristics of the polymer binders and lactose used for this experiment.

Viscosity Measurement The viscosity, η, of 10% (w/w) aqueous solution of each binder was measured using a rotation viscometer (Vistron VS, Seiki Co., Ltd.) at 20 °C.

Surface Tension Measurement The surface tension, γ_L, of 10% (w/w) aqueous solution of each binder was measured by the capillary rising method at 20 °C.

Contact Angle and Work of Immersion Measurement A small droplet (20 μl) of each 10% (w/w) binder aqueous solution was placed on a glass plate whose surface was either untreated or treated. Contact angles, θ, were determined by a photographic recording method. The work of immersion, A, was calculated from Eq. 1.

$$A = \gamma_L \cos\theta \qquad (1)$$

TABLE I. Binding Agents Used

Binder	Degree of substitution or content of functional group[a)]		Mean molecular weight, M_W[a)]	Particle density ρ_P[b)] (kg·dm^{-3})
PVP K-30		—	45000	1.14
PVP K-90		—	1,100000	1.15
HPC-EFP	$-OC_3H_6OH$	63.6%	56000	1.16
HPC-LFP	$-OC_3H_6OH$	62.1%	93000	1.16
HPMC(TC-5E)	$-OC_3H_6OH$ $-OCH_3$	9.3% 29.0%	14000	1.35
HPMC(TC-5S)	$-OC_3H_6OH$ $-OCH_3$	8.8% 28.7%	64800	1.34
Na-CMC	D.S.	0.7	42000	1.56
Lactose			360	1.53

a) Manufacturer's data. *b)* Determined by a Shimadzu-Micromeritics helium-air pycnometer.

Table II. Physicochemical Properties of 10% (w/w) Binder Solutions

Binder	Viscosity, η (mPa·s)	Surface tension, γ_L (mN·m^{-1})	Contact angle, θ, and work of immersion, A, for 10% (w/w) binder solution/untreated and treatd glass plate systems: Untreated		Treated	
			θ (°)	A (mN·m^{-1})	θ (°)	A (mN·m^{-1})
PVP K-30	8	67.9	34.7	55.8	69.7	23.6
PVP K-90	220	67.2	38.0	53.0	69.8	23.2
HPC-EFP	188	41.9	40.4	31.9	58.3	22.0
HPC-LFP	1024	40.4	46.1	28.0	60.9	19.6
HPMC(TC-5E)	58	47.3	35.3	38.6	67.3	18.3
HPMC(TC-5S)	1828	46.7	47.0	25.6	67.5	17.9
Na-CMC	11500	71.9	52.2	44.1	78.3	14.6
Lactose	1	72.8	29.7	63.2	75.8	17.9

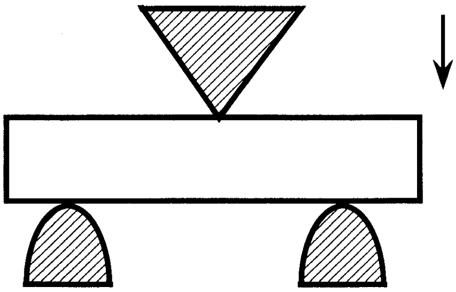

Fig. 1. Schematic Diagram of the Apparatus for Measuring the Bending Test

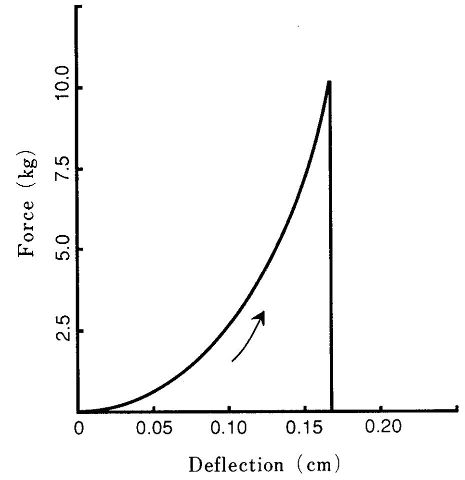

Fig. 2. Typical Force-Deflection Curve for Bending Test of Molded Tablet

Binder solution: 10% (w/w) HPC-EFP.

