Chem. Pharm. Bull. 43(3) 488—492 (1995) Vol. 43, No. 3

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

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Received September 5, 1994; accepted November 18, 1994

The effect of the physicochemical properties of binders on the strength of granules prepared by the wet method was investigated using hydrophobic and hydrophilic powders with various polymer binders. A crushing test of granules and the amount of fine granules generated during a sieving test were carried out in order to estimate the strength of the granules. In all the powder/binder systems, the surface polarities of both powders and binders, as well as the degree of polymerization of a binder, are important factors in determining the strength of granules. That is, binders and powders whose polarities are similar are capable of producing strong granules. In some systems, the strength of granules increased with the degree of polymerization of the polymer binders.

Key words granulation; polymer binder; granule strength; surface polarity; polymerizaton degree

In our previous studies, a lactose/cornstarch mixture[1] and glass beads[2] were granulated by the extruding method using various polymer binder solutions. It was found that granule strength was greatly affected by the quantity and type of polymer binder.

The influence of binder solution characteristics on the strength of granules has been studied by several investigators.[3-6] However, predicting the optimum binder selection for granulation is still difficult because the types of testing powder and binders reported have been limited and vary with the researcher.

The object of this study was to predict the optimum binder for granulation of a given powder. Powders and binders with a variety of surface properties are used for systematically carrying out. The effect of the degree of polymerization of a polymer binder on granule strength was examined for PVP and HPMC.

Experimental

Materials The sample powders used were M-5011 (*d*-2-[4-(3-metyl-2-thienyl)phenyl]propionic acid: $C_{14}H_{14}O_2S$, Maruho Co., Ltd.), which was developed as a nonsteroidal antiinflammatory antipyretic analgesic, ethenzamide (Yoshitomi Co., Ltd.), aspirin (Mitsui-Toatsu Chemical Co., Ltd.), aluminum oxide (α-alumina: Fujimi Co., Ltd.), phenacetin (Kenei-Seiyaku Co.,Ltd.) and microcrystalline cellulose (Avicel PH101: Asahikasei Co., Ltd.). Their properties are shown in Table I. The polymer binders used were hydroxypropylmethylcellulose (HPMC TC-5E, TC-5S: Shin-Etsu Chemical Co., Ltd.), hydroxypropylcellulose (HPC-EFP: Shin-Etsu Chemical Co., Ltd.) and polyvinylpyrrolidone (PVP K-30, K-90: BASF. Co., Ltd.). Table II shows the physicochemical and molecular characteristics of each binder and 10% (w/w) aqueous polymer solutions used in this study.

Determination of the Physical Properties of Binders The apparent viscosity, η, of a 10% (w/w) aqueous solution of each binder was determined using a rotation viscometer (Vistron VS, Seiki Co., Ltd.) at 20 °C. The surface tension, γ_L, of a 10% (w/w) aqueous solution of each binder was measured by the capillary rise method at 20 °C using a glass tube with a radius, r, of 0.285 mm determined by using pure water. γ_L was calculated from the following equation:

$$\gamma_L = (1/2) r h \rho g \quad (1)$$

where h is the height of the liquid in the tube, ρ is the density of the liquid, and g is the acceleration of gravity.

Granulation Eight hundred grams of sample powder were mixed with a given amount (20—720 ml) of 10% (w/w) binder aqueous solution. The mixture was kneaded at 200 rpm for 10 min using a kneader

TABLE I. Sample Powders Used

Powdered material	Mean particle diameter[a] d_p (μm)	Density[b] ρ (kg dm^{-3})	Bulk density[c] ρ_b (kg dm^{-3})
M-5011	11.1	1.22	0.182
Phenacetin	52.3	1.31	0.468
Ethenzamide	7.1	1.35	0.432
Aspirin	26.7	1.47	0.398
Microcrystalline cellulose	27.3	1.56	0.298
Aluminum oxide (α-alumina)	68.8	3.97	2.002

a) Heywood diameter determined by an image analyzer (LUZEX 500, Nireco, Ltd.). *b*) Determined by a Shimadzu-Micromeritics helium-air pycnometer. *c*) Determined by a Hosokawa Micron laboratory powder tester.

