The Relationship between Dividing Properties of Scored Tablets and Dynamic Characteristics of Various Mixed Powders

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The dividing properties of scored tablets were examined, considering the relationship with the dynamic characteristics of various mixed powders.

Powdered mixtures of lactose and cornstarch (SL/CS), lactose and microcrystalline cellulose (SL/MCC), and lactose and Perfiller® (SL/Perfiller®) in various ratios were used. The cohesive force (*C*), angle of internal friction (*δ*), flow factor (*FF*) and constant (*a*) in Kawakita's equation for tapping compaction were measured as dynamic characteristics of each powdered mixture.

A significant correlation was obtained between the coefficient of variation of the divided tablet weight and the *C* value for SL/CS and SL/Perfiller® mixtures and the *δ* value for SL/MCC mixtures. The coefficient of variation of divided tablet weight decreased with decrease in the *C* value for SL/CS and SL/Perfiller® mixtures and with increase in the *δ* value for SL/MCC mixtures. Significant correlation was also obtained between the logarithms of the dividing strength of the scored tablets and the *a* value for SL/CS mixtures, the *FF* value for SL/Perfiller® mixtures and the *δ* value for SL/MCC mixtures. Tablet dividing strength increased with decrease in the *a* value for SL/CS mixtures, with increase in the *FF* value for SL/Perfiller® mixtures and with increase in the *δ* value for SL/MCC mixtures. The dynamic characteristics of a powdered mixture influencing the tablet dividing properties thus were suggested to differ due to the physical properties of the additives, but tablet dividing properties were ultimately dependent on the formation of a uniform and denser packing of the powdered mixtures.

Keywords scored tablet; dividing strength; divided tablet weight variation; dynamic characteristic; mixed powder; multiple regression analysis

Introduction

Scored tablets are often divided, depending on the dosage a patient needs or the pharmacist dispenses. These are not necessarily always divided equally in the usual dividing operation. As an unequal division causes a variation in dosage, a uniform division of scored tablets has been required. We investigated various factors in the dividing properties of scored tablets,[1-4] and found that the dividing properties of scored tablets were greatly affected by the internal structure of the tablet, and that uniformity of the internal structure made it possible to divide it equally. The internal structure of the tablet was considered to be affected by the physical properties of the powders used for tableting. We therefore investigated the relationship between the dividing properties of scored tablets and the dynamic characteristics of powders obtained by performing shear test and tapping compaction using simple powders.[5] As the results, a significant correlation was observed between the cohesive force C relative to constant a in Kawakita's equation for tapping compaction (C/a) and the coefficient of variation of divided tablet weight. Furthermore, the C/a values correlated well with the dividing strength of the scored tablet. The scored tablets prepared from a simple powder with the smaller C/a value showed uniform division and higher dividing strength.

Tablets are, however, generally, made from a mixture of several kinds of powders. Their internal structure may fluctuate depending on the kind of powders and their mixing ratio, because the physical properties of a variety of mixed powders are different from those of each powder alone. In this paper, we investigated the relationship between the dividing properties of scored tablets and the dynamic characteristics of various mixed powders to learn the effect of the physical properties of the mixed powders on the dividing properties of the scored tablets.

Experimental

Materials Lactose (SL; JP XI), microcrystalline cellulose (MCC; Avicel®; Asahi Kasei Co., Ltd. Tokyo), cornstarch (CS; JP XI) and Perfiller® (fine granules containing Hydroxypropyl starch/aluminum silicate/microcrystalline cellulose: 6/2/2; Freund Sangyo Co., Ltd. Tokyo) were used. After sieving these materials through a 100 mesh, the powdered mixtures of lactose and cornstarch (SL/CS), lactose and microcrystalline cellulose (SL/MCC), and lactose and Perfiller® (SL/Perfiller®) were prepared in the weight ratios of 8/2, 6/4, 5/5, 4/6 and 2/8. The powders were mixed by shaking in vinyl bags for 10 min. Before compression, 0.5% (w/w) of magnesium stearate as a lubricant was added to each of the powdered mixtures in a bottle and then mixed for a further 1 min.

