Prediction of Tableting Problems such as Capping and Sticking: Theoretical Calculations

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Abstract □ Tabletability factors were developed through the use of an automated tabletability tester, and the applicability of these factors to actual manufacturing procedures was tested by the large-scale manufacturing of tablets. Use of this approach does not require knowledge of the tablet's physical properties, *e.g.*, moisture content, porosity, particle size, fluidity, and angle of repose.

Keyphrases □ Tablet formulation—prediction factors developed, applied to manufacturing procedures □ Powdered materials—capacity for tablet formulation, prediction factors developed, applied to manufacturing procedures □ Dosage forms—tablets, formulation prediction factors developed, applied to manufacturing procedures

A tabletability tester, a device used to measure the passive pressure of a lower punch and the degree of binding between the punch face and the surface of a tablet (1), was previously proposed to predict the capacity of a powdered material to form a "good" or "bad" tablet. From the direct compression of common tablet ingredients (2) with a tabletability tester, four factors were found to be critical in the making of a good tablet: (*a*) the pressure of a loaded upper punch, (*b*) the passive pressure of a lower punch, (*c*) the force of the lower punch to extrude a tablet, and (*d*) the slipping force of the tablet surface.

The observed values of these four factors were difficult to reproduce due to the lack of consistency in manual determinations. Therefore, a fully automatic tabletability tester was developed to measure the four tabletability factors. The principles of the compression fixture and the sizes of the upper punches, lower punches, and dies are identical to those described previously (1, 2).

EXPERIMENTAL

Apparatus—The compression fixture used to determine the slipping force (*SF*), the passive pressure of the lower punch (*R*), the pressure of the loaded upper punch (*U*), and the force needed to extrude a tablet by the lower punch (*E*) were essentially the same as described previously (2), but the current fixture was automated by adding an electrical mechanism.

The values of *R*, *U*, and *E* were measured by using strain gauges[1] (type S-104, resistance 119.3Ω, gauge factor 1.92); *SF* was measured by using a U-gauge (type UT, capacity 1 kg, resistance 119.30Ω, gauge factor 1.92). The actual procedure of determining the slipping force was described previously (2), but the principle is as follows. When the upper plunger of the tablet machine strikes the head of the upper punch at a constant pressure and the striking is stopped, a split die is removed and the upper plunger is pulled out. The strain gauge is activated electrically and pushes the knob attached to the upper punch. The upper punch is supported by both a ball-bearing ring and a nonskid ring. Deformation of the strain gauge is recorded on a chart. Thus, the slipping force between the punch face and the tablet surface can be determined. The tablet held in the die does not rotate while the upper punch is rotated on the tablet surface. Presumably, the binding force between the tablet side and the die wall is larger than the slipping force because *E* is in kilograms and *SF* is in grams.

The cross section of the automatic tabletability tester is illustrated in Fig. 1. Since an important feature of the tester is the device used to measure the slipping force (2), a stereogram of this device is depicted in Fig. 2. Figure 2 clarifies the independent position of the upper punch (relative to the position) when the slipping force is measured.

Table I—Formulas of Materials Compressed into Test Tablets

Material	Composition
1	Mixture[a,b]
4	Calcium cellulose gluconate[c,d]
5	Magnesium oxide–aluminum oxide–silicon dioxide[e,f] (1:1:2)
6	Magnesium, oxide–aluminum oxide–silicon dioxide[g,f] (1:1:2)
10	Microcrystalline cellulose[h,i]
12	Dibasic calcium phosphate, anhydrous[j]
13	Dibasic calcium phosphate, anhydrous light[j]
14	Dibasic calcium phosphate, anhydrous, heavy[j]
15	Magnesium silicate, JP
19	Aluminum silicate, synthetic, JP
24	Aluminum hydroxide, anhydrous[j]
29	Aluminum hydroxide gel–magnesium hydroxide[j,l]
31	Dibasic calcium phosphate[j,m]
32	Magnesium oxide–aluminum oxide–silicon dioxide (1:1:2), neutral fine particles[f,n]
33	Magnesium oxide–aluminum oxide–silicon dioxide (1:1:2), fine particles[f,o]
34	Magnesium oxide–aluminum oxide–silicon dioxide (1:1:2), superfine particles[f,p]
39	Magnesium silicate[j]
40	Aluminum silicate, synthetic[j]
42	50% Lactose–19.5% potato starch–15% microcrystalline cellulose–15% synthetic aluminum silicate– 0.5% calcium stearate

[a] Per-filler. [b] Froint Sangyo Co. Ltd., Tokyo, Japan. [c] ECG 505. [d] Gotoku Yakuhin Kogyo Co. Ltd., Tokyo, Japan. [e] Neusilin S_1. [f] Fuji Kagaku Kogyo Co. Ltd., Toyama, Japan. [g] Neusilin SG_1. [h] Avicel. [i] Asahi Kasei Kogyo Co. Ltd., Tokyo, Japan. [j] Kyowa Kagaku Kogyo Co. Ltd., Tokyo, Japan. [l] Sanalmin A. [m] Licamit U-100. [n] Neusilin SG_2. [o] Neusilin SG_3. [p] Neusilin S_2.