TABLE II. Binding Agents Used

Polymer binder	Degree of substitution or content of functional group[a]		Mean molecular weight, M_w[a]	Density ρ[b] (kg dm^{-3})	Apparent viscosity of 10% aq. soln., η, (10^{-3} Pa s)	Surface tension of 10% aq. soln., γ_L, (mN m^{-1})
HPMC (TC-5E)	$-OC_3H_6OH$	9.3%	14000	1.35	58	47.3
	$-OCH_3$	29.0%				
HPMC (TC-5S)	$-OC_3H_6OH$	8.8%	64800	1.34	1828	46.7
	$-OCH_3$	28.7%				
HPC-EFP	$-OC_3H_6OH$	63.6%	56000	1.16	188	41.9
PVP K-30		—	45000	1.14	8	67.9
PVP K-90		—	1100000	1.15	220	67.2

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

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(ERWEKA AR400), and the moist mass was forced through a 1 mm screen by hand. The extruded granules, except M-5011, were dried for 3 h at 60 °C, and those of M-5011, which had a low melting point (mp 62.0—65.0 °C), were dried for 12 h at 45 °C.

Measurement of Average Granule Particle Size and Amount of Fine Powder The average particle size and size distribution of the granules were measured by sieve analysis. 7.5 g of granules were placed on a net of 10 sieves of JP XII (0.075—1.180 mm) and shaken for 3 min, this duration being sufficient for particle separation without breaking the granules. The fraction remaining on each sieve was weighed. The cumulative percentage oversize was plotted against sieve size and the median diameter was determined. The percentage of the amount of fine (<0.106 mm) granule fraction to total amount was also calculated.

Crushing Tests for Granules and Calculation of Adhesive or Cohesive Strength between Particles The crushing load, P_g, of granules ranging in size from 0.710 to 1.00 mm was measured using the apparatus[1] previously reported. The strength of a granule, T_g, was calculated from Eq. 2, proposed by Kuno *et al.*[7]

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

where A is the cross-sectional area of a granule.

In order to compare granule strength for all powder/binder systems, a quantitative approach was used in the manner of previous paper.[2] Rumpf *et al.*[8] proposed that the relation between the fracture strength of a granule, T_g, and the binding force at a contact point of two particles in a granule, H, is expressed by Eq. 3

$$T_g = [(1-\varepsilon)k/(\pi d_p^2)]H \tag{3}$$

where d_p is the diameter of the particle, ε the porosity of the granule and k the average coordination number. H can be given by the product of the intrinsic (cohesive) strength of the binder deposited or the adhesive strength between particles and binder, σ_g, and the cross sectional area of a binder bridge or the contact area between a particle and binder, S.

$$H = S\sigma_g \tag{4}$$

Based on some simplifying assumptions, S is given by

$$S = 1.77(d_p v)^{1/2} \tag{5}$$

where v is the volume of binder existing in the neck between two particles. Using an approximation to the coordination number, k, v is finally expressed by

$$v = (\varepsilon/3)(\rho_p/\rho_b)(W_b/W_p)d_p^3 \tag{6}$$

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

A combination of 3, 4, 5 and 6 yields

$$T_g = 1.02[(1-\varepsilon)/\varepsilon^{1/2}](\rho_p/\rho_b)(W_b/W_p)^{1/2}\cdot\sigma_g \tag{7}$$

Equation 7 can be transformed into Eq. 8, when W_p is assumed to be 1 g.

$$Y_g = 0.98[\varepsilon^{1/2}/(1-\varepsilon)](\rho_b/\rho_p)^{1/2}\cdot T_g = W_b^{1/2}\cdot\sigma_g \tag{8}$$

