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Influence of Granulating Fluid Properties on Physical Properties of Kneading Mass and Granules

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In the extruding granulation process, granules are prepared by moistening blended powders, sucrose and lactose, and passing the resultant mass through a screen. Many factors affect the properties of granules in this process. The properties of the granulating fluid play an important role, especially when a water/organic solvent system is employed.

In this study, a water/isopropyl alcohol system was chosen and the effects of surface tension, viscosity, and the solubility of sucrose and lactose on the properties of the kneading mass and the granules were examined. Deformation behavior and cohesiveness of the kneading mass were influenced by liquid saturation and surface tension. No remarkable variation was observed in mean granule diameter, except in a pure isopropyl alcohol system. Granule hardness increased with the tensile strength of the kneading mass and the amounts of sucrose and lactose deposited; solubility was a dominant factor.

Keywords lactose; sucrose; surface tension; contact angle; flowability; tensile strength; granule hardness; liquid saturation

Wet granulation methods employ one of two techniques: either the powder and binder are mixed before being added to the binder vehicle, or the binder is dissolved in the vehicle first; a coherent moist mass is then formed. Water is the most widely used binder vehicle for both techniques, both for reasons of environmental protection from pollution and, technically, to avoid organic solvent residues. However, since some drugs are hydrolyzed by water, organic solvents alone, or mixed solutions of an organic solvent and water, are used as binder vehicles. Well and Walker[1] reported on the effects of the properties of a water/alcohol binder vehicle on the physical properties of granules. Terashita *et al.*[2] investigated the effects of a water/alcohol binder solution on granule size and shape. Millili and Schwartz[3] examined the strength of pellets prepared by wet granulation with water/ethanol mixtures. Leuenberger and his colleagues[4] reported the effects of an ethanol/water granulating fluid on the power consumption profiles of the kneading mass.

In the present study, we investigated the effects of water/isopropyl alcohol (IPA) granulating fluids on the tensile strength and flowability of the kneading mass, and examined the relationship between the physical properties of the kneading mass and the mean granule diameter and granule hardness.

Experimental

Materials The powders used to prepare the granules were lactose (JP XII grade DMV 200-mesh) and sucrose (Kanto Kagaku). These were passed through a 125—350-mesh sieve prior to use.

Granulating Fluids The granulating fluids used and their composition are listed in Table I.

Kneading and Granulation Granulation experiments were conducted using an extrusion-type granulator (Tsutsui Rikagaku Kikai Co., Ltd., type KAR-130) after 500 g of powder and 37.5 g of granulating fluid were kneaded in a kneading machine (Erweka LK-5 Type) for 10—20 min and passed through a 1.0 mm aperture sieve. The wet mass was stored at 20 °C and then dried at 60 °C for 3 h.

TABLE I. Physicochemical Properties of Granulating Fluids

Ratio of water/IPA (%)	Surface tension γ (mN/m)	Viscosity η (mPa·s)	Density ρ ($\times 10^3$ kg/m^3)	Solubility S_b (kg/m^3) Sucrose	Lactose
100/ 0	72.1	1.13	0.997	2147.6	151.0
75/25	26.6	2.26	0.962	1773.5	44.0
50/50	24.6	3.64	0.918	697.0	11.0
25/75	23.8	2.14	0.857	87.7	1.0
0/100	21.9	1.34	0.782	0.7	0.1

Measurement of Lactose and Sucrose Solubility The granulating fluid was saturated with lactose or sucrose by dissolving the crystals at 30 °C. The saturated solution was filtered and the supernatant was evaporated at 60 °C. The residue was weighed.

Measurement of Viscosity The viscosity of granulating fluids was determined at 24 °C using a cone-type viscometer (Tokyo Keiki Type E).

Surface Tension Measurement The surface tension of the granulating fluids was determined at 24 °C using the capillary rise method.