Preparation of Scored Tablets The powdered mixtures were compressed into scored tablets with a weight of 300 mg, a diameter of 13.2 mm and a depth of score of 0.2 mm, using a compaction instrument for KBr pellets under 700 kg/cm^2 for 1 min. Table I shows the thickness of each tablet measured by a caliper. Depth of the score of the tablets prepared in this study was about 10% of total thickness.

Dividing Method and Measurement of Dividing Strength of Scored Tablets Division and measurement of the dividing strength of scored tablets were carried out using a Rheo meter (San Kagaku Co., Ltd.) according to the method described previously.[1]

Calculation of Coefficient of Variation of Divided Tablet Weight The weight of forty divided tablets was measured using a chemical balance, and the coefficient of variation of divided tablet weight was calculated.

Shear Test Shear tests were carried out using a direct shear tester according to the method described previously.[5] The shearing cell with an inside diameter of 100 mm and a depth of 15 mm was filled with the powdered mixture and the yield locus shown in Fig. 1 was obtained by shearing at a preconsolidation stress of 3 kg. The point of intersection of the yield locus and the spindle shows the cohesive force (C). The angle of internal friction (δ), the simple yield stress (f_c) and the major principal stress (σ_1) were obtained by drawing two Mohr circles.

Measurement of Constants in Kawakita's Equation for Tapping Compaction[6] The physical parameter relating to the tapping compaction behavior of powders was represented as the constant (a) in the following Kawakita's equation (1). Tapping compactions were done using a tapping apparatus (Konishi Medical & Surgical Co., Ltd. Osaka). The powdered

Table I. Thickness of Each Tablet

Sample	Thickness[a] (mm)
Lactose/cornstarch (8/2)-tablet	1.81 ± 0.03
Lactose/cornstarch (6/4)-tablet	1.84 ± 0.05
Lactose/cornstarch (5/5)-tablet	1.92 ± 0.05
Lactose/cornstarch (4/6)-tablet	1.89 ± 0.06
Lactose/cornstarch (2/8)-tablet	1.92 ± 0.05
Lactose/Perfiller® (8/2)-tablet	1.91 ± 0.03
Lactose/Perfiller® (6/4)-tablet	1.91 ± 0.04
Lactose/Perfiller® (5/5)-tablet	1.91 ± 0.05
Lactose/Perfiller® (4/6)-tablet	1.92 ± 0.04
Lactose/Perfiller® (2/8)-tablet	1.95 ± 0.04
Lactose/microcrystalline cellulose (8/2)-tablet	1.82 ± 0.03
Lactose/microcrystalline cellulose (6/4)-tablet	1.83 ± 0.04
Lactose/microcrystalline cellulose (5/5)-tablet	1.86 ± 0.04
Lactose/microcrystalline cellulose (4/6)-tablet	1.85 ± 0.04
Lactose/microcrystalline cellulose (2/8)-tablet	1.88 ± 0.05

a) Mean ± S.D. ($n=10$).

Table II. Dynamic Characteristics of Powdered Mixtures

Sample	Mixing ratio	C[a] (kPa)	FF[b]	δ[c] (°)	a[d]
Lactose/cornstarch	8/2	0.77	5.98	16.0	0.47
	6/4	0.85	5.46	17.5	0.43
	5/5	0.53	8.62	16.0	0.44
	4/6	0.45	8.49	17.0	0.39
	2/8	0.45	8.82	19.0	0.35
Lactose/Perfiller®	8/2	0.47	8.65	15.7	0.46
	6/4	0.37	12.10	15.7	0.39
	5/5	0.37	11.96	20.3	0.41
	4/6	0.40	13.87	22.0	0.40
	2/8	0.40	16.10	27.7	0.28
Lactose/microcrystalline cellulose	8/2	1.25	3.87	22.5	0.50
	6/4	1.13	4.57	24.3	0.45
	5/5	1.20	3.65	28.5	0.47
	4/6	1.25	4.15	30.0	0.44
	2/8	1.20	3.23	32.5	0.41

a) Cohesive force. *b*) Flow factor (σ_1/f_c). *c*) Angle of internal friction. *d*) Constant in Kawakita's Eq. 1. Each value is the mean of three experiments.