When Y_g is proportional to $W_b^{1/2}$, σ_g can be given by the slope of a Y_g *vs.* $W_b^{1/2}$ plot. However, for some powder/binder systems, the linear lines obtained from plots of Y_g *vs.* $W_b^{1/2}$ do not coincide with the origin. In these cases, using W_b^*, which is considered to be the amount of binder not deposited at the necks, estimated from the intercept on the abscissa, Y_g were plotted against $(W_b - W_b^*)^{1/2}$.

$$Y_g = (W_b - W_b^*)^{1/2}\cdot\sigma_g \tag{9}$$

Thus, σ_g was calculated from the slope of the linear line that coincided with the origin.

Solid Sample Preparation For most powdered materials, solid samples for contact angle measurement were made using the compression method. The powders were compressed using a universal compressing machine, Autograph AG-5000D (Shimadzu Co., Ltd.), at a pressure of 1000 kg/cm^2. α-Alumina was received as a plate (Kyosella Co., Ltd.). For polymers, thin films were used. Each polymer was dissolved in ethanol at a concentration of 20%. The solvent was then evaporated at room temparature.

Determination of Surface Polarity The contact angle, θ, was determined by the photographic recording method. Small droplets (20 μl) of water and methylene iodide were placed on the solid surface using a microliter syringe. θ was measured more than 10 times for each material. According to Wu,[9] the interfacial free energy between a liquid and a solid (γ_{SL}) can be estimated by knowing the individual surface free energies (γ_L and γ_S) and nonpolar and polar interaction terms (ϕ^d and ϕ^p). *i.e.*,

$$\gamma_{SL} = \gamma_S + \gamma_L - 2\phi^d - 2\phi^p \tag{10}$$

$$\phi^d = 2\gamma_S^d\cdot\gamma_L^d/(\gamma_S^d + \gamma_L^d) \tag{11}$$

$$\phi^p = 2\gamma_S^p\cdot\gamma_L^p/(\gamma_S^p + \gamma_L^p) \tag{12}$$

where γ^d and γ^p are the nonpolar and polar components of the surface free energy, respectively. The surface free energy of phase i, γ_i, is given by a sum of γ_i^d and γ_i^p. The relation among the contact angle θ, γ_S, γ_L and γ_{SL} is expressed by the Young–Dupré equation:

$$\gamma_S = \gamma_L\cos\theta + \gamma_{SL} \tag{13}$$

A combination of Eqs. 10, 11, 12, and 13, yields

$$(b+c+a)\gamma_S^d\cdot\gamma_S^p + c(b-a)\gamma_S^d + b(c-a)\gamma_S^p - abc = 0 \tag{14}$$

where $a = \gamma_L/4(1+\cos\theta)$, $b = \gamma_L^d$, $c = \gamma_L^p$. The nonpolar and polar components of the two testing liquids (water and methylene iodide) are known.[9] Thus, if the contact angles of the two testing liquids on a solid are measured, two simultaneous equations can be set up to solve the two unknowns (γ_S^d and γ_S^p).

The surface polarity index, P_0, is determined by the following equation.

$$P_0 = \frac{\gamma_S^p}{\gamma_S}\times 100 \tag{15}$$

Results and Discussion

Generation of Fine Powder Particle size distribution of the granules was greatly influenced by liquid saturation.[10-14] With increasing the quantity of binder solution, the mean diameter of dried granules increased and the percentage of the fine powder generated during granulation and sieving processes decreased. However, for most powders, no distinct effect of the type of polymer binder on the generation of fine powders was observed. Special cases were α-alumina and phenacetin, typical hydrophylic and hydrophobic powders. Figures 1a and b show a variation in percentage of fine powders generated with the proportion of each binder solution added for the two powders. In α-alumina, PVPs appear to make hard granules compared to HPMCs. On the other hand, the opposite was noted for phenacetin.

Strength of Granule Figures 2a and b show variations in the strength (±S.D.) of granules, T_g, for typical granules prepared with α-alumina and phenacetin with the volume of binder solution added, V_b. In all cases, the strength of granules markedly increased with the volume of binder solution.

