Instrumented Rotary Tablet Machines II

Evaluation and Typical Applications in Pharmaceutical Research, Development, and Production Studies

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The instrumented rotary tablet machines (IRTM's) previously described have been used to study many phases of the tableting process. The performance of rotary tablet machines with respect to compressional force generated at various settings of the machine controls and to the tablets produced was analyzed and graphically described. Additional studies established the specific relationships between the dimensions and physical properties of the tablets and the compressional forces used to prepare them for a number of different tableting mixtures. These findings are compared with similar relationships obtained by others who used instrumented single punch tablet presses, specialized "static" compression methods, or empirical methods of measuring compressional force. In most cases the results obtained for rotary machines were similar to those previously reported, but in a few instances contradictory behaviors were observed. It was concluded that the excessive amount of punch-to-punch and cycle-to-cycle variation in compressional and ejectional forces that was unexpectedly found to exist for rotary tablet machines is primarily due to unequal filling of the individual dies with stock. Some applications where IRTM's were used to investigate typical tablet development and production problems are described.

THE INSTRUMENTATION of conventional rotary tablet machines so that compressional and ejectional forces can be determined under dynamic, production-type conditions has been described in the first paper of this series (1). Along with the details of their design and construction, the type and the nature of the data which can be obtained from instrumented rotary tablet machines (IRTM's) were also presented.

In the present report a series of experiments evaluated the performance of rotary tablet machines with respect to the tablets and the compressional force levels produced over the entire range of the various machine settings.

Following these investigations, another series of experiments examined the relationships between compressional force and the physical properties of the tablets produced from a variety of different tableting mixtures. These findings were compared to those previously found by others working with instrumented single stroke tablet machines (2–18), static compressional devices (19–24), empirical methods of measuring "compression" (25–29), and rotary presses (2, 30, 31).

When the basic performance of the rotary presses had been established, the IRTM's were used to study some typical tablet development and production problems.

Data from specific tableting runs as well as general observations from the studies are presented to describe the various ways that the IRTM's were used.

EXPERIMENTAL

Materials.—Since the main purpose of this paper is to describe the value of the IRTM, the details of the formulations and their preparation are being omitted. However, a variety of experimental and standard production granulations as well as a number of experimental direct compaction mixtures were studied. All formulations contained therapeutic concentrations of physiologically active ingredients. As a result, data on the compressional characteristics of actual production-type materials were collected.

Methods of Measurement and Equipment.—(*a*) Hardness values are the average for 5 to 20 tablets determined on a Strong-Cobb hardness tester[1] operated from a compressed air line.

(*b*) Fracture resistance values are also the average for 5 to 20 tablets determined by using the modified anvil and plunger for the Strong-Cobb hardness tester previously described by Endicott *et al.* (32).

(*c*) Friability values are the weight loss in per cent determined after 20 tablets were rotated in the Roche Friabilator for 4 min. at 25 r.p.m. (33).

(*d*) Disintegration times, determined by U.S.P. procedure, apparatus, and official plastic disks, are reported either as the average time or the total time required for six tablets to disintegrate. In some cases the disks were not used. Generally, the fluid used was 750 ml. of deionized water at ~37°; when a different fluid was used, this is indicated.

(*e*) Dissolutive rates, expressed in terms of the

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[1] Strong-Cobb & Co., Inc., Cleveland, Ohio.

time required for a given percentage of the drug(s) to be dissolved (*e.g.*, $T_{50\%}$) from the tablet, were determined either by using the procedures and equipment described previously by Schroeter *et al.* (34) or by using the "automated dissolution rate apparatus" described by Schroeter and Wagner (35).

(*f*) Mean tablet weights were obtained by weighing 90 to 100 tablets on torsion balances and performing the appropriate calculations. Individual tablet weights were determined to the nearest 0.1 mg. on a Mettler Gramatic balance.[2]

(*g*) Mean tablet thicknesses were obtained either by measuring the total length (to the nearest 0.01 in.) of a column of 60 to 100 tablets stacked face to face in a V-shaped trough (one side of which was a 2 ft. steel ruler) and making appropriate calculations or by measuring individual tablets with dial micrometers[3,4] (estimated to the nearest 0.0005 or 0.0001 in., respectively) and averaging the values obtained.

(*h*) Compression ratios (CR), a measure of a tablet's apparent density, were calculated either by dividing the weight of the individual tablet by its own thickness or by dividing the mean weight by the mean thickness for a tablet sample and expressing the results in "mg./in." (27, 29). The term compression ratio is used here because of its historical significance and widespread usage. To convert to mg./mm., divide the compression ratio in mg./in. by 25.4.

(*i*) Compressional and ejectional force values were obtained from the Stokes 540-35 IRTM, the Stokes 1/2 BB2–27 IRTM, or the instrumented ejectional track of the Manesty Bicota machine and the associated electronic and photographic equipment described previously (1). Mean values were determined by averaging 50 to 130 individual impulse heights (estimated to the nearest millimeter) from the photograph obtained for the determination and making appropriate calculations as described previously (1).

(*j*) Settings for the press controls were designated as follows.

Speed Settings.—These were determined either by reading the press tachometers (calibrated in tablets/min. (TPM) for the 540–35 and 1/2 BB2–27 presses) or by measuring the r.p.m. of the head and converting this to TPM for the conventional BB2–27 press.

For a 540–35 press the rate ranges from 700 to ~2400 TPM (2 tablets/station/revolution). For the 1/2 BB2-27 press the rate ranges from ~350 to 700 TPM (1 tablet/station/revolution). Since the conventional BB2–27 press produces two tablets/station/revolution, it has twice the rate (700 to 1400 TPM) of the 1/2 BB2–27 press.

Weight Cam Settings.—These were expressed in terms of "notches of weight added." For both the 540–35 and the BB2–27 presses one complete rotation of this control equals 40 notches.

Thickness Settings.—These were expressed in terms of revolutions of the appropriate control for the 540–35 press on which pointers and specially calibrated dials were installed. For the BB2–27 presses the settings were in terms of "notches;" these were converted to degrees of rotation by the factor, 7 notches = 45°, or 56 notches = one complete revolution.

(*k*) Punches and dies were regular production tools. However, the length of each punch was measured with a platform dial micrometer[5] and the diameter of each punch and die was determined by using the Sheffield Precisionaire Gage.[6] Each individual tool was labeled and its dimensions recorded. The tools were then arranged so that upper and lower punches and dies with uniform clearances were obtained for each station. These were installed so that the total length of upper and lower punches first decreased from and then increased back to the total length of the punches in the first station.

Procedures.—*Evaluation of Rotary Tablet Machine Performance.*—For these studies the general procedure for conducting the runs was as follows.

All control settings were made, checked, and "locked-in." Hopper(s) were filled to a preselected level. The press was run at the desired settings for at least 2 min. before tablets were collected or photographs taken. Then at least 125 tablets were collected (only from the instrumented side of the 540–35 IRTM) while the time exposure was being made of the oscilloscopic tracings. These tablets were bottled and labeled and the photograph identified. Then the press control being evaluated was readjusted to the next setting—with no changes being made to the others—and the entire procedure was repeated. For the "speed" control study the upper and lower limits were those of the press itself. For the weight cam and thickness control studies the upper limit occurred when the press "unloaded" because it had reached its mechanical capacity, while the lower limit was reached when tablets became too fragile to handle.

After the collections were finished for all the runs, the various measurements on the tablets and photographs were performed.

Establishment of Relationships Between Physical Properties of Tablets and Compressional Force.—Essentially the same procedure as described above was used to carry out these studies. Only the thickness control setting was adjusted to produce the compressional force changes. Except as noted, all tablet measurements were made within a short time after their compression.

Applications for Tablet Development and Production Studies.—The various procedures used for these studies will not be described in detail in this section since they will be evident when the results of the individual studies are discussed.

RESULTS AND DISCUSSION

Evaluation of the Performance of Rotary Tablet Machines.—These studies, designed to quantify the general rules of thumb that tablet men have long used in working with rotary presses, established the relationship between specific settings of the speed, weight cam, and thickness controls of the presses and of the compressional force generated.

Figures 1 and 2 typify the photographs obtained

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[2] Mettler Instrument Corp., Princeton, N. J.

[3] Federal model 22P-30, Federal Product Corp., Providence, R. I.

[4] Starrett model 1010-E, L. S. Starrett Co., Athol, Mass.

[5] Federal Platform Dial Micrometer graduated in 0.0001 in., Federal Products Corp., Providence, R. I.

[6] Sheffield Products, Dayton, Ohio.