Materials—The pharmaceutical materials were simple compounds or mixtures widely used as tablet additives in direct tableting (Table I). The materials and their numbers are identical to those used in previous experiments (2) so that the new data can be easily compared with data from the manual hand process.

A tablet hardness tester[2] was also used.

Calculations—When pressure is loaded on a powder housed in a cylinder (and the stress distribution due to the dead load of a powder itself is neglected), the vertical stress distribution in the powder layer may be shown by Eq. 1 as presented by Train and Lewis (3):

$$P/P_0 = \exp\left(-\frac{4\mu\beta h}{D}\right) \qquad \text{(Eq. 1)}$$

where P is the vertical load, h is the upper limit of the lower punch (the depth of the powder layer when compressed), D is the diameter of the cylinder, μ is the friction coefficient of the cylinder wall, β is the ratio of horizontal pressure to P, and P_0 is the loaded pressure at $h = 0$.

From Fig. 3*b*, the following equation can be derived using Eq. 1:

$$R/U = \exp\left(-\frac{4\mu'\beta'h'}{D}\right) \qquad \text{(Eq. 2)}$$

where:

$$\mu'\beta' = \frac{D(\ln U - \ln R)}{4h'} \qquad \text{(Eq. 3)}$$

and R is the passive pressure of the lower punch, U is the pressure of a loaded upper punch, and μ' and β' correspond to μ and β in Eq. 1 in the powder layer between the surfaces b and c.

[1] Shinko Tsushin Co.

[2] Monsanto.

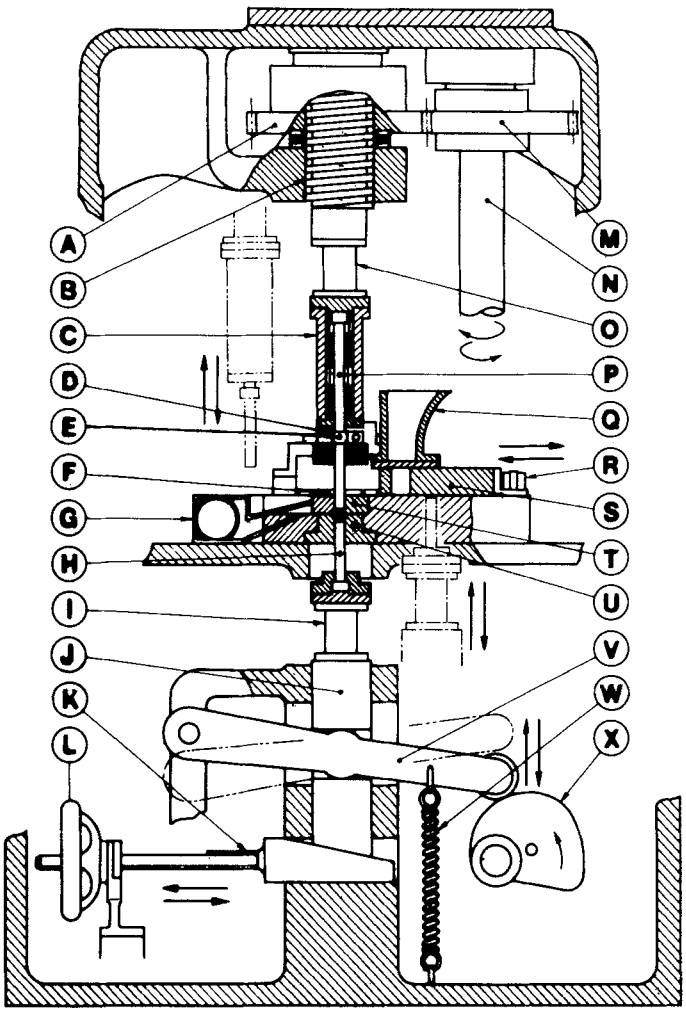

Figure 1—*Cross section of the main parts of the automatic tabletability tester. Key: A, pressure gear; B, piston; C, needle-bearing case; D, strain gauge for recording the slipping force; E, holder for the upper punch when the slipping force is measured; F, adjustment plate for the split die; G, exhaust pipe for the powder, H, lower punch; I, strain gauge for recording the force of the lower punch, J, adjustment liner for adjusting the filling depth of the powder; K, adjustment table for changing the filling depth of the powder; L, adjustment handle for controlling the quantity of the powder; M, vertical shaft gear; N, interlocker for upper punch; O, strain gauge for recording the force of the upper punch; P, upper punch; Q, hopper for powder; R, lever of feed-shoe; S, shuttle feed-shoe; T, split die; U, die base; V, push-up lever; W, spring for push-up lever; and X, push-up cam for the lower punch. The broken line illustrates a hypothetical scheme.*