In Figs. 3a and b, Y_g in Eq. 9 *vs.* $(W_b - W_b^*)^{1/2}$ plots for α-alumina and phenacetin are shown. All the σ_g values are listed in Table III.

Considering the results for σ_g, the rank order of polymer binders for granule strength is shown in Table IV. In this table, the previous results for a lactose/cornstarch mixture[1] (70/30), glass beads and trimethylsilylated (TMS treated) glass beads[2] were mentioned. For hydrophobic powders such as M-5011, phenacetin and ethenzamide, granule strength was great in the HPMC binder system. For hydrophilic powders such as α-allumina, lactose/cornstarch mixture and untreated glass beads, PVP produced hard granules. For aspirin, microcrystalline cellulose (MCC) and TMS treated glass beads,

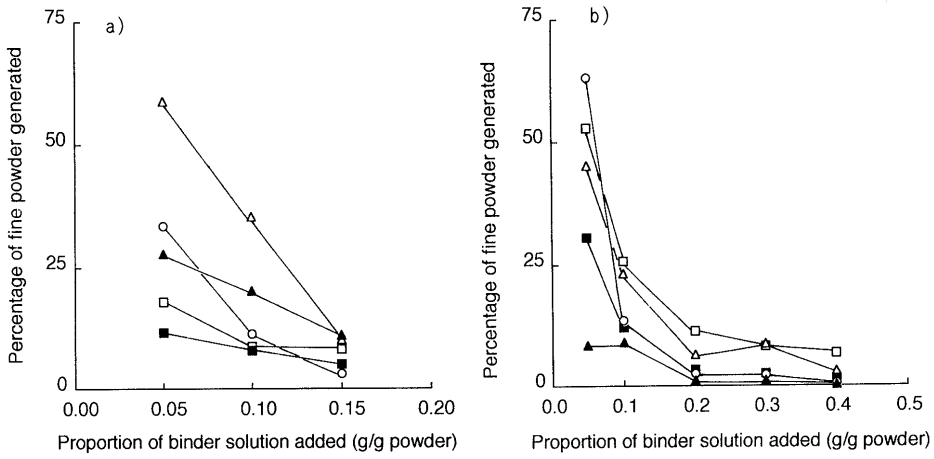

Fig. 1. Percentage of Fine Powder Generated as a Function of Binder Solution Added (g/g Powder)
a) α-Alumina. b) Phenacetin. Key: □, PVP K-30; ■, PVP K-90; ○, HPC-EFP; △, HPMC TC-5E; ▲, HPMC TC-5S.

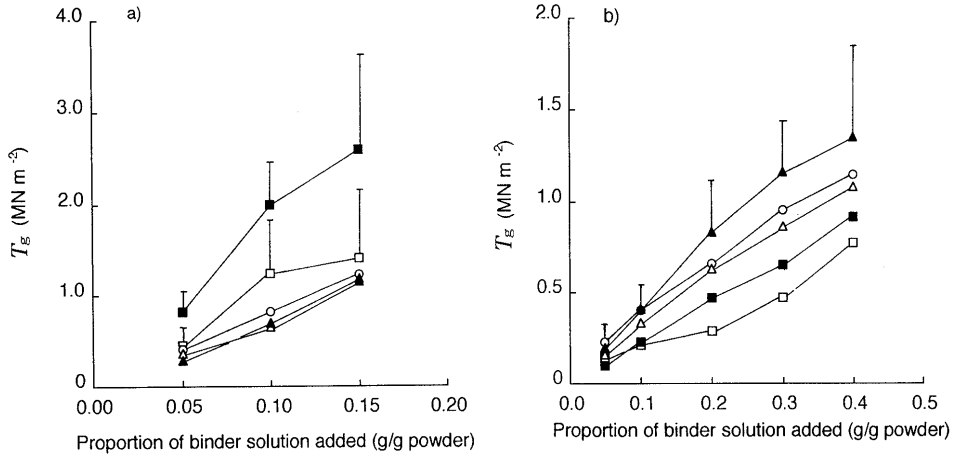

Fig. 2. T_g as a Function of Binder Solution Added (g/g Powder) Concentration of Binder Solution: 10% (w/w)
a) α-Alumina. b) Phenacetin. Key: □, PVP K-30; ■, PVP K-90; ○, HPC-EFP; △, HPMC TC-5E; ▲, HPMC TC-5S.