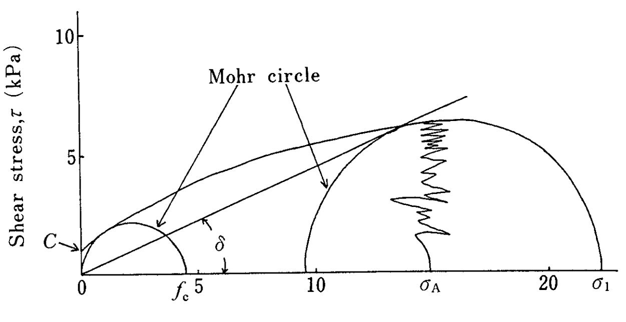

Fig. 1. Typical Yield Locus for Lactose/Microcrystalline Cellulose Mixture in Mix Ratio of 6/4

σ_A, preconsolidation stress; σ_1, major principal stress; C, cohesive force; δ, angle of internal friction; f_c, simple fall stress.

mixtures were packed loosely in a graduated cylinder and the cylinder was tapped with tapping height of 2 cm and at a speed of 100 tap/min.

$$N/C'=N/a+1/ab \quad (1)$$

$$C'=(V_o-V_n)/V_o \quad (2)$$

where N is the number of tappings, V_o is the initial volume and V_n is the volume after compaction. a and b are the constants, respectively.

Multiple Regression Analysis The relationship between the dividing properties of scored tablets and the dynamic characteristics of mixed powders was analyzed by multiple regression analysis (Multivariate Analysis Library, NEC Corp., PC-9801 digital computer).

Results and Discussion

Dynamic Characteristics of Powdered Mixtures Table II shows the dynamic characteristics of each powdered mixture obtained from the shear test and from Eq. 1.

The C value is the cohesive force between particles; the larger the C value is, the greater the adhesion force becomes. The FF (σ_1/f_c) value is an index of the flowability of powders; a larger FF value implies better flowability.[7] The δ value is the angle of friction between powder layers produced by shearing compulsorily from a state of consolidation. The a value in Eq. 1 implies the initial porosity of the powder bed[8]; the smaller the a value is, the smaller the initial porosity of the powder bed becomes.

In the case of the SL/CS mixture, the C value greatly decreased and the FF value greatly increased when the mixing ratio changed from 6/4 to 5/5. The δ value was scarcely influenced by the mixing ratio of CS, while the a value tended to decrease with increase of this mixing ratio. This may suggest that the difference in the mixing ratio of CS mainly affected the cohesive force between particles and flowability of the mixed powder.

In the case of the SL/Perfiller® mixture, the C value at a mixing ratio of 8/2 was largest among all mixing ratios, and the FF and δ values tended to increase with increase in the ratio of Perfiller®. The a value greatly decreased at a mixing ratio of 2/8 due to a great increase in the FF value. Thus, the flowability of the mixed powder was strongly affected by the difference in the ratio of Perfiller® used. The increase in the δ value was believed due to the formation of a more uniform and a denser packing condition based on the better flowability of the powder.

In the SL/MCC mixture, the C and FF values were little influenced by the mixing ratio of MCC. The δ value then increased, and the a value decreased with increase of the amount of MCC. These results suggest that the difference in the ratio of MCC used scarcely affects the cohesive force between particles and the flowability of the powder.

Thus the physical properties of powdered mixtures differed depending on the kind of additives and their ratio in the mixture.

Dividing Properties of Scored Tablets Table III shows the dividing properties of the scored tablet prepared from each mixed powder. The smaller coefficient of variation of divided tablet weight (CV) indicates an equal division of the scored tablets.