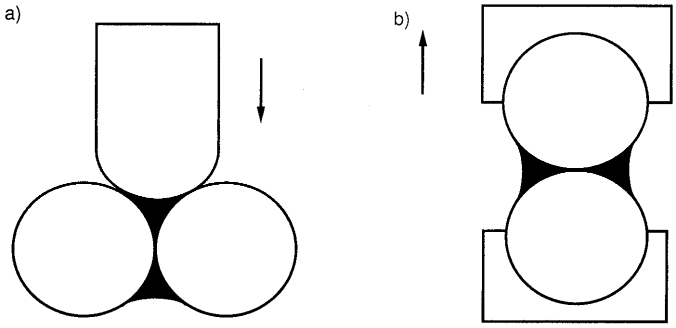

Fig. 3. Schematic Diagram of the Apparatus for Measuring the Ball Separation Test

a) Vertical separation method. b) Tensile separation method.

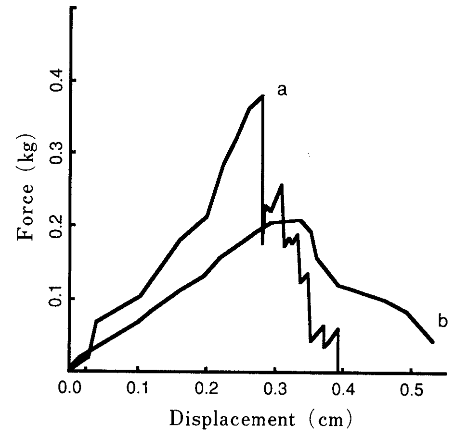

Fig. 4. Typical Record of Ball Separation Test

Binder solution: 10% (w/w) HPC-EFP.

Table II shows the physicochemical characteristics of a 10% (w/w) aqueous solution of each binder.

Granulation Eight hundred grams of glass beads were mixed with a given amount (40, 80, 120 or 160 ml) of 10% (w/w) binder aqueous solution. The mixture was kneaded at 200 rpm for 10 min using a kneader (ERWEKA AR400), and the moist mass was forced through a 1 mm screen by hand. The extruded granules were dried for 3 h at 60 °C.

Preparation of Molded Tablet The moist mass was forced into the mold (20 mm in diameter and 5 mm in depth) by hand, when no special compression force was applied, and the excess was scraped with a metal spatula. The mold plate with the moist mass was dried for 12 h at 60 °C, and a solidified tablet was taken out of the mold.

Measurements of Strength of Agglomerates 1) Granules: The crushing load, P_g, of more than 30 granules ranging in size from 0.71 to 1.0 mm was measured using the apparatus reported previously.[1] When plural peaks or notches were observed in the record, the last and highest one was chosen as the representative value. The strength of granules, T_g, was calculated from Eq. 2 proposed by Kuno *et al.*[5]

$$T_g = P_g/A \tag{2}$$

where A is the cross sectional area of a granule.

2) Molded Tablets: A regular triangular prism, 1 cm in side length and 3 cm in height, was vertically attached to the crosshead of the material testing instrument, AutoGraph-5000D (Shimadzu Co., Ltd.) (Fig. 1). A molded tablet was horizontally placed on the plate with a distance between fulcrums of 1.5 cm, and the bending test was carried out at a bending rate of 1 mm/min. A typical record is shown in Fig. 2. The strength of the tablet, T_t, was calculated from the breaking load, P_t, by Eq. 3 used by David *et al.*[6]

$$T_t = 3P_tH_0/4DL^2 \tag{3}$$

where H_0[7] is the distance between fulcrums, D is the tablet diameter and

L is the tablet thickness. Each sample was measured five times to obtain the mean ± S.D.