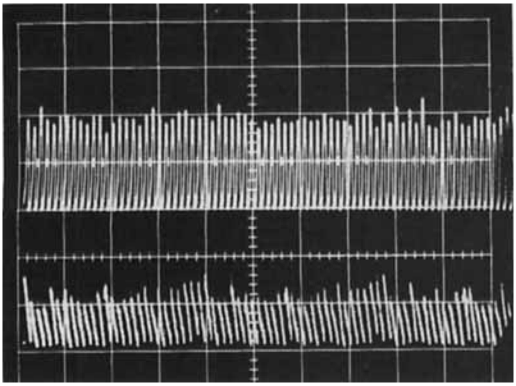

Fig. 1.—Photograph of oscilloscopic tracing of conventional granulation E compressed on $^1/_2$ BB2-27 IRTM at 420 TPM using 27-$^7/_{16}$ in. full oval tablet punches. Calibration: upper trace (C.F.), one large division = 1,540 lb.; lower trace (E.F.), one large division = 125 lb.; sweep, 1 sec./large division, left to right.

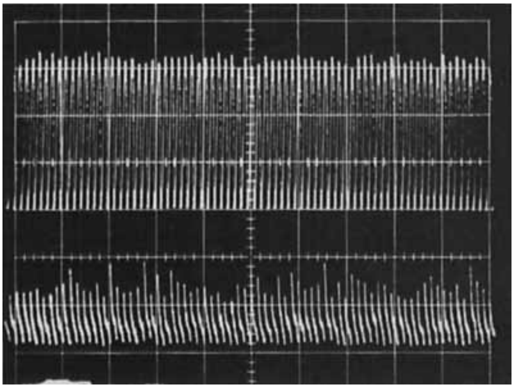

Fig. 2.—Photograph of oscilloscopic tracing of conventional granulation E compressed on $^1/_2$ BB2-27 IRTM at 420 TPM using 27-$^7/_{16}$ in. full oval punches. Calibration: upper trace (C.F.), one large division = 3080 lb.; lower trace (E.F.), one large division = 125 lb.; sweep, 1 sec./large division, left to right.

for this series; here a conventional granulation E was compressed on the 1/2 BB2-27 IRTM at two thickness settings that differed by 1 rev. of the control. The compressional and ejectional force values and the dimensions of the tablets from the samples collected as the two time exposures were being made are listed below.

	Fig. 1[7]	Fig. 2[8]
Thickness setting, °.....	360	720
Thickness, mean, in.....	0.2388	0.2338
Weight, mean, mg.......	516.5	515.0
Compression ratio, mg./in....................	2163	2203
Compressional force, lb.		
—mean..............	2910	9730
range..............	2465–3540	9240–10160
Ejectional force, lb.		
—mean..............	141	170
—range..............	100–200	125–238

In this manner the effects of various press adjustments were determined for this granulation and other tablet formulations. It was found that these effects are related mainly to the mechanical aspects of the presses and not necessarily to the composition of the formulations.

Speed Control.—The data listed in Table I were obtained when only the speed control setting of an IRTM was adjusted (by 200 TPM increments) during the compression of a previously slugged and granulated conventional granulation F. Figure 3 shows plots of the press speed *versus* (*a*) the mean tablet weight and (*b*) the mean compressional force developed. As the speed increased, the die fill decreased, the tablet weight diminished, and the compressional force being generated decreased. The apparent density and thickness of the tablets also decreased as the press speed increased. In fact, for this run the decrease in thickness was directly proportional to the decrease in weight. Furthermore, the relationship between tablet weight and compressional force approaches linearity.

In another study the weight of tablets produced and the compressional forces generated were determined for each setting when the press speed was increased by increments. Appropriate adjustments were then made to the weight cam control to obtain tablets of the initial weight at that particular speed. In all cases the compressional force being generated returned to the initial level when tablets with the proper weight were made. It should be pointed out, however, that although the compressional force levels remained constant, the dwell time (*i.e.*, the actual time that the tablet stock was subjected to the compressional force) became increasingly shorter as the press speed increased.

Weight Cam Control.—The data in Table II were obtained when the weight cam control of an IRTM was adjusted by "4 notch" increments to produce heavier tablets from conventional granulation D. In Fig. 4 it will be observed that as the fill weight cam setting was advanced, the actual weight of the tablet produced increased linearly with the setting. Figure 4 also shows that as the weight cam setting was adjusted the compressional force increased until the capacity of the press was reached (~4

TABLE I.—INFORMATION PERTAINING TO TABLETS PRODUCED WHEN SETTING OF SPEED CONTROL WAS ADJUSTED[a]

Run No., Order	Speed, TPM[b]	Wt., mg.	Thickness, in.	Compression Ratio, mg./in.	Compressional Force, lb.
1	700	595.4	.2536	2347	4555
2	900	589.7	.2531	2329	4350
3	1100	589.0	.2526	2331	4015
4	1300	577.5	.2510	2300	3570
5	1500	562.6	.2476	2272	2580
6	1700	557.0	.2464	2260	2555
7	1900	552.5	.2461	2245	2390
8	2100	535.2	.2434	2198	1770
9	2300	521.6	.2414	2160	1490
10	2400	521.2	.2420	2153	1555
11	700	597.4	2538	2353	4660

[a] Controls: constant settings for weight cam and thickness adjustments. Material: previously granulated and slugged conventional granulation F. Punches: $^7/_{16}$ in. full oval. Machine: 540-35 IRTM. [b] TPM = tablets/min. On this press 70 tablets are made per revolution.

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[7] See run 1 in Table IV.
[8] See run 9 in Table IV.

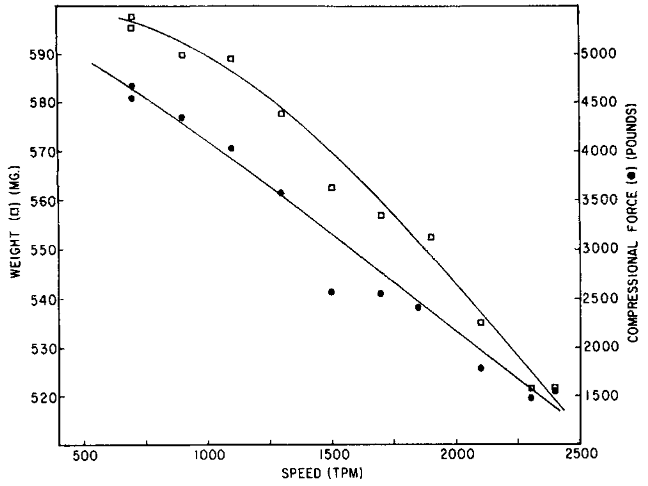

Fig. 3.—Speed *versus* weight (mean) (□) and compressional force (mean) (●).

Table II.—Information Pertaining to Tablets Produced When Setting of Weight Cam Control Was Adjusted[a]

Run No., Order	Wt. Cam, Total Notches[b]	Wt., mg.	Thickness, in.	Compression Ratio, mg./in.	Compressional Force, lb.
1	0	448.7	.2224	2018	825
2	4	462.2	.2248	2056	1040
3	8	473.7	.2260	2096	1225
4	12	484.8	.2272	2134	1530
5	16	496.2	.2290	2167	1900
6	20	507.7	.2306	2202	2410
7	24	519.1	.2324	2234	2895
8	28	530.3	.2349	2258	3385
9	32	541.2	.2373	2281	NA
10 (repeat)	32	540.6	.2373	2278	4270
11	36	552.1	.2399	2301	5000
12	40	563.7	.2427	2323	5780
13	44	576.8	.2464	2341	6840
14	48	589.4	.2502	2356	7540
15[c]	52	601.9	.2536	2373	8160
17[d]	54	608.1	.2555	2380	8235
16[d]	56	615.2	.2572	2392	8235

[a] Controls: constant settings for thickness and speed (~700 TPM) adjustments. Material: conventional granulation D. Punches: $^7/_{16}$ in. full oval. Machine: 540-35 IRTM. [b] One revolution of weight control knob = 40 notches. [c] At this setting many stations "unloaded." [d] At these settings all stations "unloaded."

tons). Less than 1.5 rev. of the weight cam control produced the entire range of fill weights (448.7 to 615.2 mg.) and compressional forces (825 to 8,235 lb.). As the weight of the tablets increased, their thickness and apparent density also increased, even though the thickness control setting was not altered during the run.

Furthermore, it can be seen that a significant portion of the curve which would be obtained with a plot of weight *versus* compressional force would be linear. This points out that the compressional force generated is apparently dependent upon the weight of the tablets or the die fill. Brake (2) and Rehberg (31) anticipated this possibility for rotary presses, and similar relationships were reported by others (8, 10, 11, 15) in their work with instrumented single stroke presses.

