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Studies on Techniques of Manufacturing Pharmacy. I. Prediction of Tableting Troubles such as Capping and Sticking. (1)

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A new compression fixture was designed for the measurement of the state of binding between a tablet surface and punch face.

It was found by the use of this device that the ability of a material to form a "good" or "bad" tablet may be predicted from two factors; the slipping force of a tablet surface and passive pressure of a lower punch. The results of measurement were also compared with tableting troubles that occur during a large-scale operation.

The recent development of special feeding devices for tableting presses has made it possible to compress powders directly into uniform tablets without the usual granulation steps. However, many of materials cannot be compressed into suitable tablets without prior treatment. At the present time the lack of basic knowledge of tableting mechanism has seriously hindered the elucidation and solution of this problem. A great majority of the published work on pharmaceutical tableting has been directed toward the evaluation of excipients such as binders, lubricants, and disintegrators. Only recently have systematic efforts been made to define the mechanism of compression, but the majority of these studies have dealt with the behavior of granules under pressure.

In 1963, Higuchi, *et al.*[2] had described a method for determining the pressure transmitted to the die wall during tablet compression to know the relation of die expansion to the transmitted pressure. It appears that materials which permit rather good conversion of normal pressure to lateral pressure tend to form good tablets as a broad and possibly too sweeping conclusion. In the next paper,[3] they concluded that side wall pressure measurements seem to be considerably valuable in providing information and characteristics of different tableting formulas. Milosovich and Shlanta[4] showed an instrument which was developed to measure stress relaxation of a powder bed under constant strain to test the concept that the process of compression of a powder bed involves time dependent flow and viscoelastic properties. Tests of factors known to influence tablet capping, hardness, and friability exhibited that these factors also had marked effect on relaxation data. The relationships between compaction forces and crushing strength, voidage, and ejection forces were evaluated by Shotton and Ganderton.[5]

Long[6] used a split die to measure the radial pressures. He studied the complete pressure cycles during loading and unloading of materials used in powder metallurgy and a theory was put forward regarding the nature of the residual radial pressure. Leigh, Carless, and Burt[7] had also reported similar studies and they concluded from reasonable evidence that the

1) Location: *Misasagi Yamashina, Higashiyama-ku, Kyoto.*
2) J.J. Windheuser, J. Misra, S.P. Eriksen, and T. Higuchi, *J. Pharm. Sci.*, **52**, 767 (1963).
3) T. Higuchi, T. Shimamoto, S.P. Eriksen, and T. Yashiki, *J. Pharm. Sci.*, **54**, 111 (1965).
4) S. Shlanta, and G. Milosovich, *J. Pharm. Sci.*, **53**, 562 (1964).
5) E. Shotton, and D. Ganderton, *J. Pharm. Pharmacol.*, **12**, Suppl. 87T (1960).
6) W.M. Long, *Powder Met.*, **6**, 173 (1960).
7) S. Leigh, J.E. Carless, and B.W. Burt, *J. Pharm. Sci.*, **56**, 888 (1967).

classification of materials that form "good" or "bad" tablets may be made from an analysis of their pressure cycles, rather than from surmise.

The object of the present investigation was to find out the type and nature of slipping force of tablet surface and passive pressure of lower punch involved during direct compression of different pharmaceutical materials and mixtures without the usual granulation steps. It was of particular interest to find whether the ability of a material or mixtures to form a "good" or "bad" tablet (particularly with respect to capping and/or sticking) was manifested in the two factors, the slipping force of a tablet surface and passive pressure of lower punch.

Experimental

Apparatus

A Kikusui No. 6 single-punch tableting machine,[8] fitted with 10 mmϕ punch (radius of curvature, 14R) was instrumented with strain gauges to monitor the passive force involved during a compression cycle, at a lower punch. The upper plunger had a flat face at the bottom and upper punch with small knob was separated completly from the body of tableting machine. The upper punch (separated type) was supported by a split special punch holder with ball bearing without interfering with the movement of the upper punch, and the die plate was suitably modified to house a split die for measurement of slipping force of a tablet surface.