Train and Lewis (3) stated that β does not show a constant value even in the same powder layer at different positions. However, if $\mu'\beta'$ is constant for the same powder in a range that is not yet known, the $\mu'\beta'$ obtained from Eq. 3 can be used for the calculation of U_1 and U_2 in Fig. 3c:

$$\ln U_1 = \ln U - \frac{4\mu'\beta' h_1}{D} \qquad \text{(Eq. 4)}$$

$$\ln U_2 = \ln R + \frac{4\mu'\beta' h_2}{D} \qquad \text{(Eq. 5)}$$

Adding Eqs. 4 and 5 yields:

$$\ln U_1 + \ln U_2 = \ln U + \ln R - \frac{4\mu'\beta'(h_1 - h_2)}{D} \qquad \text{(Eq. 6a)}$$

$$\ln U_1 U_2 = \ln UR - \frac{4\mu'\beta'(h_1 - h_2)}{D} \qquad \text{(Eq. 6b)}$$

when $h_1 = h_2$, $\ln U_1 U_2 = \ln UR$, and, logically, $U_1 = U_2$. Therefore, if $U_1 = U_2 = U_c$, the following simple relationships can be derived:

$$U_c^2 = UR \qquad \text{(Eq. 7a)}$$

$$U_c = \sqrt{UR} = K_V \qquad \text{(Eq. 7b)}$$

The pressure K_V obtained involves the pressure at the center layer of a formed tablet; K_V can be calculated without knowing the value of $\mu'\beta'$. Since K_V is concerned with vertical stress distribution, K_V should be called a "vertical factor."

In Fig. 3a, P is the pressure set mechanically at surface a. If the upper punch moves from surface a to surface b, P at surface a changes to U at surface b. Accordingly, $\mu\beta$ of a powder confined between surfaces a and b should differ from a powder confined between surfaces b and c. The former product is designated $\mu''\beta''$, and the latter is designated $\mu'\beta'$. Equations 8–12 are derived theoretically:

$$\ln U = \ln P - \frac{4h\mu''\beta''}{D} \qquad \text{(Eq. 8)}$$

$$\mu''\beta'' = \frac{D(\ln P - \ln U)}{4h} \qquad \text{(Eq. 9)}$$

$$\ln R = \ln U - \frac{4h'\mu'\beta'}{D} \qquad \text{(Eq. 10)}$$

$$\mu'\beta' = \frac{D(\ln U - \ln R)}{4h'} \qquad \text{(Eq. 11)}$$

$$\mu''\beta''/\mu'\beta' = \frac{h'(\ln P - \ln U)}{h(\ln U - \ln R)} = K_H \qquad \text{(Eq. 12)}$$

The value of K_H represents the horizontal stress distribution at the surface of a formed tablet. Since K_H is concerned with horizontal stress distribution, this value is termed a horizontal factor to contrast with K_V, the vertical factor.

It is of particular interest to ascertain whether the capacity of a material or a mixture to form a good or bad tablet (especially with respect to capping and/or sticking) could be manifested in either K_H or K_V. The ability of a powder to form a tablet is subject not only to vertical and horizontal pressure transmissions but also to the nature of the tablet surface and tablet hardness. Therefore, it is desirable to use the term "tabletability factors" for the prediction of tableting problems. This general term consists of K_H, K_V, SF (1), and tablet hardness. The significance of the surface factor is to predict the behavior of the surface

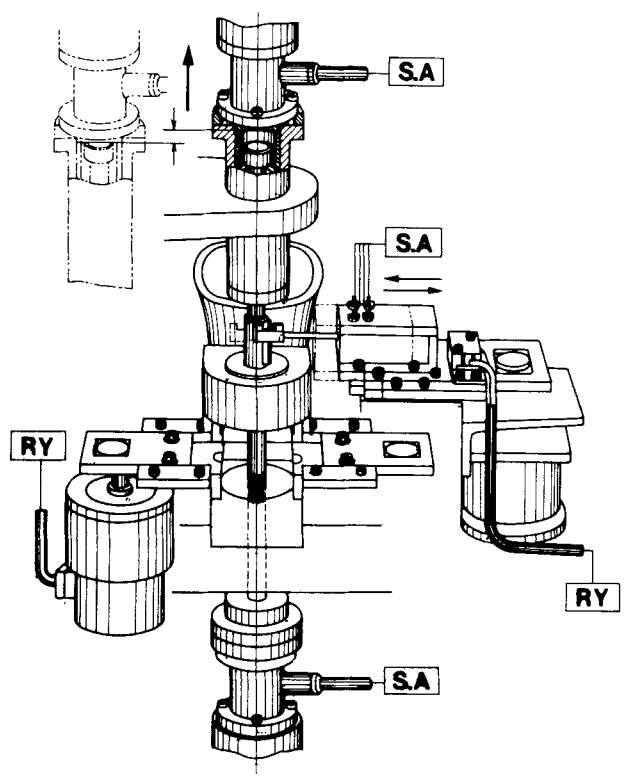

Figure 2—*Stereogram of the main parts for measuring slipping force. Key: S.A, strain amplifier; and RY, relay. The broken lines show a hypothetical scheme.*