Thickness Control.—Regulation of the thickness control to bring the upper and lower punches closer together or farther apart at the instant of compression is the usual way that a press is adjusted to control the properties of the tablets to be made once the desired fill weight is obtained. The press speed is usually optimized and is not ordinarily used to control the properties of the tablets. The data in Table III were collected when tablets were compressed at different thickness settings from an experimental granulation I on an IRTM. The two plots in Fig. 5 show the relationships between thickness control setting and (*a*) the thickness of the tablets produced and (*b*) the compressional force generated. Adjusting the thickness control to "apply more pressure"

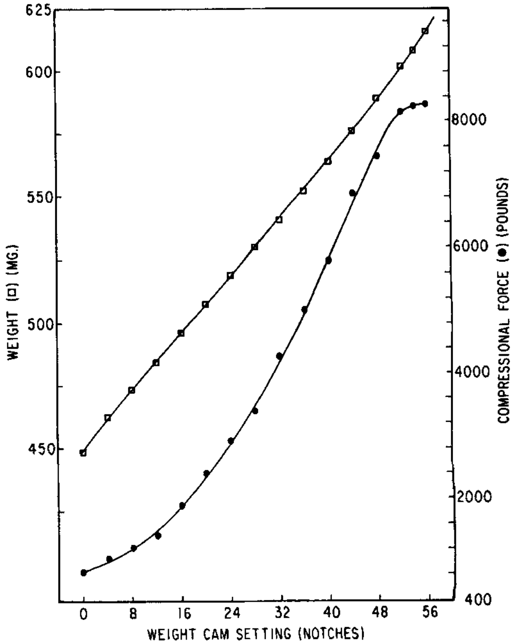

Fig. 4.—Weight cam setting *versus* weight (mean) (□) and compressional force (mean) (●).

resulted in thinner tablets being compressed at higher force levels.

The entire range of compressional forces was attained with less than 2 rev. of the thickness control. The compressional force did not change uniformly throughout the range of the thickness settings. The last 160° of rotation to the control produced as much a change in force as did the first 440°. Thus, adding a notch of "pressure" to the thickness control is not equivalent to adding a constant increment of force to the compression.

Another important observation is that the thickness decreased rapidly at first, and then leveled to a constant value, even though the pressure applied to the mass continued to increase. Since the weight of the tablets remained relatively constant during the run, the apparent density of the tablets thus increased to an asymptotic value as the thickness control was continually adjusted to produce thinner tablets. The significance of this phenomenon will be discussed later.

On the basis of these and other experiments, relationships for the press settings can be generally summarized as follows.

Increasing the press speed causes the die fill to decrease, a factor which causes the tablet weight and compressional force being generated to decrease. The tablets, therefore, become successively thinner and less dense and are ejected with a decreasing amount of force.

Adjusting the weight cam control setting to increase the die fill results in successively higher compressional and ejectional forces being generated while thicker and denser tablets are also produced. In support of these findings, Nelson *et al.* (5) showed that for a single stroke press the ejectional force increased linearly with an increase in tablet weight (and resulting thickness) when the compressional force was maintained constant.

TABLE III.—INFORMATION PERTAINING TO TABLETS PRODUCED WHEN SETTING OF THICKNESS CONTROL WAS ADJUSTED[a]

Run No., Order	Thickness Setting, °[b]	Wt., mg.	Thickness, in.	Compression Ratio, mg./in.	Compressional Force, lb.
1	360	579.7	.1930	3004	3455
2	320	583.7	.1946	2999	3080
3	280	580.0	.1955	2967	2525
4	240	579.1	.1970	2940	1935
5	200	579.0	.1991	2908	1635
6	160	581.8	.2018	2883	1455
7	120	580.6	.2043	2842	1210
8	80	583.6	.2073	2815	1120
9	40	582.1	.2100	2772	1025
10	0	580.8	.2131	2725	780
11 (repeat)	360	580.9	.1935	3002	3605
12	400	582.7	.1935	3011	4225
13	440	582.8	.1932	3017	4835
14	480	580.0	.1924	3015	5590
15	500	581.1	.1922	3023	6050
16	520	578.8	.1917	3019	6655
17	540	580.0	.1924	3015	6860
18	560	582.3	.1926	3023	7265
19	580	584.5	.1929	3030	8075
20	590	584.2	.1930	3027	8210
21	600	584.5	.1929	3030	8465
22 (repeat)	360	576.5	.1930	2987	3185

[a] Controls: constant settings for weight cam and speed (~2000 TPM) adjustments. Material: experimental granulation I. Punches: $^{15}/_{32}$ in. quarter oval. Machine: 540-35 IRTM. [b] At 0° punches were farthest apart at time of impact; at 600° they were nearest to each other.

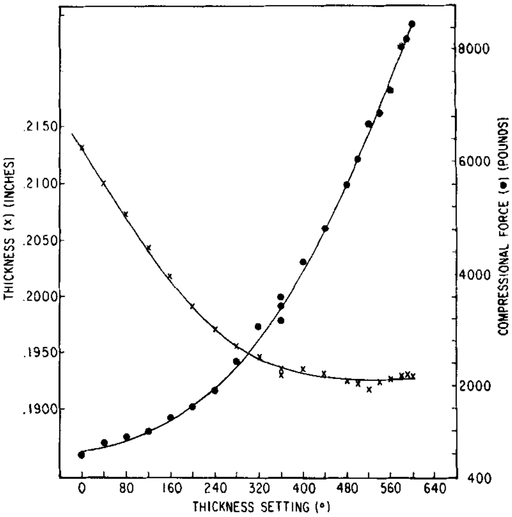

Fig. 5.—Thickness setting *versus* thickness (mean) (×) and compressional force (mean) (●).

Adjusting the thickness control setting to bring the punches closer together for the punching event causes successively thinner and denser tablets to be produced up to a point. The compressional and ejectional forces developed increase continuously throughout the entire range of press settings, even though the thickness decreases and the density increases, until each attains a nearly constant level.

Correlation of Compressional Force and Physical Properties of the Tablets.—For all the materials studied, nonlinear, but generally reproducible, relationships were found to exist between the relative setting of the thickness control and the generated compressional force. However, in attempting to correlate the physical properties of the tablets with the force used to compress them, two distinct types of behavior, predictable and nonpredictable, were found to exist for all the materials.

(*a*) The relationship between certain physical dimensions of the tablets, *e.g.*, thickness and apparent density, as well as the force required for ejection and the compressional force used in their preparation, are relatively independent of the actual material being compressed. Since all the materials behaved similarly, the compressional force profiles with respect to these properties are usually predictable.

(*b*) The relationship between certain other physical characteristics of the tablets, *e.g.*, hardness, friability, disintegration, and dissolutive rate values and the force used to compress them, are more dependent on the composition of the particular stock being tableted. Since compositions vary greatly between formulas, the effect that different levels of compressional force will have on the properties of the tablets is unpredictable. The compressional force profile must be determined for each material.

General or Predictable Relationships.—A specific case typifying predictable behavior is depicted by the data in Table IV and the plots shown in Fig. 6

TABLE IV.—INFORMATION PERTAINING TO TABLETS COMPRESSED AT DIFFERENT COMPRESSIONAL FORCE LEVELS[a]

Run No., Order	Thickness Setting,[a,b]	Wt., mg.	Thickness, in.	Compression Ratio, mg./in.	Compressional Force, lb.	Ejectional Force, lb.
1	360	516.5	.2388	2163	2910	141
2	405	516.5	.2368	2181	3740	148
3	450	516.0	.2354	2192	4080	136
4	495	516.0	.2342	2203	4975	159
5	540	515.5	.2335	2208	5700	160
6	585	515.5	.2335	2208	6870	163
7	630	516.0	.2337	2208	7700	161
8	675	516.0	.2339	2206	8930	175
9	720	515.0	.2338	2203	9730	170
10 (repeat)	360	515.5	.2380	2166	3080	146
11	315	516.5	.2399	2153	2150	143
12	270	517.5	.2408	2147	1810	119
13	225	517.5	.2431	2129	1450	104
14	180	515.2	.2462	2093	1150	85
15	135	517.3	.2498	2071	1020	87
16	90	516.6	.2533	2039	815	83
17	45	516.0	.2568	2009	685	70
18 (repeat)	360	514.6	.2377	2165	3035	114

[a] Controls: constant settings for weight cam and speed (360 TPM) adjustments. Material: conventional granulation E. Punches: 7/16 in. full oval. Machine: 1/2 BB2-27 IRTM. [b] Measured in terms of "notches" of control setting; 7 notches = 45° or 56 notches/rev. At 0° the punches were farthest apart at time of compression; at 720° the punches were nearest to each other.

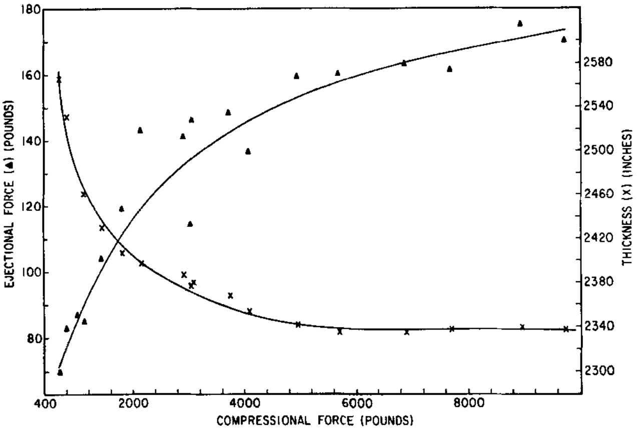

Fig. 6.—Compressional force (mean) *versus* ejectional force (▲) and thickness (X).

of compressional force *versus* (*a*) ejectional force and (*b*) mean tablet thickness. Here a conventional granulation E was compressed at various compressional force levels on an IRTM.