In any tablet mixture, the dividing strength of scored tablets (St) increased with increase in the ratio of CS, Perfiller® or MCC included. In the SL/CS mixture, however, the difference in the St value was very slight. The coefficients of variation of divided tablet weight (CV) of the scored tablets prepared from the SL/CS mixture at a mixing ratio of 8/2 or 6/4 were larger than those of scored tablets prepared from the SL/CS mixture at a mixing ratio of 5/5, 4/6 or 2/8. The CV value of scored tablets prepared from the SL/Perfiller® mixture at a mixing ratio of 8/2 was larger than those of scored tablets prepared from the SL/Perfiller® mixtures at other mixing ratios. The CV value of scored

Table III. Dividing Properties of Scored Tablets

Sample	$St^{a)}$ (kg)	$CV^{b)}$ (%)
Lactose/cornstarch (8/2)-tablet	0.25	15.9
Lactose/cornstarch (6/4)-tablet	0.26	15.7
Lactose/cornstarch (5/5)-tablet	0.25	11.8
Lactose/cornstarch (4/6)-tablet	0.30	11.8
Lactose/cornstarch (2/8)-tablet	0.32	12.8
Lactose/Perfiller® (8/2)-tablet	0.19	14.2
Lactose/Perfiller® (6/4)-tablet	0.30	11.6
Lactose/Perfiller® (5/5)-tablet	0.37	11.5
Lactose/Perfiller® (4/6)-tablet	0.44	12.3
Lactose/Perfiller® (2/8)-tablet	0.71	11.3
Lactose/microcrystalline cellulose (8/2)-tablet	0.55	11.7
Lactose/microcrystalline cellulose (6/4)-tablet	0.81	9.5
Lactose/microcrystalline cellulose (5/5)-tablet	1.24	8.1
Lactose/microcrystalline cellulose (4/6)-tablet	1.30	8.5
Lactose/microcrystalline cellulose (2/8)-tablet	2.12	6.9

a) Dividing strength of tablets, each value is the mean ($n=20$). *b*) Coefficient of variation of divided tablet weight.

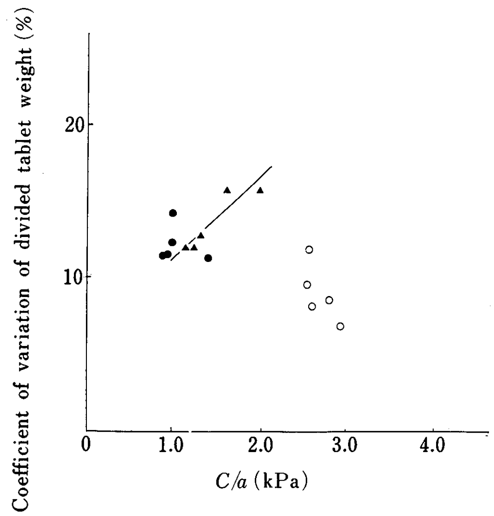

Fig. 2. Relationship between Coefficient of Variation of Divided Tablet Weight and C/a

▲, lactose/cornstarch mixture; ●, lactose/Perfiller® mixture; ○, lactose/microcrystalline cellulose mixture.

tablets prepared from the SL/MCC mixture tended to become smaller with increase in ratio of MCC.

Relationship between Dividing Properties of Scored Tablets and Dynamic Characteristics of Mixed Powders Relationship between the coefficient of variation of divided tablet weight CV and the dynamic characteristics of powders was investigated using simple powders in order to clarify the effect of the physical properties of the powders on the uniform division of scored tablets.[5] The cohesive force (C) relative to constant (a) in Eq. 1 (C/a) was selected as the most significant dynamic characteristic for simple powders by means of multiple regression analysis. It was found that the smaller the C/a value is, the smaller the CV value becomes. Since the C value is the cohesive force between particles in vertical stress $\sigma=0$, this value is considered to be related to particle mobility in filling of the initial porosity of the powder bed, *i.e.*, from the loosest packing in the initial filling to the closest packing in the initial stage of the compression process. The smaller C value implies a better mobility of particles in the initial stage of the compression process. The a value implies the initial porosity of the powder bed. Accordingly, the C/a value is believed to indicate the mobility of particles under compression relative to the porosity prior to compression. It was supposed that smaller the C/a value implies better mobility of particles under compression. That is, the particles can move easily in the initial compression process with decreasing C/a value; consequently, a more uniform and a denser packing is produced and the scored tablets show a uniform division. Thus, for each mixture, the relationship between CV and C/a value was investigated. The C/a value was calculated from Table II. The results are shown in Fig. 2.