Table II—Data on Tabletability Factors: Passive Pressure of Lower Punch, Lower Punch Force to Extrude a Tablet, Pressure of Upper Punch Loaded, and Slipping Force[a]

Material	R	E	U	SF		
				First	Second	Third
			Filling Depth 18 mm			
1	1400 ± 41	200 ± 0	1868 ± 46	122 ± 5	102 ± 4	102 ± 4
4	1100 ± 63	240 ± 25	1780 ± 49	OS	OS	OS
5	640 ± 25	120 ± 0	810 ± 49	OS	OS	OS
10	560 ± 21	100 ± 0	784 ± 14	126 ± 8	112 ± 9	104 ± 8
12	530 ± 74	120 ± 16	670 ± 107	OS	OS	OS
14	2100 ± 45	423 ± 10	OS	OS	OS	OS
19	890 ± 33	—	1096 ± 53	164 ± 4	141 ± 4	142 ± 5
29	606 ± 12	184 ± 4	788 ± 23	OS	OS	OS
39	1204 ± 4	—	1842 ± 16	OS	OS	OS
40	830 ± 20	292 ± 5	1450 ± 18	OS	OS	OS
42	2380 ± 20	OS	OS	OS	OS	OS
			Filling Depth 22 mm			
1	570 ± 12	494 ± 15	1438 ± 17			
5	300 ± 0	194 ± 3	496 ± 4			
6	216 ± 4	184 ± 4	640 ± 47			
10	128 ± 8	92 ± 5	77 ± 4			
12	384 ± 29	110 ± 12	718 ± 76			
13	364 ± 17	232 ± 19	816 ± 34			
14	920 ± 46	748 ± 64	2432 ± 94			
15	414 ± 18	384 ± 8	740 ± 8			
19	1044 ± 33	542 ± 27	2110 ± 89			
24	782 ± 12	495 ± 5	1600 ± 8			
29	188 ± 5	106 ± 4	304 ± 4			
31	390 ± 6	705 ± 5	1480 ± 20			
32	396 ± 4	302 ± 2	918 ± 9			
33	418 ± 5	356 ± 13	1056 ± 43			
34	364 ± 12	210 ± 10	860 ± 17			
39	618 ± 9	512 ± 16	1560 ± 21			
40	416 ± 4	384 ± 4	1202 ± 7			
42	630 ± 12	362 ± 5	1320 ± 9			
			Filling Depth 26 mm			
1	196 ± 4	208 ± 5	640 ± 14	83 ± 1	81 ± 3	81 ± 2
4	458 ± 18	398 ± 5	1280 ± 16	100 ± 4	87 ± 3	84 ± 4
5	96 ± 4	82 ± 7	220 ± 8	87 ± 2	80 ± 4	79 ± 3
6	200 ± 0	200 ± 0	500 ± 6	108 ± 4	104 ± 4	101 ± 3
10	34 ± 4	88 ± 5	162 ± 7	99 ± 4	92 ± 4	92 ± 4
12	100 ± 0	110 ± 10	248 ± 15	86 ± 4	80 ± 3	77 ± 1
13	80 ± 0	56 ± 6	192 ± 5	86 ± 7	82 ± 9	80 ± 10
14	162 ± 2	200 ± 0	752 ± 18	139 ± 3	125 ± 4	115 ± 7
15	300 ± 0	284 ± 16	672 ± 10	100 ± 0	89 ± 1	89 ± 1
19	208 ± 5	196 ± 4	564 ± 18	69 ± 3	83 ± 4	85 ± 2
24	100 ± 0	100 ± 0	296 ± 4	52 ± 4	44 ± 3	43 ± 3
29	56 ± 2	46 ± 4	186 ± 4	OS	OS	OS
31	250 ± 0	700 ± 0	1275 ± 25	—	—	—
32	200 ± 0	100 ± 0	584 ± 6	OS	OS	OS
33	202 ± 2	200 ± 0	856 ± 10	OS	OS	OS
34	200 ± 0	192 ± 5	444 ± 13	OS	OS	OS
39	300 ± 0	448 ± 17	880 ± 10	120 ± 6	144 ± 3	139 ± 6
40	380 ± 3	574 ± 6	1100 ± 0	OS	188 ± 5	186 ± 4
42	208 ± 4	196 ± 7	446 ± 19	106 ± 4	96 ± 2	90 ± 2

[a] All values are the mean of five experiments ±SE. Material numbers are the same as given in a previous paper (2). R = passive pressure of the lower punch in kilograms, E = force to extrude a tablet from the lower punch in kilograms, U = pressure of the loaded upper punch in kilograms, SF = slipping force of the tablet surface in grams [first, second, and third observations (1)], and OS = off scale.

between the upper punch and the surface of a tablet when a powder is compressed. As mentioned earlier (1, 2), if major tableting problems are attributed to sticking, the differences between the first, second, and third observations of the surface factors and their standard errors are relatively large.