Higher compressional forces were generated as thinner (and consequently denser) tablets were produced. Note that the tablet thickness hardly changed as the compressional force increased from 5000 to almost 10,000 lb. Thus, although the compressional force almost doubled, the apparent density of the tablets (*i.e.*, CR α1/thickness) did not increase beyond a certain asymptotic value.

The results were in general qualitative agreement with those previously found by investigators who worked with "static" methods of compression (20–22) or instrumented single stroke machines (14, 16, 18). These workers empirically plotted the density (real or apparent) or porosity *versus* the logarithm of compressional force to obtain linear relationships at all but the higher force levels. Similar semilogarithmic plots using our data are also more linear, except where tailing occurs at higher compressional force levels.

The apparent density and thickness of the tablets tend to approach constant values as the compressional force is increased. The common practice used to determine the correct degree of compression for a given tablet is to measure a few tablets as they are made and compare their thickness to a previously set standard. This procedure should be questioned since tablets with the "correct" thickness could be compressed over a wide range of compressional forces if the "acceptable standard" was within the plateau region. Certain tablet properties may be more dependent on the actual force at which the tablets were compressed than they are on the thickness or apparent densities of the tablets. The value of being able to measure the actual force of compression with an IRTM during a tableting operation, rather than attempting to determine these values by indirect methods, is obvious.

As the compressional force increased, the force

TABLE V.—INFORMATION PERTAINING TO TABLETS COMPRESSED AT DIFFERENT COMPRESSIONAL FORCE LEVELS[a]

			Mean Values Determined for the Tablets of Each Run								For the 2 Rep. Tablets Tested[e] Av. of 2 Tablets w/o Disks, min.		
Run No., Order	Prev. Desig.[b]	Thick. Set	Wt., mg.	Thick., in.	CR, mg./in.	Comp. Force, lb.	DT,[c] min.	Hard., Kg.	F.R., Kg.	Fria.,[d] % Wt. Loss	DT	$T_{50\%}$	$T_{90\%}$
1	A	700°	594.6	.2513	2366	7655	35.3	12.1	9.8	...	56	32	62.5
2	B	720°	596.1	.2516	2369	7975	33.8	12.6	9.9	.17	54	35	58
3	C	680°	592.9	.2511	2361	7225	32.5	12.3	9.5	.21	52	31.5	59
4	D	660°	591.2	.2507	2358	6735	33.2	11.6	9.7	.17	46.5	26	53
5	...	640°	590.2	.2509	2353	6350							
6	E	620°	592.1	.2513	2356	6080	27.2	11.4	9.0	.21	42.5	25	48
7	F	600°	590.1	.2510	2350	5500	27.8	12.2	8.9	.18	37.7	20	43
8	G	560°	592.3	.2517	2353	4715	24.8	11.2	8.4	.15	33	20	41
9	H	520°	590.0	.2531	2331	4275	23.8	11.7	8.5	.17	31	22.5	44
10	I	480°	592.7	.2542	2331	3650	20.7	11.1	8.5	...	27	14.5	31
11	...	440°	594.9	.2557	2326	3370							
12	J	400°	595.5	.2568	2318	2845	13.7	7.7	6.3	.13	19	12	25.5
13	K	360°	593.4	.2582	2298	2170	4.7	6.2	6.1	.17	15	10	19.5
14	L	320°	593.2	.2603	2278	1685	3.3	5.1	4.1	...	5	5	12
15	...	280°	588.2	.2621	2244	1500							
16	M	240°	595.0	.2650	2245	1345	2.5	2.5	2.9	.15	2	3	9
17 (repeat)	...	320°	590.8	.2600	2272	1790							
18	...	200°	591.1	.2675	2209	950	1.5						
19	N	160°	581.0	.2691	2159	730	1.0	.3	.5	Badly crumbled	1	2.5	8.75
20	...	120°	580.9	.2718	2137	605							
21	O	80°	580.0	.2740	2116	520	1	...	...	Badly crumbled	1	2	8.5
22	...	40°	584.0	.2771	2107	480							
23	P	0°	586.0	.2801	2092	415	1	...	...	...	1	2.5	9.5
24	Gran.	...	590.0	...	...	...	0	...	...	...	...	1.7	8.5

[a] Controls: constant settings for weight cam and speed (700 TPM) adjustments. Material: previously slugged granulation F containing phenacetin, aspirin, and caffeine. Punches: 7/16 in. full oval. Machine: 540-35 IRTM. [b] Tablets from these runs were designated by these letters in *Reference 34*. [c] Average time for 6 tablets to disintegrate with disks in pH 1.3 fluid (HCl–NaCl, $\mu = 0.1$). [d] These values were determined about 6 months later than others (after storage at room temperature). [e] Average times required for the 2 tablets tested individually. Fluid used was HCl–NaCl, pH 1.3 with $\mu = 0.1$.

required to eject the tablets also increased even though the tablets became thinner (Fig. 6). An apparent linear relationship was obtained when the ejectional force was plotted against the logarithm of the compressional force. Shotton and Ganderton (16), working with an instrumented single stroke press, found a similar relationship for unlubricated sodium chloride crystals.

If tablet thickness is plotted *versus* ejectional force, a curvilinear relationship with a negative slope is obtained; this is the converse of that reported by Nelson *et al.* (5) and discussed earlier. These anomalous findings are apparently explained because a higher force of compression increases the ejectional force more than a smaller tablet thickness reduces it (23). Furthermore, Nelson used an unlubricated granulation with a single stroke press and kept the compressional force constant while varying the tablet weight to change the thickness. In the present study where a lubricated granulation was

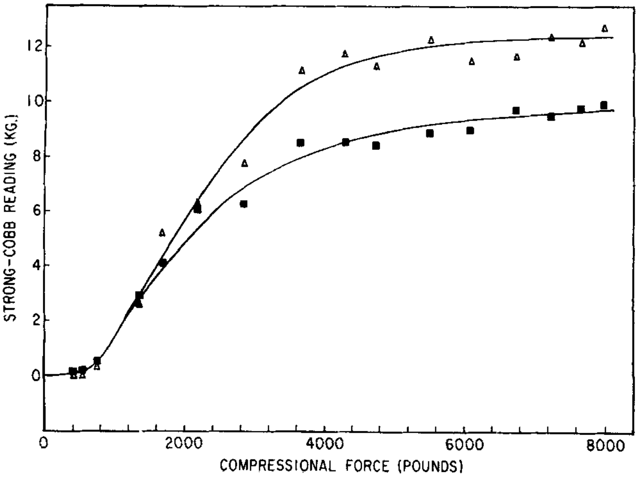

Fig. 7.—Compressional force *versus* hardness (△) and fracture resistance (■).

run on a rotary machine, the weight was held constant but the compressional force varied as the tablet thickness was changed.

For all the materials studied, the thickness and apparent density of the tablets level off even though the compressional and ejectional forces continue to increase. Because different materials reach their density plateaus at different compressional forces or with less absolute change in density, the rate of increase of tablet density with increasing compressional force possibly may be used as a measure of the bonding strength of the tablet. Elowe *et al.* (22) suggested that this in turn might be a criterion of the ease with which tablets can be compressed and reflects on the physical properties of the tablets after compression. No attempt has been made in these studies to test the validity of this proposal.

Specific or Unpredictable Relationships.—As indicated, general relationships between the compressional force and the physical properties of the tablets, such as hardness, friability, disintegration time, and dissolutive rate, were not found for the various materials studied. The specific compressional force profile for a material, or the exact way in which properties vary with compressional force, is often unpredictable and must be determined for each tableting mixture.

The following illustrates the establishment of such specific compressional profiles for one of the mixtures studied. The data in Table V were obtained when an experimental mixture containing aspirin, phenacetin, and caffeine, which had been previously wet granulated and slugged, was compressed on an IRTM. As usual, as the thickness setting was successively adjusted "to increase the pressure," thinner and denser tablets were produced—up to a point—but the compressional force generated increased continuously. Figure 7 shows that the values for tablet hardness and fracture resistance also increased to plateaus when they were plotted against compressional force. This finding confirms similar ones reported previously for "static" compression methods (20–22) and instrumented single stroke machines (15, 16, 18). Plots of the hardness or fracture resistance *versus* the logarithm of compressional force would also be linear except at the higher force levels where tailing occurs. Linear relationships would also be found for the tablets of this series if their apparent densities were plotted against either their hardness or fracture resistance values; similar findings have been reported for a specialized single stroke press (20) and a rotary press (31).