3) Ball Separation Test: Two balls, 10.45 mm in diameter and already in contact, were immersed into a binder solution. After being removed from the solution, they were dried. A plunger, shown in Fig. 3a, was vertically attached to the crosshead of AutoGraph-5000D, and the sample was separated by moving the plunger downwards at a rate of 1.0 mm/min. Figure 3 also shows an ordinary tensile separation method (Fig. 3b). Figure 4 shows a typical displacement-load record obtained by above two methods. The former method was employed for subsequent experiments, since it showed a clearer cut-off and better reproducibility than latter one. The strength, σ_B, was estimated from the separating force, P_B, using Eq. 4.

$$\sigma_B = 4P_B \tan\theta / A \qquad (4)$$

where A is the cross sectional area of the binder remaining after separation of the balls. Each sample was measured twenty times.

Results and Discussion

Untreated Glass Beads/Binder System Figures 5a and b show the variation in strength (±S.D.) of the agglomerates, T_g, for granules, and T_t for molded tablets prepared by untreated glass beads with the volume of binder solution added, V_b, in each system. In every case, the strength of agglomerates markedly increased by incresing the volume of binder solution *i.e.*, the amount of binder. Concerning the type of binder, the rank order of strength was found to be PVP K-90 > PVP K-30 > HPC (-LFP, -EFP) > Na-CMC > HPMC (TC-5S) > HPMC (TC-5E) > lactose. This result approximately coincided with earlier work where a mixture of cornstarch and lactose was used. Namely, the wettability of untreated glass beads by the polymer binder solution is considered to be one of the most important factors in determining the strength of the agglomerates. From the viewpoint of the scattering of data, the bending test of the molded tablet is superior to the granule crushing method.

It has been considered that the strength of an agglomerate is related to the physical properties of both the powdered material (substrate) and the binder used. Krycer *et al.*[2] described that three significant determinants were the wetting of the substrate by the binder, binder/substrate adhesion and binder cohesion. Rowe[8] showed that these variables could be calculated using literature values of surface free energies of various substrates and binders, and proposed that it is possible to predict trends in agglomerate strengths. Unfortunately, owing to insufficient experimental data, this proposal is not quite yet proved. Rowe[8a] also stated that for high polarity substrates, HPMC would be better than PVP as a binder. However, it was found by Cutt *et al.*[4] that glass ballotini (a high polarity substance) granules prepared from PVP were stronger and less friable than those from HPMC. The present result here, as well as in the previous work,[1] supports the data shown by Cutt *et al.* This may be related to the fact that the work of immersion of PVP is greater than that of HPMC (see Table II).

On the other hand, Ritala *et al.*[9] described that the high surface tension of PVP solution caused the moist agglomerates to have low porosity, thus increasing the granule strength. In the present study, porosity, ε, of granules and molded tablets was in the range of 0.32—0.58 and 0.37—0.45, respectively. In order to eliminate the influence of the agglomerate structure on agglomerate strength and to make it possible to numerically compare the strengths of the granules and molded tablets with those obtained by big ball separation test, the following quantitative approach based on the work of Rumpf *et al.*[10] was attempted.

Presuming that the particles forming an agglomerate are monosized and spherical, Rumpf *et al.* proposed that the relation between the strength of an agglomerate, T, and the binding force at one contact point of particles in an agglomerate, H, is expressed by Eq. 5,

$$T = [(1-\varepsilon)k/(\pi d_p^2)]H \qquad (5)$$

where d_p is the diameter of the particle, ε the porosity of the agglomerate and k the average coordination number. In this theory, the assumption that all the particle contacts separate simultaneously across the failure surface is a prerequisite. The fracture curve shown in Fig. 2 may support this assumption.

Two possible mechanisms may be involved in the failure of the present systems, one of which is the fracture within the binder bridge (cohesive failure), the other being the failure at the binder/particle interface (adhesive failure). Then, H in Eq. 5 corresponds to the strength of the polymer bridge in the former case, and the interfacial bond strength