RESULTS AND DISCUSSION

The purpose of the present work was to discover what properties of a material contribute to the formation of a good or bad tablet without knowing the physical properties of the material (*e.g.*, moisture content, porosity, particle size, fluidity, and angle of repose), and other independent factors (*e.g.*, tablet thickness and tablet size).

Presumably, these results demonstrate that the capping and/or sticking tendency of a material during tableting could be predicted primarily from data from tabletability factors. The constant values established for the tabletability tester were P = 2000 kg, h = 15.5 mm, and D = 10 mm. The passive pressure data of the loaded upper punch are shown in Tables II and III. Data for tabletability factors are shown in Table IV.

Although the force applied to the lower punch to extrude a tablet is not included in the calculation for tabletability factors *per se*, this force may serve to provide some general guidelines concerning the operation of a tableting machine. An extremely low force may result in a tendency toward capping, and an extremely high force may cause physical damage to the machine from the high binding tendency. Empirically, it was found that when more than 500 kg of pressure was required to extrude tablets (at a die depth of 22 mm), the likelihood of some damage to the machine was high.

Although these studies were only preliminary, the results suggest that tabletability factors may prove to be useful for the prediction of some tableting problems. The following interpretations of the data obtained from this study are proposed.

Table III—Tabletability and Other Factors[a]

Material	K_V	K_H	TT	TH
		Filling Depth 18 mm		
1	1617	0.10	5.44	>12
4	1399	0.30	9.94	—
5	720	1.33	4.64	4.9
10	663	1.14	5.24	>12
12	596	1.62	4.64	<2
29	691	1.23	4.64	4.2
40	1097	0.26	5.69	>12
		Filling Depth 22 mm		
1	905	0.29	10.04	>12
5	345	3.70	8.54	5.0
6	372	0.69	8.74	5.2
10	156	3.96	8.79	5.5
12	525	1.09	8.79	<2
13	545	0.68	8.34	<2
14	1496	−0.12	8.34	<2
15	553	1.05	8.34	5.0
19	1484	−0.06	9.69	12.0
24	1119	0.20	8.64	9.0
29	239	2.63	8.84	5.5
31	760	0.35	13.34	4.2
32	603	0.67	9.24	11.0
33	664	0.54	9.69	8.0
34	560	0.65	8.74	9.2
39	982	0.18	8.84	5.0
40	707	0.34	9.19	11.2
42	912	0.43	9.54	11.8

[a] All values are the mean of five experiments ±SE. Material numbers are the same as given in a previous paper (2). K_V = vertical factor; K_H = horizontal factor; TT = tablet thickness in millimeters; and TH = tablet hardness in kilograms, measured by a Monsanto tablet hardness tester.

Data in Tables II and III—Even though the poor fluidity of a material may have caused relatively large standard errors, comparisons of the present results with earlier data (2) show that the standard errors of observed values were diminished by using a fully automated tabletability tester instead of a manually operated one.

To compare the data, a standard material should be chosen and, ideally, its characteristics should take into account good compressibility, good formation, and the appearance of the tablet surface. Material 1 was selected as the standard since it came closest to meeting these criteria and included characteristics such as good lubricity and compressibility without apparent capping or sticking when incorporated as an excipient in a tablet. Material 1 consisted of a combination product whose formulation is a company trade secret. Hereafter, unless otherwise indicated, discussions of the data are based on a comparison between Material 1, the standard, and all other materials.

When the die whose filling depth (the lower limit of the lower punch) was 18 mm was used, only seven out of 19 materials gave complete data, *i.e.*, values for R as well as E and U. Materials for which only incomplete data could be obtained caused mechanical problems with the tabletability tester. For example, when Materials 19 and 39 were introduced, the force needed to extrude tablets by the lower punch registered zero. The reason for this reading was traced by observation to the fugacity of the powdered material outside of the die which flew about in all directions.

Another problem centered around the sticking tendencies of Materials 6, 13–15, 24, 31–34, and 42. An alarm bell was activated and the tester shut down automatically any time the pressure of the loaded upper punch exceeded 2500 kg. All of these materials caused a shut down at one time or another and made it impossible to obtain the mean of five consecutive and continuous tableting operations. The powders adhered heavily to the upper punch face, and the distance between the upper and lower punch faces was constantly lessened. Because of this phenomenon, the pressure of the loaded upper punch was increased during each successive operation, causing the alarm to ring and halting all operations and measurements. Since the reason for this occurrence was unknown, data for the dies with filling depths of 18 and 22 mm could not be used to predict tabletability.

However, the surface factor data obtained when using the die with a filling depth of 22 mm in a large-scale operation were better predictors of problems between the upper punch face and the tablet surface than the data obtained when using the other dies with filling depths of 18 and 26 mm. When slipping force is measured in the field to predict surface-sticking problems, a combination of high pressure and a die depth of 22 mm apparently is preferable to a combination of a more moderate pressure and a die depth of 26 mm. A powder that exhibited a very high surface factor, *i.e.*, an "off scale" powder or a powder that requires a force greater than the upper range of the instrument[3] (1), showed a strong tendency to stick to the face of the upper punch.