Although the thickness, apparent density, hardness, and fracture resistance values for the tablets of this run reach plateaus, the disintegration times (determined with and without plastic disks) and the $T_{50}\%$ and $T_{90}\%$ values for dissolutive rates continued to increase as the compressional force increased. These relationships are shown in Fig. 8. Tablets compressed with a force of about 5,800 lb. had a compression ratio of about 2,353 mg./in. and a thickness of .2517 in. while tablets compressed at about 7,600 lb. had similar values. The tablets compressed at the lower force required 40 min. for 90% of their ingredients to dissolve while those made at the higher force needed over 60 min. to release the same proportion of their ingredients. Furthermore, their disintegration times were somewhat different (28 *versus* 36 min.), yet there was very little difference in the hardness and fracture resistance values of the two samples.

For this series of tablets significant linear correlations were established between the various values for disintegration times and dissolutive rates (34). Obviously, linear correlations can also be obtained between any of these values and the compressional forces used to prepare the tablets.

Others (27, 29) have also shown that the disintegration time for certain tablets continues to increase as the compressional force is increased, even though the compression ratio of the tablets has reached a maximum. Similarly, in separate studies, Higuchi *et al.* found semilogarithmic relationships between the distintgration time and the compressional force for certain tablets made by static compression methods (20, 21) despite the fact that their porosities approached asymptotic values.

Unfortunately, the friability values for these tablets were determined quite some time after the tablets were prepared. Since compressed

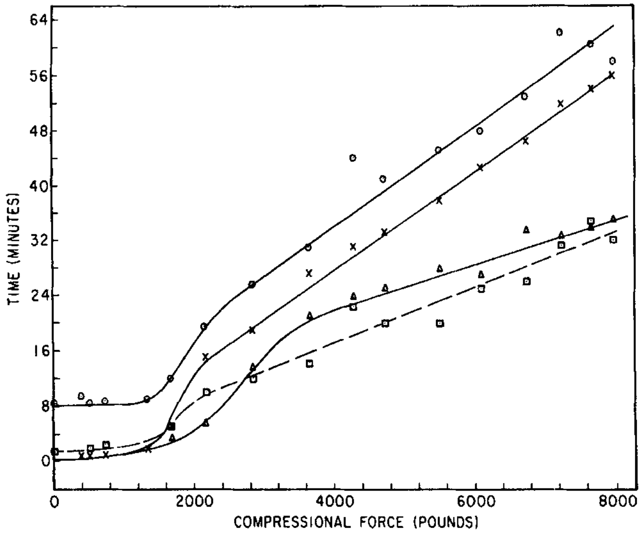

Fig. 8.—Compressional force (mean) *versus* $T_{90}\%$ (○) disintegration time w/o disks (×), disintegration time with disks (△), and $T_{50}\%$ (□).

tablets, especially those made from wet granulations, have a tendency to "set-up" upon storage (28, 29), the values listed do not reflect the true friabilities of the tablets at "time zero." Initially, the tablets made at compressional forces of less than 2,000 lb. were quite fragile.

As indicated, the above relationships were specific for the particular material in question. Different relationships with respect to the compressional force used to prepare the tablets were found for the other materials studied. For example, as the compressional force was increased over the range of 500 to 9,000 lb., the properties of the tablets were found to vary as follows.

The *hardness* values may increase continuously; increase and then level off; increase, level off, and then increase again, or increase to a maximum and then decrease. Similarly, the *fracture resistance* values may increase continuously; increase and then level off; increase to a maximum and then decrease; or not necessarily parallel the hardness values. The *friabilities* may decrease sharply from high values to plateau at lower ones; decrease more slowly from high values to plateau at lower ones; decrease to a minimal value and then increase again; or not necessarily be correlated with the hardness or fracture resistance values.

The *disintegration times* (with disks) may increase continuously; increase continuously with only a short plateau; increase only slightly and level off over a wide range; increase to a maximum and then decrease; decrease slightly, then increase continuously; or not necessarily be correlated with hardness or friability. The *dissolutive times* may increase from low values to level off at high values; increase from very short times to level off at only slightly longer times; vary randomly at intermediate values with no apparent relation to compressional force; increase from moderately long times to level off at very long times; increase to a maximal time and then decrease again; or not necessarily be correlated with disintegration times.

A unique finding of these studies was that for one of the conventional tablet granulations E, maxima were found for the hardness, fracture resistance, and disintegration and dissolutive times with respect to compressional forces. The friability reached a minimal value. As the compressional force increased, however, the hardness, fracture resistance values, and disintegration and dissolutive times decreased while the friability values increased.

Examples of many of these different types of behaviors have been reported previously by other investigators using a variety of methods to measure tablet properties and the degree or force of compression for single stroke machines (2–12, 15–18), specialized static compressional methods (19–23), empirical methods of varying compression (24–29), and in three cases, rotary machines (2, 30, 31).

Thus, for all materials, although tablets cease to become thinner or more dense when the compressional force is increased beyond a given point, predictions cannot always be made regarding the relationships between the compressional force and other physical properties of the tablets. Certain characteristics, *e.g.*, hardness, fracture resistance, disintegration time, dissolutive rate, and friability, may be affected more by the nature of the formulation or the medicaments than they are by the compressional force used to prepare them. This fact has not always been clearly established in the literature.

Interdependency of Tablet Uniformity and Force Variations.—For the foregoing studies the mean values from a large number of individual measurements and determinations were used to establish the various relationships. However, some general statements can be made regarding the individual compressional and ejectional force values observed during the runs.

Usually rotary tablet machines are thought to provide more uniform compression than do the single stroke machines. Contrary to expectations, however, large punch-to-punch and cycle-to-cycle variations in compressional and ejectional forces were found to exist. Brake also mentioned that the individual compressional forces varied more than expected during the exploratory work with his partially instrumented rotary tablet machine (2). Rehberg (31) also anticipated this possibility.

The degree of variation found in this study was not the same for all runs; for some the compressional force variation was observed to be as high as ±40% of the mean. In other runs much greater uniformity was displayed. Furthermore, the variation is usually larger at the lower compressional force levels and smaller at the higher compressional force levels because "unloading" of the press occurs at some stations; this tends to eliminate the high peaks that otherwise would be observed. For instance, in Fig. 1 the variation in compressional force is about ±18%, but in Fig. 2, at the higher compressional force level, the variation is only about ±5%.

The variation observed is also smaller when good flowing granulations or direct compaction mixtures are compressed with the aid of mechanical die filling equipment. Some of the most "uniform" compressional force tracings were observed when direct compaction mixtures made up of essentially lubricated spray-dried lactose were compressed.

It has been shown in Figs. 3 and 4 that the compressional force developed is directly related to the weight of the tablets being compressed. These data, the above observations, and previous findings by other workers who used single stroke (2, 8, 10, 11, 15) or rotary (2, 31) tablet presses indicate that the prime reason for the tablet-to-tablet and cycle-to-cycle variation in compressional force levels noted with a rotary tablet machine is apparently that the individual dies are being filled unequally. Rehberg (31) found that the weight variations of tablets made with rotary presses were normal distributions. Although compressional forces were not measured, Rehberg postulated that the compressional force was proportional to the weight of the tablet made. Thus, anything which causes more uniform filling of the dies should produce a more uniform compressional force impulse picture. Because the finer mesh particles of direct compaction mixtures fill the dies more uniformly than the coarser material of the conventional granulations, more uniform compressional force impulse heights are observed when the former materials are compressed (8, 36–38). (See Figs. 12 and 13 also.)

In addition to the fact that unequal die filling affects compressional force uniformity, evidence from these studies suggests that small differences in the punch and die dimensions may also be a contributing factor by influencing not only the volume of fill (tablet weight) but the degree of compression (tablet thickness) as well. A die fitted with a short lower punch should receive a larger charge than a die fitted with a long one; thus, this station would deliver a heavier tablet. A long upper punch will always exert a higher compressional force than a short one when opposed by lower punches of the same length with dies filled with equal charges. Obviously, in sets of tools for presses with 16 to 51 stations a wide variety of combinations is possible. When the effect of the variations in die and punch diameters is introduced, the problem becomes even more complex. Others have pointed out that such variations exist within a set and from set to set as well (40–42).

The punch-to-punch and cycle-to-cycle variations in ejectional force occur for at least two reasons, because variations in compressional force occur and because variations in the lengths and the clearances of the tools exist for almost every set-up. In addition, tools wear unevenly (40, 42). It can be seen in Fig. 9 (where this was demonstrated for two different compressional force levels) that compression at uniform force levels (by adjusting the "overload" setting point to a lower value) does not produce tablets which are ejected with uniform forces. As expected, a higher ejectional force was required for the tablets produced at the higher compressional force level.