Measurement of Contact Angle Compact plates of powder were prepared in a highly polished steel punch and die assembly, 2.0 cm in diameter and 0.2 cm thick. These compact plates were cut off at the following dimensions: length, 1.5 cm; width, 1.0 cm; thickness, 0.2 cm. The plates of powder were suspended from a strain gauge (Type UT200GR Minebea Co., Ltd.) and the contact angle was determined by liquid penetration and by Wilhelmy plate technique.

Measurement of Tensile Strength of Kneading Mass A split cell-type tensile tester was used to measure tensile strength. The operation of this tester was described previously.[5]

Measurement of Flow Properties of Kneading Mass The apparatus used was the constant volume type and the shear cell was similar to the Jenike cell designed by Tsunakawa and Aoki.[6] The operation of this tester has been described.[7] Constant temperature and humidity (24 °C, 44% RH) was maintained in the laboratory during the tests.

Measurement of Granule Size Distribution Granule size distribution was determined using JIS standard sieves vibrated on a Powder Tester (Hosokawa Micron Co., Ltd.) for 3 min.

Granule Hardness Measurement Granule hardness was measured with a hardness tester, as shown in Fig. 1. The test granule was placed on an electronic balance plate and the rod was driven down at a speed of

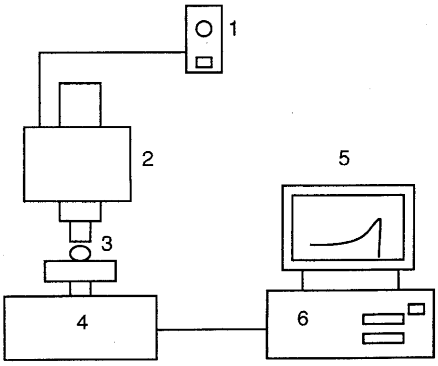

Fig. 1. Schematic Diagram of Apparatus for Measuring Granule Hardness

1, displacement controller; 2, motor; 3, sample; 4, electronic balance; 5, monitor; 6, computer.

1.04×10^{-3} m/s until the granule was crushed. The weight needed to crush the granule was measured by an electronic balance and the data were analyzed by computer.

Results and Discussion

Properties of Granulating Fluids The physicochemical properties of the granulating fluids are shown in Table II. These results are the average of three to five measurements. As the concentration of IPA rose, surface tension and the contact angle decreased; viscosity tended to increase to a maximum value at 50% IPA. The solubility of lactose and sucrose decreased in proportion to the concentration of IPA, and was almost zero at an IPA concentration of 100%. The solubility of sucrose was 13 times that of lactose.

Effects of Adhesion Tension on the Physical Properties of Kneading Mass 1) Tensile Strength of Kneading Mass: According to Rumpf[8)] the tensile strength T of a moist agglomerate is due to the adhesive force AL acting at the coordination points. Assuming that the particles forming the agglomerate are monosized and spherical the tensile strength can be expressed by the following equation:

$$T=[(1-\varepsilon)/\pi]k(AL/d^2) \tag{1}$$

where ε is the porosity of the agglomerate, k is the average coordination number, and d is the average diameter.

In the present study, it was assumed that the adhesive force Al was the result of the presence of a liquid bridge between two monosized particles. The relationship between the adhesive force of the liquid bridge and the dimensionless adhesive force F_a is expressed as follows:

$$AL=\gamma dF_a=\gamma df(\beta,\theta,a/d) \tag{2}$$

where γ is the surface tension of the liquid, β is the center angle according to the size of the liquid bridge and can be replaced by the liquid volume divided by the volume of the solid particles, θ is the liquid to solid contact angle, and a is the distance between two particles at coordination points.