The fact that dies of different depths must be selected according to the directions of the forces or factors measured is an indication that when a powder is compressed, its various properties are changed and it no longer maintains the original physical relationships and proportions between those properties.

Table IV—Data obtained with a die depth of 26 mm showed no contradictions such as a negative value for K_H. To interpret the data, four assumptions were made:

1. An adequate value of the vertical factor, K_V, should exist for the formation of a good tablet from a powder. A material having a small K_V cannot be compressed into tablet form due to the poor transmittance of pressure.
2. An adequate value of the horizontal factor, K_H, should exist for the formation of a good tablet from a powder. Generally, the horizontal factor is considered to be the ratio of the compression stress of a powder occupying an upper space in a die (from surface a to b in Fig. 3*a*) to that of a powder occupying a lower space in a die (from surface b to c). Obviously, these two stress distributions must be different from each other. On the one hand, if a material has a relatively small K_H, the pressure of an upper punch can easily reach the surface of a tablet being compressed. However, if a material shows a large K_H, the pressure of an upper punch cannot reach the surface of a tablet effectively. An ideal K_H value is around 1.0.
3. The logical interrelationship between K_V and K_H is when: (*a*) K_V is large and K_H is small (capping would take place between the hard layer on the top and the tablet body below) and (*b*) K_V is small and K_H is large (capping would take place between the soft layer on the top surface of a tablet and its body) (Fig. 4).
4. The balance between the horizontal factor, K_H, and the vertical factor, K_V, can govern the tabletability of a powder. By definition, a good balance is reached when a powder could be compressed into a tablet with uniform compactness throughout its layers, but the numerical values of such a condition are still unknown. However, it should be possible to attain a numerical balance experimentally by repeated trials of many different kinds of materials and by a comparison of results from large-scale tablet manufacturing operations.

If these assumptions are applied, it is easier to understand the reasons for the capping problems encountered in industry. In addition, these assumptions indicate that a favorable balance of vertical and horizontal components in tableting is normally difficult to attain in large-scale production. It makes little difference if the values for K_H or K_V are large or small, as long as a suitable ratio or balance is maintained between the two components. This concept also takes into account the reality that, in a tableting operation, the production of acceptable thin tablets is easier than the production of acceptable thick ones.

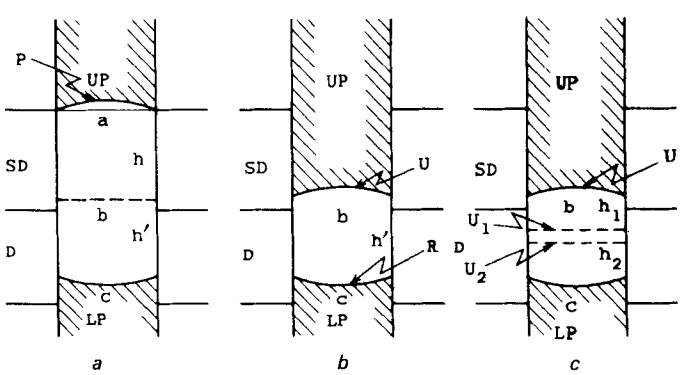

Figure 3—*Compression process. Key: UP, upper punch; LP, lower punch; SD, split die; D, die;* a, *top surface of the split die;* b, *lowest limit of the upper punch;* c, *lowest limit of the lower punch;* P, U, *and* R, *pressures at surfaces a, b, and c, respectively;* h *and* h′, *distances between surfaces a and b and surfaces b and c, respectively; and* h_1 *and* h_2, *distances between surfaces b and c, respectively.*

[3] Visigraph.

Table IV—Tabletability Factors for the Prediction of the Tabletability of a Powder[a]

Material	TT	TH	K_V^{26}	K_H^{26}	SF^{22} First	SF^{22} Second	SF^{22} Third
1	12.59	9.8	354	0.90	112 ± 4	118 ± 10	120 ± 11
4	14.84	<2	766	0.58	—	—	—
5	11.74	5.0	145	2.19	OS	OS	OS
6	11.84	12.0	316	1.27	OS	OS	OS
10	11.74	2.0	74	1.32	72 ± 2	72 ± 2	72 ± 2
12	11.34	0	157	1.78	OS	OS	OS
13	11.74	0	124	2.20	OS	OS	OS
14	11.64	<2	349	0.52	158 ± 8	147 ± 6	144 ± 7
15	11.84	4.5	449	1.13	OS	OS	OS
19	11.84	5.5	343	1.06	148 ± 6	144 ± 7	144 ± 7
24	11.74	3.0	172	1.45	OS	OS	OS
29	10.84	<2	102	1.41	OS	OS	OS
31	15.34	5.0	565	0.40	OS	OS	OS
32	11.74	7.5	342	0.95	OS	OS	OS
33	11.44	8.0	416	0.46	OS	OS	OS
34	11.34	9.0	298	1.46	OS	OS	OS
39	11.64	<2	514	0.62	128 ± 3	111 ± 5	107 ± 4
40	11.84	7.0	647	0.47	190 ± 3	178 ± 8	176 ± 9
42	11.74	3.2	305	1.62	68 ± 3	63 ± 3	62 ± 3

[a] All values are the mean of five experiments ±SE. TT = tablet thickness in millimeters (filling depth 26 mm), TH = tablet hardness in kilograms (filling depth 26 mm), K_V^{26} = vertical factor (filling depth 26 mm), K_H^{26} = horizontal factor (filling depth 26 mm), and SF^{22} = surface factor in grams (filling depth 22 mm).