In the SL/CS mixtures, a significant correlation ($r=0.925$, $p<0.05$) was obtained between the CV and C/a values; the smaller the C/a value is, the smaller the CV value becomes, that is, the scored tablets show more equal division. However, no correlation was obtained in the SL/Perfiller® and SL/MCC mixtures, suggesting that the relationship for simple powders is not applicable to SL/Perfiller® and SL/MCC mixtures but only to SL/CS mixtures. The relationship between the CV value and the dynamic characteristics of each powdered mixture was then deter-

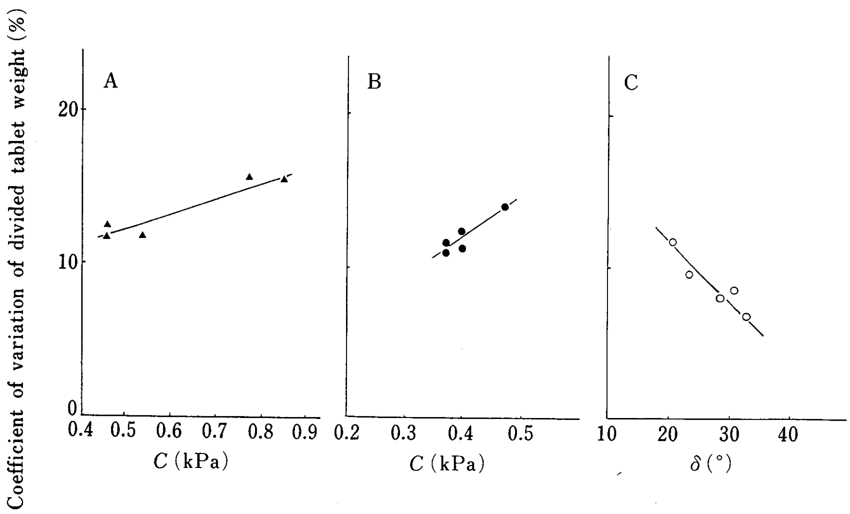

Fig. 3. Relationship between Coefficient of Variation of Divided Tablet Weight and Dynamic Characteristics of Mixed Powders

A, SL/CS mixture; B, SL/Perfiller® mixture; C, SL/MCC mixture.

mined by multiple regression analysis (Fig. 3).

In each mixture, a significant correlation was obtained between the *CV* value and one dynamic characteristic of the powdered mixture. The cohesive force *C* for SL/CS ($r=0.931$, $p<0.05$) and SL/Perfiller® mixtures ($r=0.921$, $p<0.05$) and the angle of internal friction δ value for SL/MCC mixtures ($r=-0.937$, $p<0.05$) were selected as the most significant dynamic characteristics. It was found that the *CV* value decreased with decrease in the *C* value for SL/CS and SL/Perfiller® mixtures and with increase in the δ value for SL/MCC mixtures. In the SL/CS mixtures, the correlation coefficient between the *CV* and *C* values was a little larger than that between the *CV* and C/a values, indicating that the *CV* value is mainly influenced by the *C* value. As described previously, decrease in *C* value implies a better mobility of particles under compression. Therefore, a more uniform and denser packing is produced by compression with decreasing *C* value, and the scored tablet showed a uniform division. Since the δ value is the angle of friction between powder layers produced by shearing compulsorily from a state of consolidation, the greater the shear stress is, the larger the δ value becomes, and greater shear stress reflects uniformity and greater density. Accordingly, the increase in the δ value reflects the formation of a more uniform and denser packing. It was therefore suggested that the coefficient of variation of divided tablet weight was dependent on the uniformity and packing density of powdered mixture.