Table II. Contact Angle and Adhesion Tension of Granulating Fluids

Ratio of water/ IPA (%)	Sucrose: Contact angle θ (°)	Sucrose: $\cos\theta$	Sucrose: Adhesion tension $\gamma\cos\theta$ (mN/m)	Lactose: Contact angle θ (°)	Lactose: $\cos\theta$	Lactose: Adhesion tension $\gamma\cos\theta$ (mN/m)
100/ 0	36.7	0.802	57.8	37.5	0.793	57.2
75/25	25.8	0.900	23.9	34.8	0.821	21.8
50/50	24.9	0.907	22.3	27.5	0.887	21.8
25/75	24.6	0.909	21.6	24.5	0.910	21.7
0/100	23.9	0.914	20.1	21.7	0.929	20.3

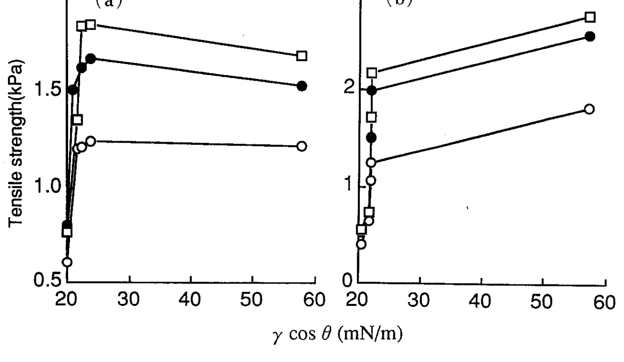

Fig. 2. Relationship between Tensile Strength and Adhesion Tension ($\gamma\cos\theta$)

(a) sucrose; (b) lactose. Precompression stress: ○, 10 kPa; ●, 20 kPa; □, 25 kPa.

The adhesive force AL of the liquid bridge is therefore proportional to the surface tension, the particle diameter, and a function of the center angle, the contact angle, and the dimensionless quotient.

We investigated the influence of the adhesion tension, which included the surface tension and contact angle, on the tensile strength.

Figure 2 shows the relationship between the tensile strength (T) and the adhesion tension ($\gamma\cos\theta$) determined by measuring the surface free energy for sucrose and lactose. The tensile strength increased rapidly as the adhesion tension increased and then leveled off (for lactose), or slightly decreased (for sucrose). It is not clear from these results whether the tensile strength is affected by changes in the solubility of solids, as mentioned below.

2) Flowability of Kneading Mass: A typical yield locus for the kneading mass of lactose is shown in Fig. 3, where σ is the consolidation stress, σ_1 is the major consolidation stress, τ is the shear stress, f_c is the unconfined yield stress, C is the cohesive stress, and T is the tensile strength. Tsunakawa[9)] denoted the ratio of f_c to $\rho_a g$, where ρ_a is the bulk density of the powders and g is the gravitational acceleration, as the flowability index (FI). This value corresponds to the maximum height of the powder layer under the force of gravity. Consequently, the FI value should generally decrease as the flowability of the powder increases.

Figure 4 shows the relationship between the flowability index FI of the kneading mass and the adhesion tension $\gamma\cos\theta$ for sucrose and lactose. FI values increased with increasing adhesion tension up to 22—24 mN/m, except

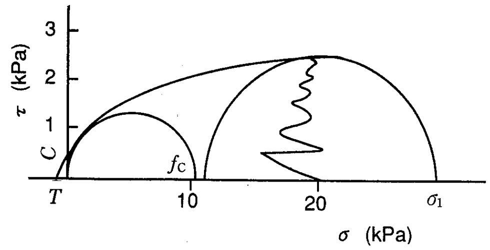

Fig. 3. Typical Yield Loci for Kneading Mass

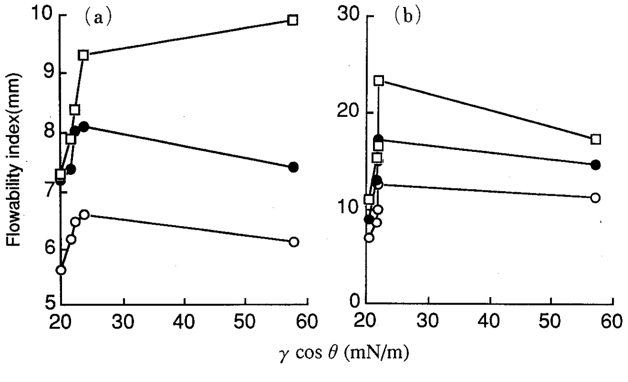

Fig. 4. Relationship between Flowability Index and Adhesion Tension ($\gamma\cos\theta$)

(a) sucrose; (b) lactose. Precompression stress: ○, 10 kPa; ●, 20 kPa; □, 25 kPa.