In this discussion, the compressibility of a powder was based on the balance of the two factors during tableting. However, some materials rated high on the tabletability factor but could not be compressed into a tablet because of their poor binding characteristics. In these cases, results can be justified by measuring tablet hardness.

The substances used in the present experiment were primarily tablet additives. Therefore, few of the substances could be compressed to form good tablets in actual production practice[4]. The results of the experiment were categorized and analyzed as follows.

Material Compressed into Good Tablets by Using the Tabletability Tester, Not on a Large-Scale Manufacturing Basis (Table IV)—Material 1 was compressed to form a good tablet (tablet hardness = 8.2 kg). Materials 15 and 19 exhibited a K_V^{26} and K_H^{26} similar to those of Material 1, but the SF^{22} of Material 15 was "off scale" and could not be compressed into an acceptable tablet. Material 19 was compressed into a tablet (hardness ≅ 1.0 kg), but its SF^{22} was somewhat scattered.

Material 5 exhibited a small K_V^{26} and a large K_H^{26}, but it produced a good tablet. This result could be explained on the basis of Assumption 4; *i.e.*, it could have attained a suitable balance between K_V and K_H. Otherwise, Material 5, whose SF^{22} was off scale, showed a strong sticking tendency to the face of the upper punch and could not be compressed regularly into good tablets under regular production procedures.

The results with Material 24 were similar to those of Material 5. Material 24 could be made into good tablets by using the tabletability tester, for possibly the same reasons as with Material 5, but its SF^{22} was also off scale; it could not be compressed into good tablets under regular production conditions because of sticking and cracking. The reason for cracking may be due to the relatively smaller K_H^{26} value when compared to that of Material 5; the K_H of No. 24 was not strong enough to form a thicker, harder layer to prevent cracking.

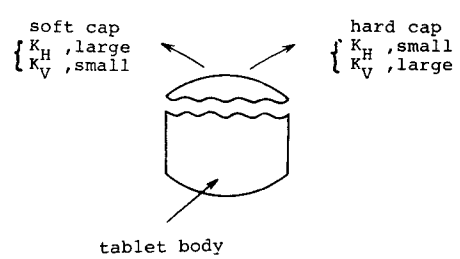

Figure 4—*Diagram of capping.*

[4] Tablet machine RT-S15-H, Kikusui Seisakusho Co., Kyoto, Japan. This machine had an 8-mm (5/16-in.) diameter standard-faced punch and die system, a tableting speed of 15 rpm, and an upper limit of the lower punch of 7.5 mm. When a powder was tabletable, about 30 kg of the powder was tableted continuously.

Material Compressed to Form Good Tablets on a Large-Scale Manufacturing Basis—Material 4 had a small K_H^{26} and a large K_V^{26} with a good balance between them. Although the SF^{22} of Material 4 was not measured, it was possible to make a good tablet, especially when relatively thin tablets were produced. The hardness of the tablets averaged about 7.8 kg (in actual tablet manufacturing).

Material 10 had a large K_H^{26} and a small K_V^{26}, but the balance between these factors allowed it to be compressed into a good tablet. The SF^{22} of Material 10 was somewhat scattered, and the lubricity of the tablet surface was poorer than others. The hardness of a tablet produced in actual tablet manufacturing was about 2.2 kg, but it was possible to make good tablets, especially when thin tablets were required.

Tableting problems arising from large-scale production procedures included the definite capping of tablets from Materials 6, 12–14, 29, 31, 33, 34, 39, 40, and 42. These materials exhibited K_H^{26} values that had both small and large variances from the ideal value of 1.0. Furthermore, there was strong adherence of Materials 5, 6, 12, 13, 15, 29, and 31–34 to the face of the upper punch after capping. All of these materials had an SF^{22} that was off scale. A creaking sound was also heard between the die and the lower punch when introducing Materials 14, 19, 24, 31, and 39. All of these materials required more than 500 kg of pressure to extrude the tablets.

The present investigation demonstrated the possibility of using tabletability factors to predict some tableting problems. It may be surmised that when a given powder sample exhibits a large K_V^{26}, it may be desirable to mix in a powder with a small K_V^{26} or K_H^{26}. Changes in K_V and K_H under these mixed powder conditions will be investigated at a later time.