The whole instrumentation and main apparatus in detail were shown in Fig. 1 and 2. To monitor the passive pressure of the lower punch, the strain gauge (type S-104, Shinko Tsushin Co., Ltd., resistance 119.3 Ω, gauge factor 1.92) was connected in series, power supply unit (Type: DS 6/RX, Shinkoh Communication Ind. Co., Ltd., Kanagawa), dynamic strain amplifier (Type: DS 6/RX, Shinkoh Communication Ind. Co., Ltd.) and Visigraph FR-201 (San-ei Instrument Co., Ltd., Tokyo).

U-Gauge (Type: UT, capacity 1 kg, resistance 119.30 Ω, gauge factor 1.92) was used to monitor the slipping force of a tablet surface, and connected in the same series as in measurement of the passive pressure of lower punch.

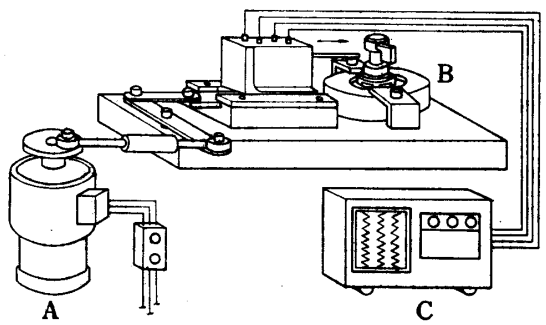

Fig. 1. Testing Instrument equipped with Compression Fixture

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A: pushing device with a strain gauge working on the knob of the upper punch, B: compression fixture for measurement of slipping force of a tablet surface and passive pressure of lower puch, C: oscillograph

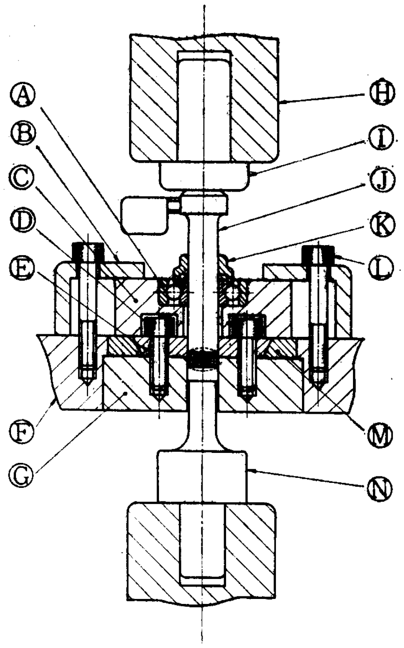

Fig. 2. Compression Fixture for Measurement of Slipping Force of a Tablet Surface and Passive Pressure of Lower Punch

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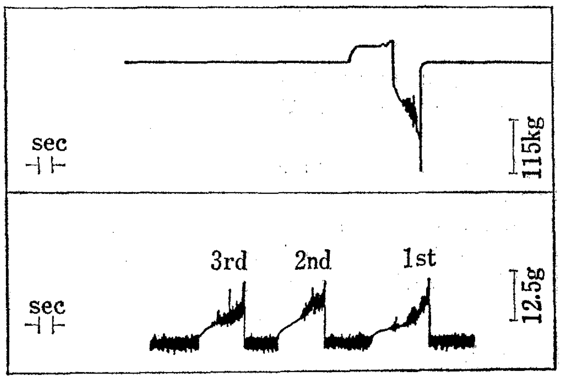
A: ball-bearing ring, B: fixing panel, C: holder for upper punch (separate type), D: screw, E: die (separate type), F: die plate, G: die base, H: upper plunger, I: compression sheet for upper punch, J: upper punch, K: non-skid ring, L: screw, M: ring for fixing of die (separated type), N: lower punch

Procedure

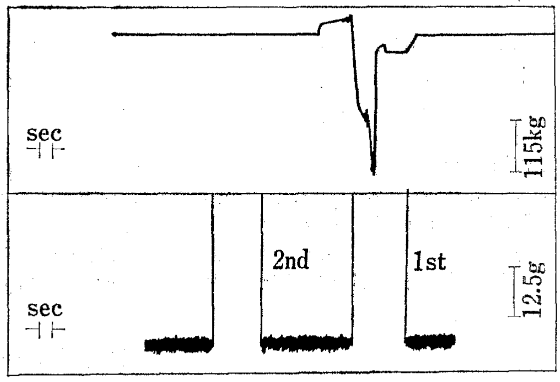
Actual procedure of the measurements was described as follows:

1) A split die was housed in the base die in die plate and fixed with two screws.
2) The face of lower punch was brought down to maximum depth.