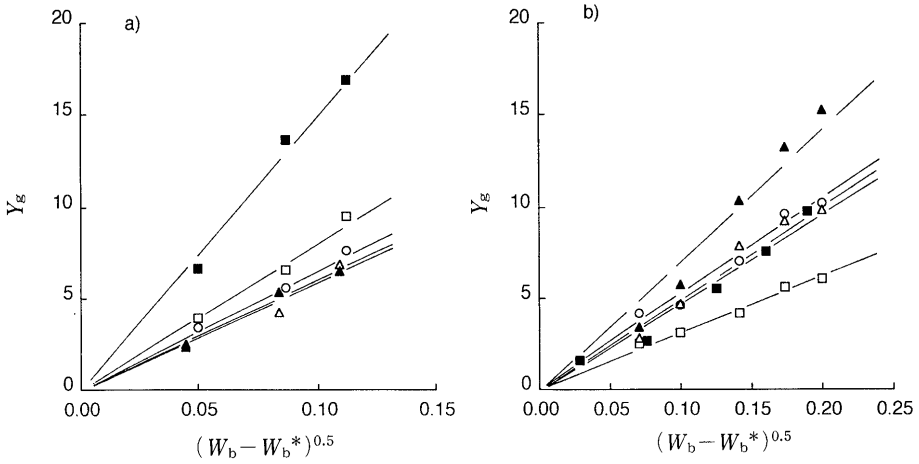

Fig. 3. Y_g as a Function of Square Root of Effective Weight Content of Binder, $(W_b - W_b^*)^{0.5}$
a) α-Alumina. b) Phenacetin. Key: □, PVP K-30; ■, PVP K-90; ○, HPC-EFP; △, HPMC TC-5E, ▲, HPMC TC-5S.

the effects of the type of binder were indistinct. It would thus appear that granule strength is correlated with the surface properties of powders and binders.

Surface Polarity of Powder and Polymer In order to characterize the surfaces of powders and polymer binders, the concept of "surface polarity" was introduced. Table V shows the contact angles of water and methylene iodide on various substrates. Using these values, the surface free energy per square centimeter of the solid γ_S, dispersion (nonpolar) component γ_S^d and polar component γ_S^p were obtained for each material. These are listed in Table V together with the index of polarity (P_0). Low P_0^S (polarity

TABLE III. Adhesion or Cohesion Strengths between Powder Particles (σ_g, MN m^{-2}) Obtained by the Fracture Tests of Granules

Powdered material	HPC-EFP	PVP K-30	PVP K-90	HPMC TC-5E	HPMC TC-5S
M-5011	6.1	6.5	6.1	9.6	10.1
Phenacetin	5.2	2.9	5.1	5.7	8.7
Ethenzamide	6.9	5.9	7.1	7.2	11.2
TMS treated glass beads[2)]	3.4	3.8	5.2	2.7	3.6
Aspirin	8.8	8.4	9.5	7.8	9.3
Microcrystalline cellulose	10.9	5.6	14.3	8.4	10.3
Lactose/cornstarch mixture (70/30[1)])	7.3	7.5	13.0	5.0	3.0
Aluminum oxide	6.9	8.9	16.7	6.6	6.6
Glass beads[2)]	5.1	9.6	16.2	3.4	4.2