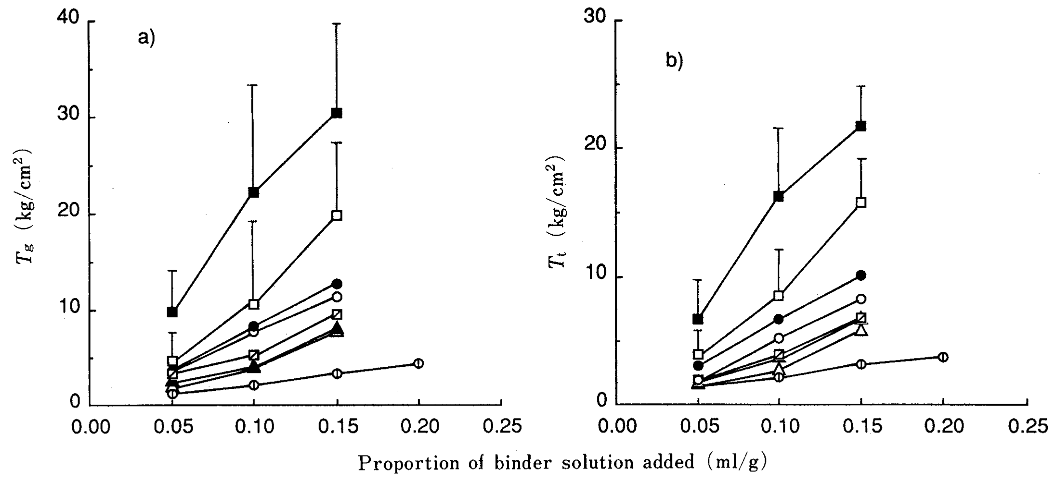

Fig. 5. T_g and T_t as a Function of Binder Solution Added (ml/g Powder)

Concentration of binding solution: 10% (w/w) for polymers, saturated solution for lactose. Sample: untreated glass beads. Key: □, PVP K-30; ■, PVP K-90; ○, HPC-EFP; ●, HPC-LFP; △, HPMC TC-5E; ▲, HPMC TC-5S; ⊠, Na-CMC; ⦶, Lactose.

in the latter.

If the failure between two particles is assumed to occur within a solid binder bridge, H can be given by Eq. 6.

$$H=S\sigma \tag{6}$$

where S is the cross sectional area of a solid bridge, and σ the intrinsic strength of the binder deposited.

From the simple model shown in Fig. 6, Onoda[11] proposed that the volume of the binder existing in the neck between two particles, v, is givin by Eq. 7, provided that the radius of the narrowest portion, r, is sufficiently larger than h.

$$v \fallingdotseq \pi r^4/d_p \tag{7}$$

From Eq. 7, the cross-sectional area, S is given by

$$S=\pi r^2=1.77(d_p v)^{1/2} \tag{8}$$

If V_b represents the total volume of a binder in an agglomerate, then

$$v=V_b/n \tag{9}$$

where n is the total number of necks, which is calculated by Eq. 10

$$n=(6/\pi)(V_p/d_p^3)(k/2) \tag{10}$$

where V_p is the total volume of particles in the agglomerate.

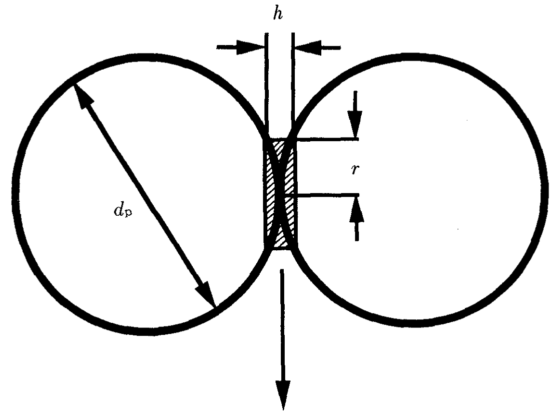

Fig. 6. Approximate Bond Geometry for Two Mono-Sized Spheres

Since k is the average number of touching neighbors around each particle and its value approximately equals π/ε according to Smith *et al.*,[12] v is finally expressed by

$$v=(\varepsilon/3)(V_b/V_p)d_p^3=(\varepsilon/3)(\rho_p/\rho_b)(W_b/W_p)d_p^3 \tag{11}$$

where ρ_p and ρ_b are the density of particles and binder, and W_p and W_b are the weight of particles and binder, respectively.