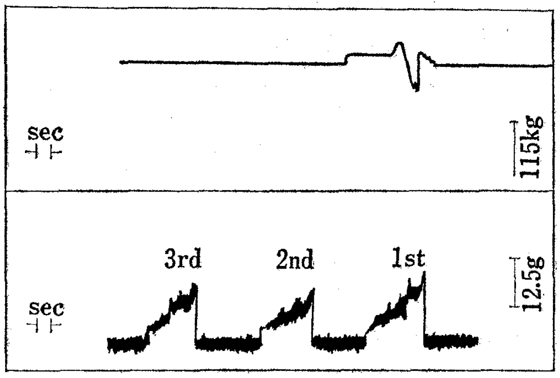
8) Kikusui Seisakusho Co., Ltd., Kyoto.



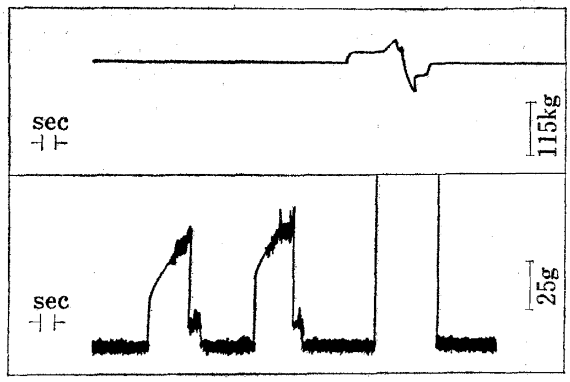
Formula No. 14 shown in Table I.



Formula No. 22 shown in Table I.



Tablet additive No. 7 shown in Table I.



Tablet additive No. 8 shown in Table I.

Fig. 3. Record of Passive Pressure of Lower Punch and Slipping Force of Tablet Surface as a Function of Time on Oscillograms

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upper half, passive pressure of lower punch; lower half, slipping force of tablet surface

3) Pharmaceutical materials for direct compression was filled in the die cavity.

4) The upper punch (separate type) with both ball–bearing ring and non–skid ring was set on a powder material at the position slightly lower than the upper face of the split die.

5) The special split holder of the upper punch was set with screws around the upper punch with both ball–bearing ring and non–skid ring loose.

6) The upper plunger of the tablet machine hits the head of upper punch at constant pressure by hand. This hitting should be stopped so that the position of the bottom of upper punch is within 0.5 mm above the bottom face of a split die. When the position of the bottom of upper punch is more higher, the tablet formed will be broken after removal of the holder of the upper punch and a split die for measurement of slipping force of a tablet surface. Contrarily, when the position is lower, then some friction will occur between the upper punch and the base die at the measurement. Use of a graduated upper punch will make it easier to stop the hitting at such a desirable position.

7) A split die was taken out after removal of the special split holder of the upper punch and this holder was re-set as before.

8) The non–skid ring around the upper punch was fixed with the ball bearing ring in the holder.

9) The upper plunger was pulled out from the upper punch.

10) The strain gauge which moves by electromotive force pushes the knob attached to the upper punch. The position of the knob was previously set at a right angle to the direction of the needle of the strain gauge. Deformation of the strain gauge was recorded at a chart speed of 4 mm/sec, using the Visigraph.

The procedure described above is for the first observation of the slipping force of a tablet surface. The second and the third observations were determined by re-setting of position of the knob as before without tableting newly. Measurement of slipping force was repeated three times because it was considered that there would be no variation in the measured values of slipping force among the 1st, 2nd, and 3rd measurements. If, on the other hand, there were sticking between the upper punch face and tablet surface, or capping occurred near the tablet surface, there should be a variation in the measured values in three repeated measurements.

Materials

Pharmaceutical materials used in the experiments were plain compound or mixtures which are widely used by direct tableting, and the formulas of these materials are shown in Table I.