In conclusion, it should be reiterated that the purposes of this study were to find a practical use for data obtained from a tabletability tester and to predict tableting problems. It was not intended to provide a detailed theoretical discussion of the data obtained. Further treatment of the theoretical considerations of the compression of powder-like materials can be found in Ref. 4. Although the present work was undertaken to obtain practical information from compression data, a major question still remains as to the final definition of the horizontal factor, since $\mu''\beta''$ in Eqs. 8 and 9 has no theoretical basis at all. The use of the horizontal factor seems to be helpful in predicting tableting problems when a powder is compressed into tablets in a large-scale operation instead of a tabletability tester. Therefore, further evaluation of this factor as a practical method for predicting tableting problems in a large-scale manufacturing procedure is still necessary.

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ˣ To whom inquiries should be directed.

Indolizine Derivatives with Biological Activity I: *N'*-Substituted Hydrazides of Indolizine-2-carboxylic Acid

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Abstract □ The synthesis and antimonoamine oxidase activity of some *N'*-substituted hydrazides of indolizine-2-carboxylic acid are described. They all inhibit monoamine oxidase and are more active than iproniazid. The structure–activity relationships also are discussed.

Keyphrases □ Indolizine-2-carboxylic acid hydrazides—synthesized, screened for effect on monoamine oxidase activity □ Hydrazides, *N'*-substituted—of indolizine-2-carboxylic acid synthesized, screened for effect on monoamine oxidase activity □ Monoamine oxidase activity—effect of various *N'*-substituted hydrazides of indolizine-2-carboxylic acid □ Structure–activity relationships—*N'*-substituted hydrazides of indolizine-2-carboxylic acid screened for effect on monoamine oxidase activity

Numerous *N'*-substituted hydrazides of indolecarboxylic acids have been synthesized in recent years as potential psychotherapeutic agents, and their inhibiting activity on monoamine oxidase has been tested *in vitro* (1, 2). The fundamental characteristic of such derivatives, some of which have proved to be intensely active, is the association in a single compound of a functional group with known antimonoamine oxidase activity, such as the hydrazide group, and the indole system. The indole system is present in various natural and synthetic compounds distinguished by psychotropic properties. The present paper reports the synthesis and study of the antimonoamine oxidase activity of a series of *N'*-substituted hydrazides of indolizine-2-carboxylic acid, which are analogs of the indole derivatives.

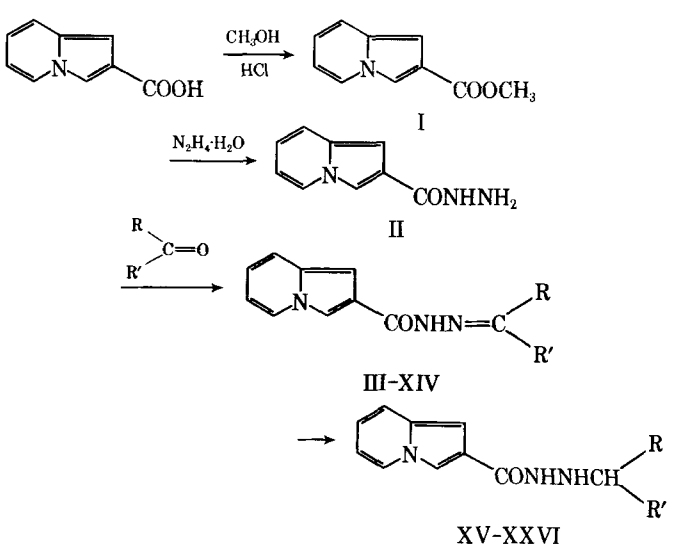
There are few literature reports on analogs of biologically active indole derivatives in which indole is replaced by indolizine. 1-Indolizinylalanine (3) has been prepared as a potential tryptophan antimetabolite; 1-indolizineacetic acid (4), an analog of 3-indoleacetic acid, has shown moderate auxinic activity; and numerous alkylindolizines (5), arylindolizines (6), and alkylaminoalkylindolizines (7, 8) have been synthesized and shown to influence the central nervous system.

Some 1-indolizineacetic acids (9, 10) possess analgesic and anti-inflammatory activity. Several indolizine analogs of indoxole (11, 12), a well-known anti-inflammatory agent, were synthesized recently.

CHEMISTRY

The *N'*-substituted hydrazides of indolizine-2-carboxylic acid (XV–XXVI) were synthesized according to Scheme I. On treatment with hydrazine hydrate, methyl indolizine-2-carboxylate (I), obtained by esterification of the corresponding acid (13) with methanol, gave indolizine-2-carboxylic acid hydrazide (II). The latter, by reaction with aldehydes and ketones, yielded the corresponding hydrazones, which were reduced with sodium borohydride.

It is not possible to perform the reduction of benzylidenehydrazide (IX) by this method. It was performed with lithium aluminum hydride or with hydrogen in the presence of palladium-on-charcoal and traces of acetic acid. At the end of each reduction, the IR spectrum of the product obtained indicated that the characteristic band of the C=N group of the initial hydrazones had disappeared.



Scheme I