A combination of Eqs. 5, 6, 8 and 11, yields

$$T=1.02[(1-\varepsilon)/\varepsilon^{1/2}](\rho_p/\rho_b)^{1/2}(W_b/W_p)^{1/2}\sigma \tag{12}$$

Equation 12 can be transformed into Eq. 13 when W_p is assumed to be 1 g.

$$Y=0.98[(\varepsilon^{1/2})/(1-\varepsilon)](\rho_b/\rho_p)^{1/2}\cdot T=W_b^{1/2}\sigma \tag{13}$$

Using the obtained values of T_g and T_t for untreated glass beads, Y_g and Y_t were plotted against $W_b^{1/2}$. The linear lines shown in Figs. 7a and b were obtained. However, these lines do not coincide with the origin. Thus, the values of W_b^* were estimated from their interecepts on the abscissa. These values were considered to correspond to the amount of binder not deposited at the necks, *i.e.*, that which adhered to the surface of particles other than at the necks. When data were plotted taking the $(W_b-W_b^*)^{1/2}$ on the abscissa, Figs. 8a and b were obtained. The σ_g and σ_t calculated from the slopes are shown in Table III. Both values were in accord with each other and the rank order in the type of binder was similar to that of the agglomerate strength.

In the above formulation, it was assumed that the cohesive failure of an agglomerate occurred within the binder bridge. In case of the adhesive failure, S in Eq. 6 signifies the contact area between binder and particle. If this area is considered to be approximately equal to the cross sectional area of the binder neck according to the model shown in Fig. 6, Eq. 13 can also be applicable, while σ represents the interfacial bond strength.

It is difficult to determine which type of failure occurs. Cutt *et al.*[4] examined the agglomerate failure using a scanning electron microscope (SEM) and concluded that glass granules formed with PVP undergo cohesive failure and those formed with HPMC undergo adhesive failure. On the other hand, Millier *et al.*[13] said that examination of the agglomerate failure using a SEM shows that adhesive

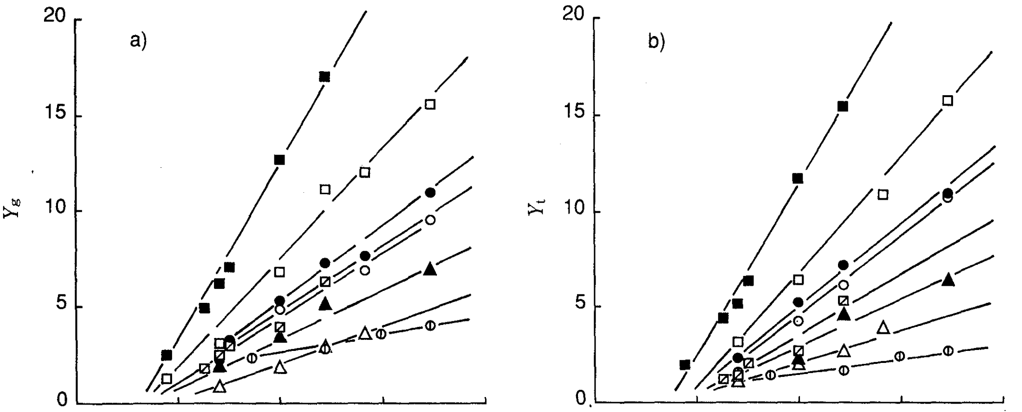

Fig. 7. Y_g and Y_t Values as a Function of Square Root of Weight Content of Binder, $W_b^{0.5}$

Sample: untreated glass beads. Key: □, PVP K-30; ■, PVP K-90; ○, HPC-EFP; ●, HPC-LFP; △, HPMC TC-5E; ▲, HPMC TC-5S; ▨, Na-CMC; ⦶, lactose.