These materials were sieved through 60-mesh sieves, and mixed well by V-shaped mixing apparatus (Tokuju Kosakusho, Tokyo).

When slipping force of a tablet surface and passive pressure of lower punch were to be determined, 0.60 to 0.65 g of each powder material was used for making a tablet.

On the other hand, about 30 kg of tablet materials (tablet weight, about 0.23 g) of each material were tableted by the tablet machine (RT–S 15-H, 8 mmϕ, R-face, 16 rpm, Kikusui Seisakusho Co., Ltd.) to know the ability of a material to form a "good" or "bad" tablet (particulary with respect to capping and/or sticking).

Results and Discussion

The purpose of the present investigation was to find what the properties of a material is to form "good" or "bad" tablets without knowing the physical properties of the material, such as moisture content, porosity, particle size, fluidity, angle of repose, *etc.*, and also independent of tablet thickness, tablet size, or preliminary test of tableting, *etc.*

Presumably, the results obtained here showed that the capping and/or sticking tendency of a material when tableting could be predicted from the data of both slipping force of a tablet surface and passive pressure of lower punch.

The data of slipping force of a tablet surface and passive pressure of lower punch are shown in Table II, for materials having a tendency for sticking or sticking and capping. The mean values of these determinations of all materials used in the experiments are shown in Table III. To find the relationship between these measurements and the results of tableting the materials in industrial manufacturing conditions, the results from tableting on a large scale by direct-tableting machine, "Kikusui RT–S, 15-H", are also shown in Table III, describing the presence of capping and/or sticking, tablet hardness, disintegration time, and tablet thickness.

Preliminary experiments showed that both small variation in the rate of compression and pressure of upper punch had actually no significant effect on the slipping force of a tablet surface and the passive pressure of lower punch. Therefore, the rate of compression and pressure of upper punch were adjusted to be constant at about 1 cm/sec and within the range of 891$\pm$36 kg, respectively, by hand process. Moving rate of the strain-gauge to push the knob of the upper punch was 5 mm/sec.

Although these studies are more or less preliminary in nature, the present results suggested that measurements of slipping force of a tablet surface and passive pressure of lower punch developed during the formation of a pharmaceutical tablet may provide a useful indication for prediction of tableting troubles.

As a broad and possibly too sweeping a conclusion, the following interpretations are proposed.

(A) Materials which show the following results tend to form "good" tablets (Group A in Table III).

(1) Differences among the values of 1st, 2nd and 3rd observations were not significant.

(2) Differences among the values of i, ii, iii, iv and v observations were also not significant.

(3) Materials showing higher passive pressure of lower punch such as 200 to 300 kg with relatively small standard errors within about 50 kg tend to form good tablets without either capping or sticking tendency.

(B) Materials which provide the following results tend to form tablets with sticking tendency (Group B in Table III).

(1) Differences among the values of 1st, 2nd, and 3rd observations were recognized.

(2) Observed values of i, ii, iii, iv, and v were increased with increased repetition of observations, successively, or scale out.