Results from some preliminary work as well as literature supplied by equipment manufacturers suggest that, if the overload system of the press were set so that the press continuously "unloaded" and all the tablets were compressed at the same force, tablets with uniform densities would be obtained. It has also been reasoned that tablets with uniform densities would have uniform physical characteristics, *i.e.*, disintegration times, dissolutive rates, hardness values, and friabilities. Less tablet-to-tablet variation in a lot would be observed. However, when this was attempted experimentally, there was no dramatic increase in uniformity of tablet densities or other properties because such a procedure does not improve the uniformity of flow or die filling. Actually, the presses could be damaged unless they were equipped with specialized "unloading" systems.

However, it is obvious that tablet-to-tablet variations as well as lot-to-lot variations with respect to the physical properties of the tablets may be due in some cases to the variation in compressional force used in their preparation. Since weight variations contribute mainly to the compressional force variations, the former may also be considered to influence greatly the physical properties of the individual tablets (8, 11, 15, 30, 31, 39). In the study mentioned previously, Rehberg (31) showed that for a series of three different tablet formulations compressed on a rotary press at constant settings, their thickness, density, hardness, and disintegration time all increased linearly as the tablet weight increased. He concluded that this occurred because heavier tablets were compressed at higher forces. Brake also suggested that hardness and disintegration might be correlated with the compressional force used to prepare the tablets (2). Thus, anything that can be done to insure compression of equal die fills at uniform and reproducible force levels will contribute greatly to the production of tablets which are uniform within a lot and from lot to lot (7, 8, 11, 31, 36, 37, 43, 44).

Applications of the IRTM for Tablet Development and Production Studies.—The foregoing material described the use of the IRTM for some types of basic or research studies. An extension of these studies led to the use of IRTM's to study both developmental and production tableting problems on the "floor" rather than at the bench. Some of these uses are described below. Where applicable, references to previously published investigations of a related nature are included in the discussions.

Tablet Development Studies.—(*a*) The IRTM has been used to determine the optimum lubrication system for a given stock by screening lubricants and

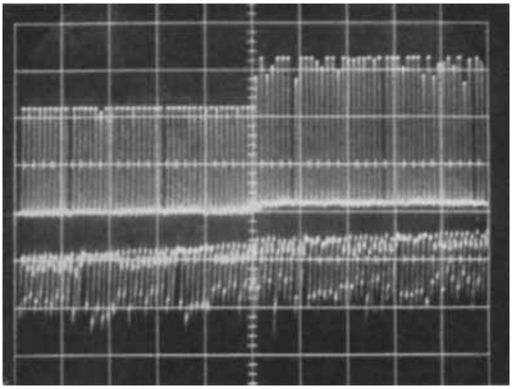

Fig. 9.—Photograph of oscilloscopic tracing of direct compaction mixture *A* compressed on 540-35 IRTM with Force-Flo-Feeder (FFF) at about 1000 TPM using 17-$^7/_{16}$ in. full oval punches. The upper punches were removed from every other station. Calibration: upper trace (C.F.), one large division = 2,700 lb.; lower trace (E.F.), one large division, = 25 lb.; sweep, 1 sec./large division, left to right. Overload setting on left side, 3 tons; on right side, 4 tons.

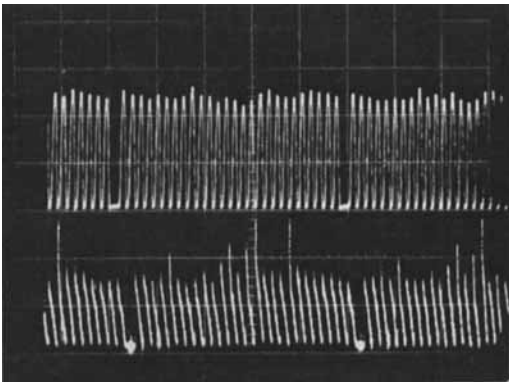

Fig. 10.—Photograph of oscilloscopic tracing of direct compaction mixture *B* with IX concentration of lubricant compressed on $^1/_2$ BB2-27 IRTM with FFF at about 660 TPM using 26-$^7/_{16}$ in. full oval punches (upper punch removed from one section). Calibration: upper trace (C.F.), one large division = 1540 lb.; lower trace (E.F.), one large division = 125 lb.; sweep, 0.5 sec./large division, left to right,

lubricant concentrations (3–5, 9–11, 13, 14, 17, 24). Figure 10 shows the compressional and ejectional forces generated for a given direct compaction mixture *B*. When the lubricant concentration was doubled with all the other variables being kept constant, the force required to eject the tablet was reduced to the level shown in Fig. 11. Note that with the increase in lubricant, the ejectional force impulses also became more uniform. When the lubricant concentration was tripled, only a slight additional decrease in ejectional force was observed. Thus, on the basis of ejectional force level, the optimum lubricant concentration for this formulation was considered to be between 2 to 3 times the initial concentration.

(*b*) The IRTM has been used to study and compare the relative flowability of various tableting mixtures. One way to evaluate how well a particular stock flows is to determine the weight variation of a collected sample of tablets. When the mixture flows well, the individual tablet weight variation is usually low; but if the flowability is poor, the individual weight variation will be high. As previously indicated, since the compressional force is directly proportional to the tablet weight or die fill, the degree of uniformity of the compressional force impulses should be a measure of the relative flowability of the mixture being tableted.

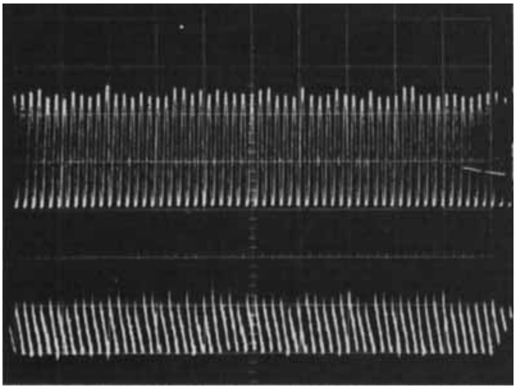

Fig. 11.—Photograph of oscilloscopic tracing of direct compaction mixture *B* with 2X concentration of lubricant compressed on $^1/_2$ BB2-27 IRTM with FFF at about 660 TPM using 26–$^7/_{16}$ in. full oval punches (upper punch removed from one section). Calibration: upper trace (C.F.), one large division = 1540 lb.; lower trace (E.F.), one large division = 125 lb.; sweep, 0.5 sec./large division, left to right.

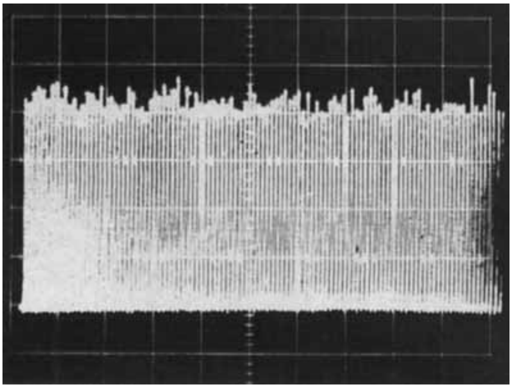

Fig. 12.—Photograph of oscilloscopic tracing of direct compaction mixture *C* compressed on $^1/_2$ BB2-27 IRTM with FFF at 700 TPM using 27–$^7/_{16}$ in. full oval punches. Calibration: upper trace (C.F.), one large division = 1065 lb.; lower trace (E.F.), not shown; sweep, 1 sec./large division, left to right.

This is demonstrated by the following experiment in which 500-mg. tablets of a direct compaction mixture *C* and a conventional granulation E containing the same three active ingredients were each compressed on an IRTM. About 125 tablets were collected as the photographs of the compressional force impulses were being made during each run. One hundred tablets from each sample were weighed individually to the nearest 0.1 mg. The tablets compressed from the direct compaction mixture were found to have a lower weight variation than the tablets made from the standard granulation (coefficient of variation 0.52% *versus* 0.92%).

Figure 12 is the photograph obtained during the compression of the direct compaction mixture while the photograph in Fig. 13 was made when the conventional granulation was compressed. Data from these photographs show that the coefficient of variation for the compressional force impulses is less for the direct compaction mixture (4.49% *versus* 6.15%).

Both with respect to weight variation of individual tablets and compressional force impulse variation, the flowability of the direct compaction mixture was found to be superior to that of the conventional granulation.

Thus, the IRTM provided an instantaneous and continuous indication of the relative flowability of a tableting material in contrast to the more time-consuming method of weighing a representative number of individual tablets after a run has been finished (31, 36, 37, 39, 43, 44).