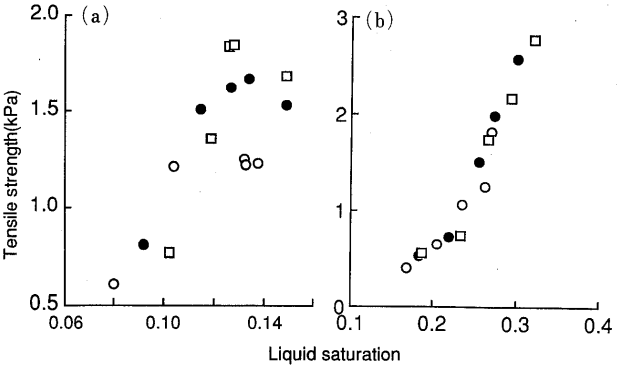

Fig. 5. Relationship between Tensile Strength and Liquid Saturation

(a) sucrose; (b) lactose. Precompression stress: ○, 10 kPa; ●, 20 kPa; □, 25 kPa.

when the precompression stress for sucrose was 25 kPa. The flowability index changed with the value of $\gamma \cos \theta$ in the same manner as did the tensile strength of the kneading mass.

3) Effects of Liquid Saturation on Tensile Strength: It is well known that the tensile strength of moist agglomerates especially for drugs soluble in aqueous solutions, is dependent on liquid saturation. In the present study, we investigated the relationship between the tensile strength of the kneading mass and liquid saturation. Liquid saturation is calculated by the following equation:

$$S = VL/V\varepsilon \qquad (3)$$

where S is the liquid saturation, VL is the volume of fluid in the kneading mass, V is the bulk volume of powder, and ε is the porosity of the kneading mass calculated from the amount of indissoluble powder.

Figure 5 shows tensile strength plotted against liquid saturation. At saturations above 0.15 the tensile strength of the kneading mass increased proportionally for lactose (Fig. 5b). But for sucrose (Fig. 5a), the tensile strength decreased at the highest saturation value. Moreover, under the same liquid saturation all the samples showed approximately equal tensile strength of kneading mass.

The distribution of liquid in an agglomerate proceeding from the pendular state to the capillary and slurry states depends on the amount of liquid saturations (S). In the pendular state ($0 < S < S_b$), a single liquid bridge is formed between the particles. In the funicular state ($S_b < S < S_c$), the tensile strength is due to the liquid bridge and capillary tension as the pores are filled with liquid. In the critical capillary state ($S = S_c$), where the pores are completely filled, the tensile strength is highest, then it suddenly decreases in the slurry state ($S > S_c$). Schubert[10] reported that the tensile strength shows its maximum value at $S_c = 0.95$.

Therefore, as shown by the results for sucrose (Fig. 5a), the tensile strength, which decreased at over 0.12 of liquid saturation was due to the solubility of sucrose, and not to: $S > S_c$.

Table III. Multiple Linear Regression Analysis

Coefficient	Tensile strength Y_1	Flowability index Y_2	Mean granule diameter Y_3	Granule hardness Y_4
b_0	−398.0	−447.0	10.4	−13.6
b_1	3.39	4.10	−0.310 (NS)	2.13
b_2	6.82	7.00	−0.210	1.79
b_3	5.08	5.35	1.24	1.32
b_4	0.047	0.003	—	−0.031
b_5	−0.035	−0.050	—	−0.026
b_6	−0.062	−0.062	—	—
b_7	—	—	0.006	—
b_8	−0.024	−0.022	—	—
b_9	—	0.007	−0.003 (NS)	—
R	0.933	0.961	0.857	0.980
R^2	0.791	0.867	0.627	0.944

At $p < 0.05$. —, not found. NS, not significant.