Table I. Formulas of Materials Compressed into Test Tablets

Section A. formulas of active ingredients

Formula No.	Composition (in %)
1—3 1—8 1—10	powdered swertia herb 5.5, diastase 22.8 ext. scopol. 1.1, additive 3, 8, or 10 70.6
2—1	magnesium oxide 24.0, ext. scopol. 2.4, 1-menthol 0.8, additives 1 72.8
3—1	diastase 20.0, pancreatin 20.0, powdered swertia herb. 6.0, magnesium oxide 10.0, additives 1 44.0
4—2	powdered phellodendron 40.0, additives 2 60.0
5—3	bisatin 5.5, magnesium oxide 13.9, additives 3 80.6
6—10	phenacetin 5.5, magnesium oxide 13.9, additives 10 80.6
7—4	quinine hydrochloride 15.0, aminopyrine 25.0, additives 4 60.0
8—10	phenacetin 24.5, caffeine 7.3, chlorophenylamine maleate 0.4, additives 10 49.8
9—1	aminopyrine 8.3, phenacetin 22.0, noscapin 1.4, coff. et nat. benz. 16.5, additives 1 51.8
10—8	hustagin (Sankyo Co., Ltd.) 40.0, noscapin 10.0, additives 8 50.0
11—3	dyphylline (NND)15.8, bromvalerylurea 31.5, *dl*-methylephedrin hydrochloride 2.7, additives 3 50.0
12—3 12—8	powdered glycyrrhiza 3.9, powdered pueraria 11.7 powdered ephedra 8.8, powdered zingiber 5.9, powdered zizyphus inermis 5.9, powdered cinnam. cort. 6.9, powdered paeonia 6.9, additives 3 or 8 50.0
13	phenovalin 100.0
14	antiprotaozoan[a]
15	antiprotaozoan[a]
16	remedies for peptic ulcer[a]
17	lactose 70.0, potato starch 29.0, magnesium stearate 1.0
18	agents for liver diseases[a]
19	amobarbital 100.0
20	acetanilide 35.0, lactose 60.0, magnesium stearate 5.0
21	pancreatin 50.0, diastase 50.0
22	quinine sulfate 40.0, lactose 60.0
23	guaiacol glycerol ether 100.0
24	agents for liver diseases[b]
25	noscapine hydrochloride 100.0
26	heavy magnesium oxide 100.0
27	cathartic agents[a]

Section B. composition of tablet additives

Additive No.	Composition (in %)
1	lactose 25.0, potato starch 50.0, avicel (Asahi Kasei Kogyo Co., Ltd.) 15.0, alumin. silic. synth. 5.0, lubri wax (Froint Sangyo Co., Ltd.) 5.0
2	lactose 25.0, potato starch 40.0, avicel 15.0, alumin. silic. synth. 20.0
3	perfiller-101 (Froint Sangyo Co., Ltd.) 75.0, avicel 15.0, alumin. silic. synth. 5.0, lubri wax 5.0
4	lactose 25.0, potato starch 35.0, avicel 15.0, alumin. silic. synth. 15.0, magnesium stearate 0.5, Licamit U-100 (Froint Sangyo Co., Ltd.) 9.5
5	granulated lactose 25.0, potato starch 35.0, avicel 15.0, alumin. silic. synth. 15.0, magnesium stearate 0.5, Licamit U-100 9.5
6	lactose 30.0, potato starch 70.0
7	avicel 30.0, granulated lactose 68.0, magnesium stearate 1.0, silic. oxide 1.0
8	lactose 70.0, calc. phos. dibas. 30.0
9	lactose 30.0, potato starch 30.0, avicel 25.0, alumin. silic. synth. 10.0, talc 3.0 silic. oxide 1.0, magesium stearate 1.0
10	alumin. silic. synth. 50.0, sanalmin SN-A (Kyowa Kagaku Kogyo Co., Ltd.) 50.0

a) A special formula now in use of a certain firm but which cannot be published.
b) A special formula now in use of a cetain firm but which cannot be published and known to be attended with tableting troubles.

TABLE II. Data of Slipping Force of Tablet Surface and Passive Pressure of Lower Punch