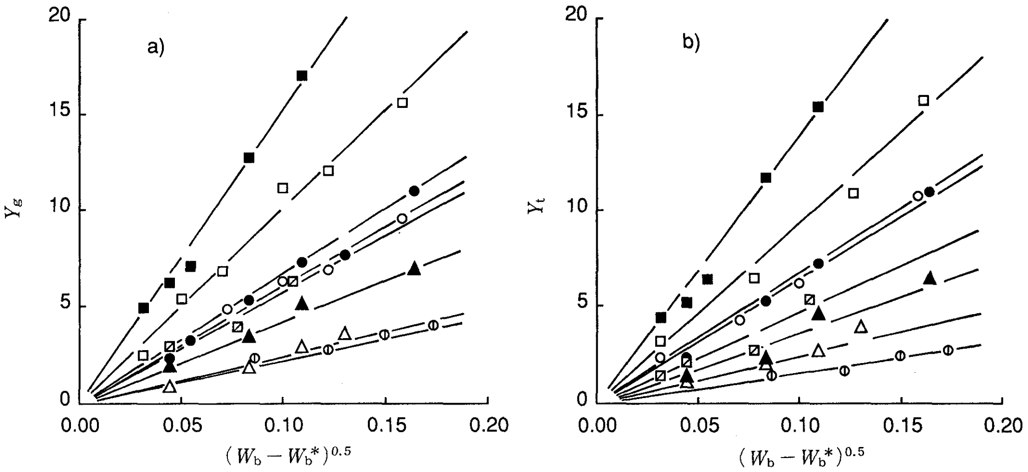

Fig. 8. Y_g and Y_t Values as a Function of $(W_b - W_b^*)^{0.5}$

Sample: untreated glass beads. Key: □, PVP K-30; ■, PVP K-90; ○, HPC-EFP; ●, HPC-LFP; △, HPMC TC-5E; ▲, HPMC TC-5S; ⧄, Na-CMC; ⦶: Lactose.

Table III. Adhesion or Cohesion Strengths between Particles Obtained by the Fracture Tests for Granules and Molded Tablets and the Separation Tests for Big Glass Balls

Binder	Untreated glass beads			TMS treated glass beads		
	Granule, σ_g (kg·cm^{-2})	Tablet, σ_t (kg·cm^{-2})	Ball, σ_B (kg·cm^{-2})	Granule, σ_g (kg·cm^{-2})	Tablet, σ_t (kg·cm^{-2})	Ball, σ_B (kg·cm^{-2})
PVP(K-30)	96.0	99.2	91.4±44.2[a] (18)[b]	37.6	54.4	23.1±11.9 (18)
PVP(K-90)	161.8	150.9	156.6±27.9 (16)	51.6	61.3	28.4±12.9 (18)
HPC-EFP	50.6	63.0	60.5±11.2 (18)	33.5	46.9	58.2±20.0 (16)
HPC-LFP	66.4	66.0	64.6±16.3 (17)	45.8	45.9	53.4±20.8 (17)
HPMC(TC-5E)	33.8	31.3	32.3±15.2 (18)	26.8	28.9	29.8±18.3 (17)
HPMC(TC-5S)	41.6	41.2	47.0±28.1 (18)	35.7	37.9	32.7±22.5 (19)
Na-CMC	49.0	48.3	48.4±19.2 (15)	34.2	39.3	—
Lactose	19.7	15.7	—	7.4	12.8	—

a) Mean value±S.D. *b*) Sample numbers used for calculation are in parentheses.