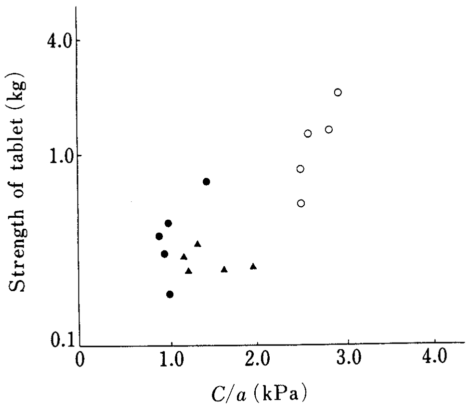

Fig. 4. Relationship between Dividing Strength of Scored Tablets and C/a

▲, lactose/cornstarch mixture; ●, lactose/Perfiller® mixture; ○, lactose/microcrystalline cellulose mixture.

In a previous paper,[5] a significant correlation was obtained between *St* and C/a value for simple powders, similar to the case of *CV*, and it was found that the smaller the C/a value is, the greater the *St* value becomes. Thus, relationship between *St* and the dynamic characteristics of mixed powders was investigated in the same way as described above (for *CV* value). The relationship between *St* and C/a value for each mixture is shown in Fig. 4.

No correlation between *St* and C/a was found for any mixture, suggesting that the relationship for simple powders is not be applicable to mixed powders. The results obtained by multiple regression analysis for each mixture are shown in Fig. 5.

A statistically significant correlation was obtained between the *St* value and one dynamic characteristic of the powdered mixture for any mixture. The dynamic characteristic correlating most significant to the *St* value was different among the three mixtures and were identified as: the constant *a* in Eq. 1 for SL/CS mixtures ($r=-0.975$, $p<0.01$), the flow factor *FF* for SL/Perfiller® mixtures ($r=0.984$, $p<0.01$) and the angle of internal friction δ for SL/MCC mixtures ($r=0.984$, $p<0.01$). From these results, it was found that the *St* value increased with decrease in the *a* value for SL/CS mixtures, with increase in the *FF* value for SL/Perfiller® mixtures and with increase in the δ value for SL/MCC mixtures. The decrease in the *a* value implies a decrease in the initial porosity of the powder bed, *i.e.*, a decrease in the porosity of the bed prior to compression. This lower porosity prior to compression is believed to allow the resulting uniformity and greater density. Also beneficial to this result is the better flowability of powders, as implied by the *FF* value; this permits the particles to shift to a stable position. As stated, the increase in δ value reflects that a more uniform and denser packing is produced by compression. The above findings thus suggest that the dynamic characteristics of powdered mixtures differed in their influence on the dividing strength of the scored tablets as a result of their physical properties, but that this strength was ultimately determined by the uniformity and packing density of the mixture.

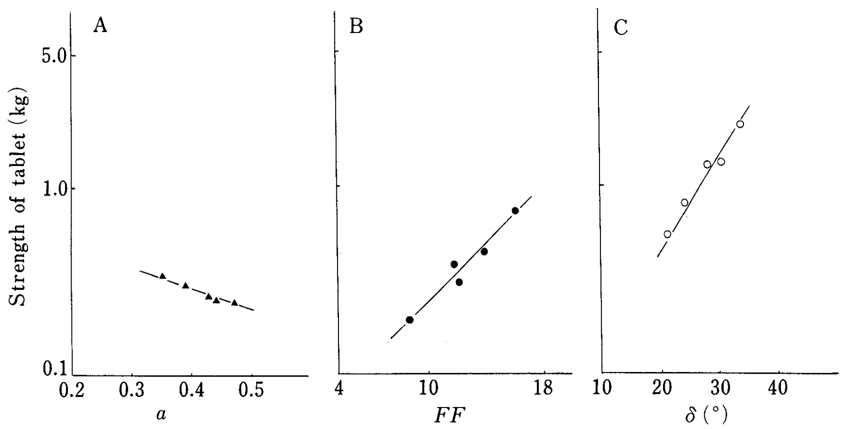

Fig. 5. Relationship between Dividing Strength of Scored Tablets and Dynamic Characteristics of Mixed Powder

A, SL/CS mixture; B, SL/Perfiller® mixture; C, SL/MCC mixture.

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