Group	Formula No.	R-P[a]	Slipping force of tablet surface[b] 1st (g)	2nd (g)	3rd (g)	Passive pressure of lower punch (kg)
A	14	i	22	23	22	413
		ii	22	32	37	418
		iii	33	32	29	308
		iv	28	14	15	330
		v	29	20	23	303
	15	i	31	23	23	248
		ii	23	23	26	356
		iii	19	22	14	220
		iv	28	18	20	319
		v	33	31	23	341
	18	i	24	20	20	275
		ii	19	20	20	308
		iii	15	18	17	303
		iv	22	28	31	264
	19	i	43	32	33	303
		ii	29	32	31	275
		iii	28	38	36	303
		iv	33	41	36	165
		v	35	41	49	176
	27	i	33	22	20	319
		ii	29	18	18	253
		iii	26	17	18	319
		iv	32	22	22	341
		v	41	28	27	275
	2—1[c]	i	44	29	29	292
		ii	52	28	28	314
		iii	26	19	15	363
		iv	70	32	48	198
B	13	i	24	24	24	319
		ii	36	27	27	264
		iii	38	27	13	303
		iv	42	28	28	347
		v	42	22	28	356
	9—1	i	19	29	29	165
		ii	33	41	41	281
		iii	35	36	36	303
		iv	40	42	43	347
		v	42	29	36	356
	17	i	55	29	29	356
		ii	54	26	27	330
		iii	57	29	19	319
		iv	61	29	29	374
	TA-5[e]	i	49	41	41	228
		ii	19	18	17	167
		iii	51	40	40	210
		iv	78	70	77	149
		v	74	74	80	162
	TA-9	i	133	46	38	247
		ii	51	26	26	254
		iii	102	35	35	261
		iv	65	33	31	228
		v	26	26	26	286
	23	i	63	26	26	231
		ii	54	29	29	176
		iii	82	60	61	356
		iv	200>[d]	26	35	385
		v	200>	26	27	303
	25	i	29	27	27	347
		ii	35	19	17	330
		iii	200>	102	29	319
		iv	32	35	33	253
		v	200>	101	100	319
	12—3	i	200>	128	128	209
		ii	77	77	77	314
		iii	200>	121	121	237
		iv	146	96	96	226
		v	115	79	72	319
	22	i	200>	200>	200>	319
		ii	200>	200>	200>	193
		iii	200>	200>	200>	330
		iv	200>	31	10	330
		v	200>	200>	200>	253
C	7—4	i	26	23	29	149
		ii	26	26	26	330
		iii	26	26	23	198
		iv	38	35	36	308
		v	57	36	36	356
	16	i	19	15	15	99
		ii	20	22	22	358
		iii	15	20	19	248
		iv	17	23	23	193
		v	15	12	10	264
	1—3	i	54	31	31	138
		ii	56	31	31	110
		iii	102	77	74	231
		iv	38	36	36	356
		v	59	38	38	165
	20	i	27	19	20	176
		ii	23	23	26	248
		iii	31	31	31	176
		iv	27	26	26	193
		v	28	23	28	198
C	21	i	22	23	20	116
		ii	10	22	22	198
		iii	22	23	23	154
		iv	20	20	23	193
	TA-4	i	57	47	47	149
		ii	66	57	64	319
		iii	55	47	45	105
		iv	77	49	51	88
		v	74	65	59	94
	TA-7	i	97	70	72	127
		ii	102	80	80	138
		iii	72	56	56	94
		iv	89	69	51	127
		v	89	89	72	220
D	4—2	i	40	38	38	330
		ii	32	29	28	466
		iii	28	19	19	462
		iv	23	28	20	253
		v	20	22	24	440
	TA-1	i	43	38	40	182
		ii	89	51	46	253
		iii	98	72	42	204
		iv	98	43	50	116
		v	69	40	42	182
	11—3	i	35	32	32	396
		ii	36	33	33	209
		iii	45	38	37	440
		iv	89	74	78	160
		v	102	102	102	220
	TA-3	i	40	29	28	127
		ii	57	47	40	149
		iii	64	31	28	127
		iv	87	72	69	143
		v	57	40	47	198
	TA-2	i	13	15	15	154
		ii	30	40	43	88
		iii	70	74	82	72
		iv	68	80	49	127
		v	78	65	78	171
	TA-10	i	46	51	51	110
		ii	43	46	46	62
		iii	156	102	102	56
		iv	66	64	72	44
		v	161	153	153	56
	24	i	200>	31	26	121
		ii	168	59	46	138
		iii	102	41	43	143
		iv	200>	123	49	127
	3—1	i	59	31	31	204
		ii	200>	29	32	341
		iii	59	38	38	209
		iv	200>	29	33	138
		v	96	29	28	275
	5—3	i	200>	115	115	138
		ii	31	31	31	226
		iii	102	179	200>	187
		iv	179	179	179	231
	TA-6	i	61	28	28	56
		ii	200>	200>	200>	161
		iii	134	31	36	166
		iv	185	200>	200>	110
		v	200>	41	41	176
	1—8	i	200>	200>	200>	176
		ii	200>	200>	200>	72
		iii	200>	200>	200>	94
	1—10	i	200>	200>	200>	55
		ii	200>	200>	200>	99
		iii	200>	200>	200>	99
	12—8	i	83	45	45	138
		ii	200>	26	26	154
		iii	200>	103	153	116
	10—8	i	20	20	20	116
		ii	200>	200>	200>	121
	6—10	i	200>	200>	200>	110
		ii	26	26	26	171
		iii	26	26	26	83
		iv	27	26	27	116
		v	72	45	38	99
	8—10	i	200>	200>	200>	198
		ii	200>	200>	200>	138
		iii	200>	200>	200>	143
	26	i	42	42	46	55
		ii	59	49	38	11
		iii	45	45	44	44
		iv	200>	40	40	83
	TA-8	i	102	200>	200>	110
		ii	133	92	92	143
		iii	200>	147	128	110