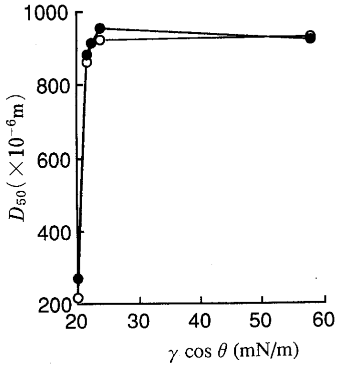

Fig. 6. Effect of Adhesion Tension ($\gamma \cos \theta$) on Mean Granule Diameter (D_{50})

○, sucrose; ●, lactose.

Multiple Regression Analysis As stated before, the tensile strength and flowability of the kneading mass are influenced by certain factors of surface tension, contact angle, and liquid saturation. In this study, we used general multiple linear regression analysis to analyze the data obtained from the experiments on tensile strength and the flowability index of the kneading mass. The general quadratic response model is:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1X_2 + b_5X_1X_3 + b_6X_2X_3 + b_7X_1^2 + b_8X_2^2 + b_9X_3^2 \qquad (4)$$

where Y is the response, *e.g.*, tensile strength and flowability index of the kneading mass, X_1, X_2, and X_3 are physicochemical properties of granulating fluids, *e.g.*, surface tension, cosine of contact angle, and liquid saturation, and the coefficients b_0, b_1, $\cdots$ b_9 are the least squares regression coefficients.

To present all three variables in one plot the factor levels had to be normalized, and the following equation was used for this:

$$N = [(X - L)/(H - L)] \times 100 \qquad (5)$$

where N is the normalized factor level, X is the non-normalized factor level, and L and H are the lowest and highest levels, respectively, for a specific factor.

The results of the regression analysis are shown in Table III. The multiple regression coefficients for tensile strength and flowability index were good. Tensile strength and flowability are affected by the following factors in the following order:

$\cos \theta >$ liquid saturation $>$ surface tension

However, the properties of the kneading mass are independent of granulating fluid viscosity. A highly viscous

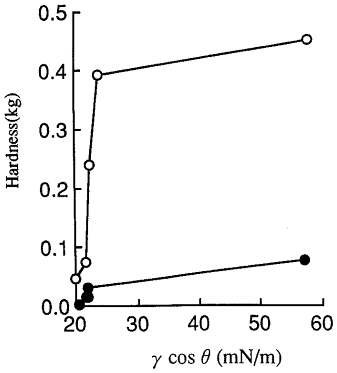

Fig. 7. Effects of Adhesion Tension ($\gamma\cos\theta$) on Granule Hardness

○, sucrose; ●, lactose.

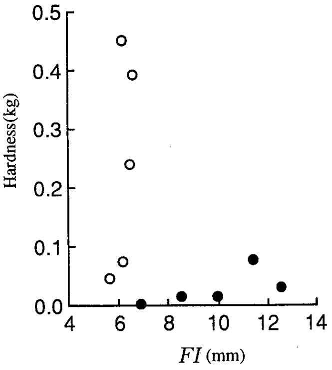

Fig. 9. Relationship between Granule Hardness and Flowability Index (*FI*) at 10 kPa

○, sucrose; ●, lactose.

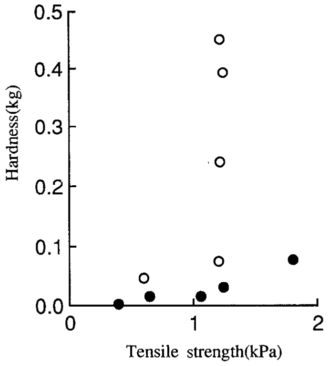

Fig. 8. Relationship between Granule Hardness and Tensile Strength at 10 kPa

○, sucrose; ●, lactose.