TABLE IV. Rank Order of Polymer Binder for Granules Strength

Powdered material	Polymer binder
M-5011	HPMC TC-5S, HPMC TC-5E > PVP K-30, HPC-EFP, PVP K-90
Phenacetin	HPMC TC-5S > HPMC TC-5E, HPC-EFP, PVP K-90 > PVP K-30
Ethenzamide	HPMC TC-5S > HPMC TC-5E, PVP K-90, HPC-EFP > PVP K-30
TMS treated glass beads[2)]	PVP K-90 > PVP K-30, HPMC TC-5S, HPC-EFP > HPMC TC-5E
Aspirin	PVP K-90, HPMC TC-5S, HPC-EFP, PVP K-30, HPMC TC-5E
Microcrystalline cellulose	PVP K-90 > HPC-EFP, HPMC TC-5S, HPMC TC-5E > PVP K-30
Lactose/cornstarch mixture[1)]	PVP K-90 > PVP K-30, HPC-EFP > HPMC TC-5E > HPMC TC-5S
Aluminum oxide	PVP K-90 > PVP K-30 > HPC-EFP, HPMC TC-5S, HPMC TC-5E
Glass beads[2)]	PVP K-90 > PVP K-30 > HPC-EFP > HPMC TC-5S, HPMC TC-5E

TABLE V. Contact Angles and Surface Free Energies for Various Solids Using Water and Methylene Iodide

Material	Type of solid sample[a)]	Contact angle[b)] (°)		Surface free energy (mN·m^{-1})			Polarity (%)
		Water	Methylene iodide	γ_s^d	γ_s^p	γ_s	P_0
M-5011	T	69.8±3.7	17.2±2.1[c)]	48.2	10.4	58.6	18
Phenacetin	T	69.9±3.5	23.1±1.5[c)]	46.5	10.6	57.1	19
Ethenzamide	T	66.8±1.9	20.3±3.0[c)]	49.4	11.8	59.2	20
TMS treated glass beads[2)]	P	74.2±2.6	66.9±2.6	26.9	13.3	40.2	33
Aspirin	T	45.4±3.6	33.7±2.9	42.6	22.9	65.5	35
Microcrystalline cellulose	T	35.6±2.8	22.4±3.1[c)]	46.9	26.6	73.5	36
Lactose/cornstarch mixture[1)]	T	27.8±2.3[c)]	21.2±1.2[c)]	47.2	29.7	76.9	39
Aluminum oxide	P	39.1±2.3	47.2±4.2	36.5	28.0	64.5	43
Glass beads[2)]	P	29.6±1.8	43.9±3.3	38.0	31.8	69.8	46
HPMC TC-5E	F	61.2±2.7	40.7±3.1	39.5	16.0	55.5	29
HPMC TC-5S	F	65.8±3.8	42.5±2.2	38.7	14.0	52.7	27
HPC-EFP	F	55.7±3.3	40.9±3.2	39.4	18.7	58.1	32
PVP K-30	F	47.3±2.7	41.6±3.1	39.1	23.0	62.1	37
PVP K-90	F	45.3±2.0	40.1±2.4	39.8	23.8	63.6	37

a) T, tablet; P, plate; F, film. *b*) Mean value±S.D. calculated from more than 10 data. *c*) Estimated by extrapolation to the time zero.

index of powder) was shown for M-5011, phenacetin and ethenzamide. α-Alumina, glass beads and lactose/cornstarch showed high P_0^S. Aspirin, MCC and TMS treated glass beads gave intermediate values. In regard to polymer binders, the order of P_0^B (polarity index of polymer binder) was found to be PVP > HPC > HPMC.