All compressions were made to a pressure of 891 ± 36 kg on the upper punch. Moving rate of the strain-gauge to push the knob of the upper punch was 5 mm/sec. Weight of a test tablet was 0.6 g.

a) R-P shows number of repetition of tableting after removal of the former tablet only by extrusion of the lower punch without any cleaning of the die and/or the punch faces.

b) The second and the third observations of slipping force were determined by re-setting the position of the knob as before without tableting newly.

c) Numerals on the right hand indicate the tablet additive No. shown in Table I, Section B.

d) The needle of the oscillograph scaled out showing above 200 g of slipping force. However, in Table III, mean value of slipping force of a material which has above 200 g shown in Table II, was shown. In such a case, mean value is not so essential and is calculated from the data obtained by reducing the sensibility of oscillograph.

e) Tablet additive No. with no active ingredients.

TABLE III. Data Obtained from the Compression of Various Materials

Group	Formula No.	Mean values of SF[d)] 1st (g)	2nd (g)	3rd (g)	Mean values of LP[e)] (kg)	Hardness[f)] (kg)	Tablet thickness (mm)	D.T.[g)] (min)	Tendency of Stick.[h)]	Cap.[i)]
A	14	27± 5[c)]	24± 8	25± 8	354± 56	5.6	4.3	1	—	—
	15	27± 6	23± 5	21± 5	297± 59	5.7	4.2	1	—	—
	18	20± 4	21± 4	22± 6	287± 21	4.7	4.2	10	—	—
	19	34± 6	37± 4	37± 7	244± 68	4.3	3.6	60>	—	—
	27	32± 6	21± 4	21± 3	301± 35	4.2	3.6	10	—	—
	2—1[a)]	49± 19	27± 5	30± 14	292± 68	6.8	3.9	5	—	—
B	13	37± 7	26± 2	24± 6	318± 36	6.3	4.6	1	±	—
	9—1	34± 9	35± 6	37± 5	290± 45	5.5	4.6	1	±	—
	17	57± 3	28± 1	21± 8	345± 25	4.4	5.2	1	±	—
	TA—5[b)]	54± 23	49± 23	51± 38	188± 42	12.2	5.0	2	+	—
	TA—9	75± 42	33± 8	31± 5	215± 95	6.4	4.5	3	+	—
	23	SO[j)]	30± 6	36± 14	290± 86	untabletable[k)]			++	—
	25	SO	57± 41	41± 33	314± 27	untabletable			++	—
	12— 3	SO	100± 23	99± 25	261± 51	untabletable			++	—
	22	SO	SO	SO	285± 60	untabletable			++	—
C	7— 4	35± 13	29± 6	30± 6	268± 95	6.2	4.9	5	—	±
	16	17± 2	18± 5	18± 5	232± 95	4.3	5.1	2	±	±
	1— 3	52± 9	43± 16	42± 18	200± 98	8.6	4.7	30	—	±
	20	28± 3	25± 4	26± 4	198± 29	1.5	4.7	60>	—	+
	21	19± 6	22± 1	22± 1	165± 38	untabletable			—	++
	TA—4	65± 10	53± 8	53± 8	151± 96	5.3	4.4	15	—	+
	TA—7	90± 11	73± 12	66± 12	141± 47	6.1	5.0	3	—	+
D	4— 2	29± 8	27± 7	24± 8	390± 94	7.0	4.4	60>	±	±
	TA—1	80± 24	49± 14	44± 5	187± 49	5.0	3.9	1	±	±
	11— 3	61± 32	56± 31	56± 31	285±124	9.0	5.1	10	+	±
	TA—3	61± 17	54± 18	42± 17	149± 29	11.0	4.3	15	+	+
	TA—2	52± 29	54± 27	53± 27	122± 42	3.7	4.5	1	+	++
	TA—10	94± 59	83± 44	85± 44	66± 25	untabletable			+	++
	24	SO	64± 41	41± 10	132± 10	untabletable			++	+
	3— 1	SO	31± 4	32± 4	233± 76	6.1	4.8	40	++	±
	5— 3	SO	126± 66	SO	195± 43	untabletable			++	±
	TA—6	183± 90	108± 98	119± 99	134± 50	untabletalbe			++	+
	1— 8	SO	SO	SO	111± 55	untabletable			++	++
	1—10	SO	SO	127±117	84± 20	untabletable			++	++
	12— 8	SO	58± 40	75± 67	136± 19	untabletable			++	++
	10— 8	SO	112±130	SO	118± 4	untabletable			++	++
	6—10	SO	35± 13	SO	116± 33	untabletable			++	++
	8—10	SO	SO	SO	160± 33	untabletable			++	++
	26	SO	44± 4	42± 3	48± 25	untabletable			++	++
	TA—8	SO	165± 83	175±114	121± 19	untabletable			++	++