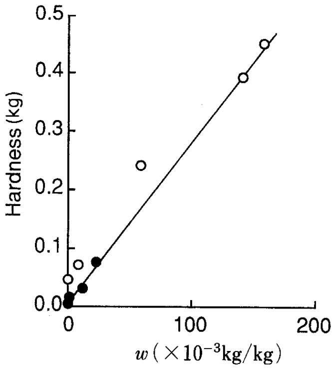

Fig. 10. Effects of Amount of Solid Deposit (w) on Granule Hardness

○, sucrose; ●, lactose.

binder solution will be nonhomogeneously distributed between the particles and this might result in a weaker kneading mass due to insufficient bonding force.[11] In this study, since the granulating fluids were of low viscosity, their viscosity is considered to have had no effect, as shown in Table I.

Effects of Adhesion Tension on Physical Properties of Granules Figure 6 shows the mean granule diameter (D_{50}) as a function of adhesion tension ($\gamma\cos\theta$); the diameter was obtained from granulating fluids with a wide range of composition. From these results, we concluded that the deposits of sucrose and lactose that occurred after the kneading mass was dried acted as solid bridges between particles.

Figure 7 shows the relationship between granule hardness and adhesion tension. For sucrose, granule hardness increased rapidly with increases in the adhesion tension while for lactose the increase was gradual under these circumstances.

Effects of Physical Properties of Kneading Mass and the Amount of Solid Deposited on Granule Hardness For both sucrose and lactose, the mean granule diameter did not change with changes in tensile strength except in a pure IPA system, which indicates that such a system does not provide suitable granulation.

Figure 8 shows the relationship between tensile strength and granule hardness for sucrose and lactose. For sucrose, the hardness increased sharply with increases in the tensile strength.

Figure 9 shows the relationship between the flowability index (*FI*) and granule hardness for sucrose and lactose. These results showed a similar tendency to those shown in Fig. 8. Granule hardness decreased at the highest flowability index value due to the amount of solid deposited, as outline hereunder.

If the drying of agglomerates that are filled with lactose or sucrose solutions starts at high liquid saturation (S), evaporation begins at the agglomerate surface. The liquid flows to the surface by means of capillary suction and the dissolved substance recrystallizes and forms a solid bridge. The tensile strength of the granule changes in accordance with the amount of solid deposit. Granule hardness (H) was plotted against the amount of solid deposit (w) obtained from the solubility of the solid, as shown in Fig. 10. All experimental data points for sucrose and lactose were approximately on a straight line.

We attempted general multiple linear regression analysis for the mean granule diameter and granule hardness experiments. A general quadratic response model is Eq. 4, where Y is the response, *e.g.*, mean granule diameter and granule hardness, and X_1, X_2, and X_3 are the physical properties of the kneading mass, *e.g.*, tensile strength, flowability index, and the amount of solid deposited.

Equation 5 was used to normalize the different levels. The results of the regression analysis are shown in Table III. The multiple regression coefficient for granule hardness was excellent (0.944). The multiple correlation coefficient for mean granule diameter was 0.627, and this was responsible for the great difference (see Table I) in solubility between lactose and sucrose during the granulation process.

Granule hardness was affected by changes in three factors, tensile strength, flowability index, and amount of solid deposit. The solid deposit acts as a secondary binding agent after drying.

Conclusion

In conclusion, profound differences occur in the properties of the kneading mass and of granules when the binder solvent is changed. The tensile strength and flowability index of the kneading mass increases with slight increases in the surface free energy, $\gamma \cos \theta$, in the initial stage.

For lactose, the tensile strength of the kneading mass showed approximately equal values at the same liquid saturation.

Granule hardness is significantly influenced by the amount of solid deposit which functions as a secondary binding agent. The mean granule diameter is also affected by the amount of solid deposit.

General multiple linear regression analysis showed good results with regard to tensile strength, flowability, and granule hardness.

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