(*c*) The IRTM has been used to compress similar

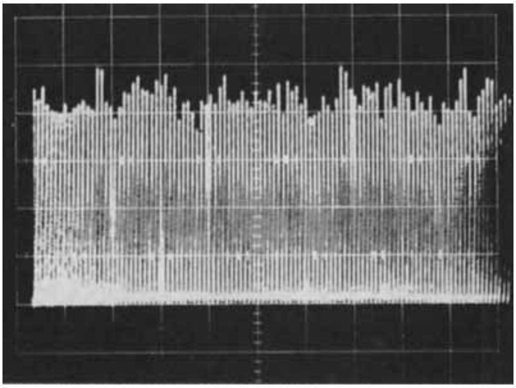

Fig. 13.—Photograph of oscilloscopic tracing of conventional granulation E compressed on $^1/_2$ BB2-27 IRTM with FFF at 700 TPM using 27–$^7/_{16}$ in. full oval punches. Calibration: upper trace (C.F.), one large division = 1065 lb.; lower trace (E.F.), not shown; sweep, 1 sec./large division, left to right. [The calibration differs between Figs. 12 and 13 and the other photographs shown for the $^1/_2$ BB2-27 presses. The sensitivity for these gauges was then 1 mv. of output per 1065 lb. of applied force with a 6 v. input (see *Footnote 8* in *Reference 1*).]

TABLE VI.—INFORMATION PERTAINING TO TABLETS PREPARED BY A DIRECT COMPACTION PROCESS

Run No.	Dry Binder Disintegrant	Flow Promoting Agent	Force, lb.		Friability, % Wt. Loss	Hardness, Strong-Cobb, Kg.	Dist. Time,[a] sec.	
			Comp.	Eject.			w	w/o
1	Yes	No	6000	125	.468	4.5	30	45
2	Yes	No	6000	125	1 of 20 capped	5.0	35	35
3	Yes	No	6000	125	.350	4.7	30	70
4	Yes	No	6100	125	.559	4.0	30	45
5	Yes	Yes	6100	125	.295	5.9	70	240
6	Yes	No	6100	125	.369	4.4	30	45
7	Yes	Yes	6000	125	.247	5.3	45	180
8	Yes	Yes	4500	100	.202	5.6	135	240
9	No	Yes	4500	100	.232	5.4	45	105
10	No	Yes	4500	100	.199	5.5	45	90
11	No	Yes	4500	100	.194	6.0	30	90
12	No	Yes	4500	100	.227	6.0	60	105
13	No	Yes	4500	100	.249	6.1	45	90
14	No	Yes	4500	100	.240	6.8	45	120
15L[b]	No	Yes	4500	...	.232	6.9	60	150
15R[b]	No	Yes	...	...	.220	6.3	45	120

[a] Total time for 6 tablets to disintegrate; w = with disks; w/o = without disks in deionized H_2O at 37°. [b] Dual compression BB2-27; only left side of press was instrumented; right side was set by comparing it to left.

formulas at constant and preselected compressional force levels. In this manner the real effects of an added ingredient or modified manufacturing procedure can be definitely determined (5, 7, 8, 12, 27). For example, during the development of a tablet prepared by a direct compaction process, the various formulations were compressed at the same force to determine the effects of both a dry binder-disintegrant and a flow promoting agent on the physical properties of the tablet. Some of the results obtained are shown in Table VI.

The flow promoting agent was so effective that the dry binder-disintegrant was no longer required because firmer tablets with acceptable disintegration times could be produced at lower compressional forces. Since there was less weight variation, there was also more uniformity in physical properties of the tablets; thus, individual units which were too soft or too hard were avoided. The mean ejectional force required was also reduced ∼20% from 125 to 100 lb.

In another study involving a standard production granulation, it was found that by changing both the lubricating and disintegrating agents as well as their concentrations and using a finer mesh granule, the compressional force required to produce tablets with an acceptable hardness, friability, and dissolutive rate could be reduced from more than 5000 lb. to less than 2500 lb. The ejectional force required was concurrently reduced, too, not only because the compressional force level was decreased, but also because better lubricants were included.

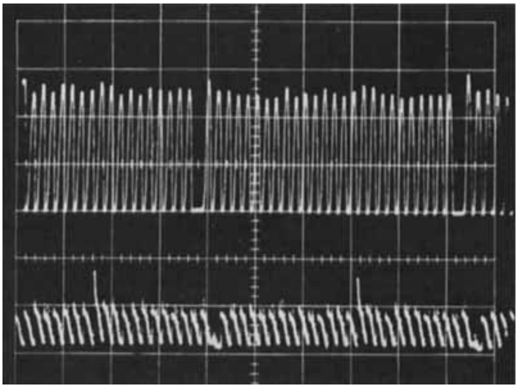

Fig. 14.—Photograph of oscilloscopic tracing of direct compaction mixture *B* compressed on $^1/_2$ BB2-27 IRTM with FFF at 600 TPM using 27-$^7/_{16}$ in. full oval punches (upper punch removed from station No. 1). Calibration: upper trace (C.F.), one large division = 3080 lb.; lower trace (E.F.), one large division = 125 lb.; sweep, 0.5 sec./large division, left to right.

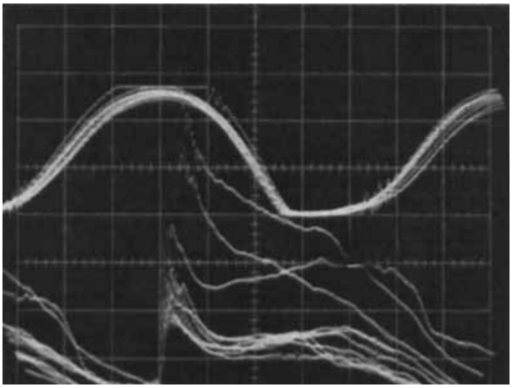

Fig. 15.—Photograph of oscilloscopic tracing of conventional granulation G compressed on 540-35 IRTM at 1500 TPM using 35-$^{15}/_{32}$ in. quarter oval punches. Calibration: upper trace (C.F.), one large division = 2700 lb.; lower trace (E.F.), one large division = 25 lb.; sweep, 10 msec./large division, left to right. Overload setting ∼3.5 tons.

Lower compressional and ejectional force requirements in rotary tablet machines mean reduced wear and longer life for punches, dies, and machine components, *e.g.*, cam tracks, compression rolls, and bearings (41, 42).

Production Activities.—(*a*) The IRTM has been useful in detecting and locating a malfunction of the machine or tools earlier than this can usually be accomplished by conventional methods. Observation of the oscilloscope gives an instantaneous picture of machine performance.

For example, as shown in Fig. 14, one punching station was repeatedly responsible for an abnormally high ejectional force impulse (6). By removing the upper punch from station No. 1 and thus causing no tablet to be formed and no ejectional impulse to be produced for this station, the troublesome station was determined to be No. 16. Upon close examination, the lower punch in this station was found to have a deformed tip. When another lower punch was substituted, the high impulses disappeared.

Recently, an operator experienced difficulty in maintaining the desired tablet weight for a normally well-running granulation. Unfortunately, by using traditional methods, quite some time was required to trace the difficulty to a lower punch with a broken tip. Since the tip would not always drop completely, the die would not obtain the correct fill, and thus tablets with an incorrect weight were made at least two times per revolution. If, however, an IRTM had been in use, the trouble would have been located much more rapidly with less loss of granulation.

The use of the IRTM to detect a machine malfunction is illustrated in Fig. 15 where a combination of a time exposure and a rapid oscilloscopic sweep captured a number of successive compression and ejection events (23). Although one punch "unloaded," a relatively uniform compressional force level is shown. (Note the characteristic plateau in the compressional force curve for this tablet that is produced with the 540–35 IRTM.) The compressional forces ranged from 6500 to 7300 lb. (equivalent to pressures of 36,600 to 42,300 p.s.i.). However, there is an extreme variation in both initial peak height and shape of the ejectional force tracings for three of the tablets. The profiles for the other tablets are lower and relatively uniform. The complete profile of one of the "high peak" tracings (the lowest of the three) differs from the other two by the display of a plateau followed by a sharp drop to the baseline. This indicates that there was a considerable force required to keep the tablet (or punch) moving in the die until ejection occurred. For these tablets forces up to three to four times the "normal" ejectional force were observed. The normal ejectional pressure was about 290 p.s.i. while the binding tablets required pressures ranging from 870 to 1160 p.s.i. to eject them. The incidence of a higher impulse corresponded to a tendency for the punches to bind during the actual run.

Application of suitable amounts of lubricants to the lower punch shafts reduced the binding tendencies and eliminated the "high peak" tracings previously observed. Concurrently, the squeaking which had been heard was eliminated.