a) Numerals on the right hand of formula numbers show the number of tablet additives shown in Table I, Section B.
b) TA shows the formula number of tablet additives when no active ingredients were mixed for the tests.
c) mean value with standard error
d) slipping force of a tablet surface
e) passive pressure of lower punch
f) Using the Monsanto hardness tester.
g) disintegration time determined by the method described in J.P. VII
h) and *i*) Sticking and capping, respectively, in appearance of tablets manufactured from large amount of a material such as about 30 kg. Nevertheless, tableting could not be performed because of tableting troubles in most of the groups of B, C, and D except A.
—: none, ±: questionable, +: medium ++,: severe
j) SO shows scale out recorded on an oscillogram.
k) acceptable tablet could not be obtained.
note: Hardness was measured with the first test tablet, and thickness and disintegration time with the second tablet.

(3) There was no apparent relationship between sticking tendency and passive pressure of lower punch.

(C) Materials which exhibit the following resutls tend to form tablets having capping tendency (Group C in Table III).

(1) No relationship between slipping force of tablet surface and capping was recognized.

(2) Passive pressure of lower punch was lower with increased capping tendency and remarkable capping was observed when the pressure was extremely low such as about 100 kg.

(D) Materials which indicate the following results tend to form tablets having both tendency of sticking and capping (Group D in Table III).

(1) Differences among the values of 1st, 2nd, and 3rd observations were significant.

(2) Observed values of i, ii, iii, iv, and v increased with increasing repetition of observations, successively.

(3) Passive pressure of lower punch was lower with increasing capping tendency.

(E) Materials which show the following results tend to be tabletable in short time but untabletable in continuous tableting (some of Group B, C, and D in Table III).

(1) Differences among the values of 1st, 2nd, and 3rd observations were variable and not so significant.

(2) Observed values of i, ii, iii, iv, and v increased slightly with increasing repetition of observations and/or accompanied with relatively large standard errors.

(3) Passive pressure of lower punch was not so low but relatively large standard error was present.

In addition to the results obtained as aobve, the behavior of slipping force of a tablet There and passive pressure of lower punch in oscillograms is shown in Fig. 3 for reference. surface was hardly any difference in stress relaxation and time lag to reach the maximum pressure in oscillorgams among all the materials and indistinguishable for detection of capping and/or sticking tendency.

In conclusion, the measurement of slipping force between tablet surface and punch face would be one of the main factors for prediction of extremely severe tableting troubles but determination of passive pressure of lower punch was also effective for prediction of complicated tableting troubles as one of supplementary factors. It seems to be more helpful for prediction of tableting troubles to measure compression pressure of upper punch, accepted pressure of die wall, and pressure of lower punch for ejection of a tablet, *etc.*, with measurement of the slipping force. On the other hand, it is possible that behavior of the surface between punch face and a tablet surface could be observed by measurement of not only the slipping force but also force of snapping or pulling off of the upper punch (separate type) from the tablet surface. Relationships among these factors will be reported in the next paper.

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