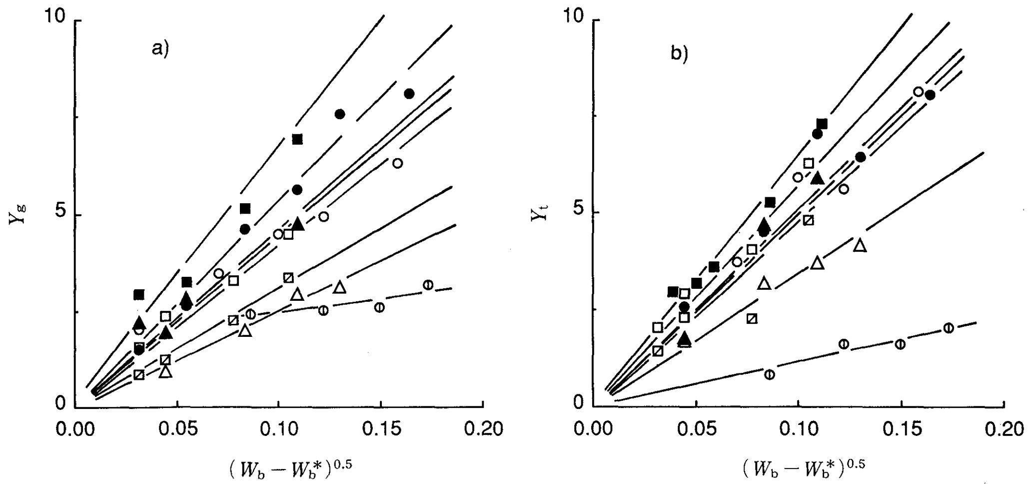

Fig. 9. Y_g and Y_t Values as a Function of $(W_b - W_b^*)^{0.5}$

Sample: TMCS-treated glass beads. Key: □, PVP K-30; ■, PVP K-90; ○, HPC-EFP; ●, HPC-LFP; △, HPMC TC-5E; ▲, HPMC TC-5S; ⧄, Na-CMC; ⦶, Lactose.

failure predominated in the glass/PVP system. Rowe *et al.*[8b] suggested the presence of both types of failure in glass/PVP and glass/HPMC systems from the values of the interaction parameter, ϕ, calculated by the literature values of the surface free energies. In our present work, while it seemed that both types of failure occurred in all the untreated glass/binder systems, cohesive failure appeared to be predominant for the agglomerates formed with PVP as a result of the examination with a SEM and optical metallograph. Thus, for the PVP binder, the binder/particle adhesion is thought to be superior to the binder cohesion.

The effect of the degree of polymerization (DP) was clearly observed in the PVP binder system. It was found that an increase in the DP of the polymer binder increased the σ

value. This may be because the higher DP, the greater binder cohesion.

In Table III, the strengths obtained by the big ball separation test are shown as σ_B. The tests were performed 20 times in every system. It was found, however, that abnormal separation, in which no peak of load was observed, sometimes occurred. Using the data of normal separation, the number of which is indicated in parentheses, the mean separation strengths σ_B and S.D. were calculated.

In a rough estimate, the values of σ_B were in fair agreement with σ_g and σ_t values calculated by Eq. 13 based on Rumpf's theory.

Treated Glass Beads/Binder System Figures 9a and b are the results of the surface treated glass beads/binder systems. Through the same procedure as untreated glass bead systems, the strengths between particles are obtained, which are also shown in Table III.

It is evident, in all the systems, that the agglomerates prepared from treated glass are weaker in strength than those from untreated glass. This fact is partly consistent with the data reported by Cutt *et al.*,[4] and with the predictions by Rowe *et al.*[8b] The decrease in work of immersion may account for the results. In addition, it seemed that the effect of the type of binder on the strength of agglomerates became weaker, compared with the untreated glass bead systems. For example, there was no great difference in strength between agglomerates prepared with HPC and those prepared with PVP. HPC has an affinity for both hydrophilic and hydrophobic materials. Thus, HPC is considered to be a favorable binder for the granulation of a variety of powders.

Conclusion

The strength of an agglomerate is related to the physical properties of both the powdered material and the binder. The concrete discriptions are as follows.

1) For the polymer binder/untreated glass bead systems, the wettability of the testing powder by the binder solution is one of the most important factors determining agglomerate strength. A polymer solution which has high surface tension and a low contact angle for an untreated substrate such as PVP solution makes a strong agglomerate. The effect of the cohesive property of a binder was observed in PVP binder systems. The agglomerate strength for the PVP K-90 binder system was greater than that for the PVP K-30 binder system. The binder cohesion increases with an increasing degree of polymerization.

2) As a whole, the agglomerates prepared from treated glass beads whose surface is hydrophobic show less strength than the untreated beads. The HPC solution, which has low surface tension (surface active property) and a low contact angle for an untreated substrate, makes considerably strong agglomerates. On the other hand, the strength of agglomerates prepared by PVP solution decreased remarkably compared to the untreated glass bead systems. These finding can also be interpreted on the basis of the wetting of the surface treated substrate.

3) The numerical values of three kinds of σ(σ_g, σ_t and σ_B), which are the bond strength between the two particles, were in fairly good agreement for the polymer binder/untreated glass systems.

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