(*b*) Another use of an IRTM was to determine whether the ejectional forces required for a regular double press coated tablet (DPCT) made on a Manesty Bicota (triple turret) tablet press were actually excessive to the point of causing a breakdown of the press. Pictures of the ejectional force tracings were taken and compared for tablets compressed at 10 to 12 different thickness settings for six different standard production granulations (using only the

TABLE VII.—PERTINENT INFORMATION ABOUT SCALE-UP AND PILOT SIZE LOTS OF DIRECT COMPACTION FORMULA RUN ON IRTM'S

Run No.	Lot Size	Machine	Comp. Force, lb.	Thickness, in.	Hardness, S-C, Kg.	Friability,[a] % Wt. Loss	Disintegration Time,[b] sec. w	Disintegration Time,[b] sec. w/o
1	30 M	1/2 BB2	4500	.227–.232	6.0	.227	30	90
2	30 M	1/2 BB2	4500	.227–.232	6.1	.249	60	105
3	100 M	BB2	4500	.228–.233	L 6.0	.150	45	90
					R 5.9	.315	45	90
4	100 M	BB2	4500	.228–.233	L 5.1	.290	45	90
					R 5.6	.241	60	90
5	100 M	BB2	4500	.228–.233	L 5.7	.290	45	105
					R 5.6	.326	45	105
6	30 M	1/2 BB2	4500	.227–.232	6.0	.194	30	90
7	100 M	1/2 BB2	4500	.230	6.8	.240	45	120
8	400 M	BB2	4500	.228–.234	L 6.0	0/20	45	75
					R 5.7	0/20	45	75
9	100 M	1/2 BB2	4500	.228–.233	7.0	.261	60	90
10	100 M	1/2 BB2	4500	.228–.233	7.3	.270	60	120
11	100 M	1/2 BB2	4500	.228–.233	7.0	.242	60	105
12	1 $\overline{M}$	BB2	4500	.230	L 5.2	.216	45	75
					R 6.3	.198	45	90
12R	1 $\overline{M}$	BB2	4500	.230	L 7.2	0/20	45	75
					R 7.5	0/20	45	75
13	1 $\overline{M}$	BB2	4500	.230	5.6	.150	45	70
14	1.2 $\overline{M}$	BB2	4500	.229–.232	L 5.6	.150	45	90
					R 5.8	.180	60	150
15	1.2 $\overline{M}$	BB2	5000	.230	L 6.3	.180	60	120
					R 6.2	.290	60	120
16	1.2 $\overline{M}$	BB2	4500	.230	L 7.2	.238	60	90
					R 7.2	.165	60	90
17	1.2 $\overline{M}$	BB2	5500	.230	5.5	.250	60	120
18	1.2 $\overline{M}$	BB2	4500	.230	L 6.1	.218	45	90
					R 5.9	.238	45	90

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[a] 0/20 means no capped tablets were found after 4 min. of friabilation. [b] Total time for 6 tablets to disintegrate in deionized H_2O at 37°; w = with disks; w/o = without disks.

third turret) as well as for the entire DPCT formula. Other formulations tested included granulations for three press coated tablet (PCT) coatings, a chewable vitamin, an APC combination, and a sulfonylurea compound.

It was concluded that the forces required to eject the entire DPCT or the tablets made of its coating granulation alone on the third turret were not any higher than those required to eject tablets of the same size made (on the third turret) of the other granulations studied at equivalent thickness settings. Thus, the lubrication of the DPCT formulation was apparently not responsible for the excessive wear to certain members of the Manesty press (3–5, 9–11, 13, 14, 17, 24).

(*c*) The IRTM was used to provide a type of "set-up" and "in-process" control for a specific product on a routine production basis (7, 43, 44). For this purpose a standard Stokes BB2–27 press was "instrumented" by transferring to it the strain gauged eyebolt from the 1/2 BB2–27 IRTM. The system was used to adjust the thickness control so that a preselected force level was obtained for consecutive laboratory scale-up and pilot lots of a new formulation. Previously, it had been found that tablets compressed at a force of 4500 lb. from a specific direct compaction mixture possessed certain desirable physical properties (Table VI). The runs were then monitored to maintain this compressional force level by using the IRTM.

The data in Table VII will attest to the success attained by controlling this variable more closely than heretofore has been possible.

The physical properties of the tablets for the various runs were very similar and exhibited no marked variation from lot to lot. Note that, for two of the large size lots, it was necessary to compress the tablets at somewhat higher force levels to obtain tablets with the desirable characteristics. These formulations were somewhat drier than the others reported and this may be the reason higher pressures were required to produce the necessary bond.

Not all of the tablets of run 12 were compressed when the stock was first prepared. The remaining material was compressed into tablets 2 months later. Note that the physical properties of the tablets (run 12R), except for the hardness values, are quite similar to those found initially in run 12 (Table VII).

If, during the run, the compressional force level shifted markedly from the norm, the tablet operator usually found that heavier or lighter than theoretical weight tablets were being prepared. Appropriate adjustments to the weight cam control brought the force level back to normal. Thus, the IRTM provided not only a way of reproducing batches of uniform tablets from consecutive runs, but also a means of in-process control. Perhaps it was equipment and methods like this that Swintosky, Kennon, and Tingstad visualized when they prophesied in their 1955 paper, "These data suggest that by (a) judicious selection of disintegrant, (b) suitable choice of tablet composition, and (c) *regulation of the compressional force to precise and known values, the rates of tablet disintegration and drug release may be controlled*," (7) (emphasis added).

As a result of these investigations, two conventional BB2–27 presses have been instrumented to measure both compressional and ejectional forces for both sides. These presses are now used routinely in the production of the new formula and are also available for other production oriented studies. (See Fig. 5, *Reference 1.*)

The foregoing examples have served to describe and demonstrate the use and usefulness of the IRTM at this time. These will in turn suggest many more studies in which the IRTM can be used to obtain valuable data to resolve other tableting problems. Some of these studies have already been carried out in this laboratory and future communications will cover in greater detail some of these as well as those only briefly mentioned in this report.

SUMMARY

The use and usefulness of instrumented rotary tablet machines to study a variety of tableting problems, both fundamental and applied, were described and discussed.

Using the two IRTM's and a variety of tablet formulations, fundamental information concerning the performance of rotary tablet machines was obtained. General relationships were established between the relative settings of the three press controls (speed, thickness, and weight cam) on the one hand, and certain physical characteristics of the tablets (thickness, weight, and density) and the compressional and ejectional forces generated in their preparation on the other.

General relationships between the force of compression and the physical properties of the tablets, such as weight, thickness, density, and the force required to eject them, were found to be relatively independent of the material being compressed and quite similar for all materials studied.

As others have found by using different methods to measure the variables, certain other physical characteristics of the tablets, such as hardness, friability, disintegration time, and dissolutive rates, were apparently affected by the nature of the formulations or the medicaments as well as by the compressional force involved in their preparation. Contrasting behaviors for different formulations were described.

It was concluded that the relatively large punch-to-punch and cycle-to-cycle variations in compressional and ejectional force levels, which were unexpectedly found to exist during tableting on rotary presses, were apparently due to unequal filling of the dies. When formulations were run which flowed well or which were induced to flow into the dies by mechanical means, compressional, and ejectional force impulse heights became more uniform and weight deviations decreased.

Descriptions of the manner in which the IRTM's were useful in studying typical development and production tableting problems included their use to: (*a*) screen and compare lubricants and lubricant concentrations; (*b*) determine and compare the relative flowabilities of tablet formulations; (*c*) compress experimental and developmental formulas at constant and preselected force levels; (*d*) detect and locate press or tool malfunction more rapidly than by conventional means; (*e*) determine whether the degree of lubrication for a given formulation was adequate to permit compression on a specific tablet press; (*f*) provide a means of "set-up"

and "in-process" control to obtain routinely both tablet-to-tablet and lot-to-lot uniformity for a production formulation.

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Notes

Antagonism of Propoxyphene Poisoning in Albino Mice with Nalorphine HCl, Methylene Blue, and Tolonium Chloride

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The intraperitoneal administration of propoxyphene HCl to albino mice at a dosage level of 200 mg./Kg. ($LD_{99.5}$) was lethal to 98 per cent of the controls. The prophylactic subcutaneous administration of nalorphine HCl alone, or in combination with either methylene blue or tolonium chloride, significantly increased the number of survivors with the greatest degree of protection being afforded by the nalorphine–dye combinations.

Harpel and Mann (1) recently demonstrated the antidotal effectiveness of subcutaneously administered nalorphine HCl and methylene blue, alone and in combination, prior to lethal doses of propoxyphene HCl in mice. The greatest amount of protection against the lethality of the analgesic occurred when nalorphine and methylene blue were administered 5 min. before propoxyphene HCl.

The purpose of this investigation was to confirm the results previously obtained with nalorphine and methylene blue in mice and to determine whether tolonium chloride (toluidine blue), a dye chemically related to methylene blue, also possessed antidotal qualities.

EXPERIMENTAL

Three hundred and fifty adult male albino mice (Huntingdon Farms, HTF strain), weighing between 20 and 25 Gm., were used in this study. Prior to treatment, the animals were caged in groups of 25 for several days and had access to laboratory chow (Purina) and water *ad libitum*.

The following solutions were prepared with distilled water: propoxyphene HCl, 2.0%, and methyl-

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