In choosing a binder for granulation, Lowe[15)] found that the thermodynamics of cohesion and adhesion based on the knowledge of either solubility parameters or surface free energies on both the powders and binders should be considered. He stated that the actual experimental measurements of paracetamol granule friability and tablet strength reported by Krycer *et al.*[3)] can adequately be explained. Zajic and Buckton[6)] examined the correlation between granule friability and surface free energy for MCC. The hypothesis of this study is based on the polarities of powders and polymer binders. That is, the surface polarity of a powder, P_0^S, and binder, P_0^B, are considered to be very important factors in determining the strength of granules. Figure 4 shows the variation in σ_g against P_0^S/P_0^B. With increasing of the ratio, P_0^S/P_0^B, the σ_g of powders having high P_0^S was reduced; by contrast, σ_g rose for powders having low P_0^S. This means that powders and binders whose polarities are similar are capable of producing strong granules. No significant alternation in σ_g was observed for powders with an intermediate magnitude of P_0^S. Rowe's statement that HPMC would be better than PVP as a binder is consistent with the present results for substances having a low polarity index. However, his estimated values of P_0^B are inconsistent

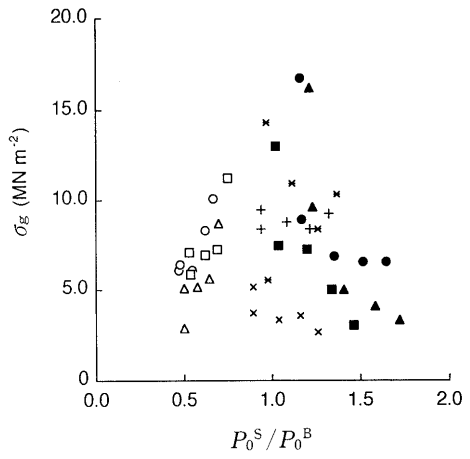

Fig. 4. Relationship between Granule Strength, σ_g, and P_0^S/P_0^B

Key: ○, M-5011; △, phenacetin; □, ethenzamide, ×, TMS treated glass beads, +, aspirin; ■, lactose/cornstarch mixture; ●, aluminum oxide (α-alumina); ▲, glass beads; ⁎, microcrystalline cellulose (MCC).

with ours. Thus, his suggestion is somewhat inadequate, especially for powders having high surface polarities.

Effect of the Degree of Polymerization (D.P.) of a Polymer Binder Special regard should be given to the degree of polymerization of a polymer binder.

There are few reports on the effect of D.P. or molecular weight of polymer binders on granulation. Baykera *et al.*[16] found an order of PVP K-90 > (MC-1000, MC-300, MC-50), PVP K-30 > PVP K-25 for the friability of granules of lactose/cornstarch/Elcema-P50. Georgakopolos *et al.*[17] carried out a friability test on lactose granules prepared by fluidized bed granulation using elastic binding agents (PVP and gelatin), and reported a rank order of gelatin-250 > gelatin-200 > gelatin-150 > gelatin-99 > PVP-40000 > PVP-24000 > PVP-10000 for friability. In the present work, we used two PVPs and HPMCs having different degrees of polymerization. Table III and Fig. 4 show an increase in granule strength which corresponds with the molecular weight of PVP. Misev[18] reported that the mechanical properties of polymers could be expressed as follows:

$$X = X_\infty - \frac{A}{M_n} \tag{16}$$

where X is the property considered (*e.g.* ductility, brittleness, elasticity), X_∞ is its value at a very high molecular weight, A is an experimental constant, and M_n is the average molecular weight number. When the volume of binder deposited at the neck between particles determines granule strength, the mechanical strength of the binder and, consequently, the D.P. of the polymer is an important factor. Zajic *et al.*[6] and Krycer *et al.*[3] do not consider the D. P. of polymer binders. Since they used a considerably low D. P. of PVP, no definite conclusion regarding the order of polymer binders for granule friability could be drawn.

Conclusions

1) In wet granulation, the surface polarity of both powders and polymer binders are important factors in determining the strength of granules. Binders and powders whose surface polarities are similar produce strong granules.

2) In a certain polymer binder, the mechanical properties of the granules are affected by D.P. The strength of granules increases with the D.P. for each polymer.

Acknowledgment We would like to acknowledge the encouragement of Dr. Y. Imazato, the director of Maruho R & D Laboratories.

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