Lactose USP (Beadlets) and Dextrose (PAF 2011): Two New Agents for Direct Compression

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Abstract □ Lactose USP (beadlets) and dextrose (PAF 2011) have been evaluated and compared with two commonly used agents for direct compression—spray-dried lactose USP and anhydrous lactose USP—as to their relative physical properties and stability for tableting by direct compression. The compression characteristics of all four materials were defined with the aid of a rotary tablet machine instrumented with strain gauges. Compression and ejection forces were monitored continuously and correlated with tablet hardness, friability, weight variation, and disintegration times. It was concluded that the two new agents are generally superior to the other materials tested for use as fillers for direct compression. Both exhibited excellent flow and compressional characteristics. Neither agent represents an improvement over the older materials with regard to physical stability.

Keyphrases □ Lactose (beadlets), dextrose, evaluation—direct compression □ Dextrose, lactose beadlets—spray-dried, anhydrous lactose comparison □ Tablets, direct compression—lactose beadlets, dextrose, anhydrous, spray-dried lactose □ Physical properties, tablets—lactose beadlets, spray-dried, anhydrous lactose, dextrose

Most therapeutic agents lack the compression and flow characteristics required for tableting on a rotary tablet press and must be processed prior to the tableting operation. Classically, the techniques of granulation, either the wet method or the dry granulation method, have been used for this purpose. Each of these time-consuming procedures often necessitates the use of specialized equipment. Wet granulation is unsuitable for materials that are heat or solvent labile. In addition, the incorporation of active ingredients into granules often leads to decreased drug availability.

At present, one of the most promising alternatives to granulation techniques is direct compression. It is for this reason that the concept of compressing pharmaceuticals directly into tablets has received much attention in the past decade (1–8).

The process of direct compression, by definition, involves the blending of the active ingredient with a compressible, free-flowing agent for direct compression, along with required lubricants and disintegrating agents. Direct compression allows optimum utilization of production time. Since the active ingredient is not incorporated into a granule, tablet dissolution becomes more dependent on compression force and less subject to other, less controllable parameters.

The ideal agent for direct compression should be compressible, free-flowing, inert with respect to chemical and physical reactivity, and relatively inexpensive. To date, no single agent has been found that is suitable for all direct compression formulas. If such an agent was available, it would surely gain rapid and widespread acceptance throughout the pharmaceutical industry.

Samples of two new agents for direct compression, *i.e.*, lactose USP (beadlets)[1] and dextrose–corn syrup solids,[2] hereafter termed dextrose (PAF 2011), were obtained for study. The first of these materials is a form of lactose USP monohydrate, spray-dried, which has been specially processed to form white, free-flowing "beads" having a very faint caramel-like odor similar to that of spray-dried lactose. Dextrose (PAF 2011) is produced by the controlled hydrolysis of starch and is composed of 95–96% dextrose combined with 4–5% higher saccharides. The result is a white, free-flowing, odorless material composed of aggregated, porous, crystalline beads. The two materials have been evaluated and compared with two agents commonly used for direct compression, namely, spray-dried lactose USP[1] and anhydrous lactose USP,[3] as to their relative physical properties and stability with respect to tableting by direct compression.

Microcrystalline cellulose, a widely used agent for direct compression, was not included in this study for comparative purposes since it has been reviewed thoroughly in previous publications (3, 9).

EXPERIMENTAL

Materials—Lactose USP was employed as a control in physical and color stability tests. Lubrication of tablets was accomplished by the addition of 1% of either magnesium stearate USP or stearic acid USP. Starch USP was used as the disintegrating agent in samples used to determine disintegration times. Where the effect of amines on the tablets was to be determined, *d*-amphetamine sulfate USP or phenylephrine hydrochloride USP was incorporated in the formulations at a concentration of 10% by weight.

Test Methods and Equipment—*Tablet Machines*—The compression characteristics of all four materials for direct compression were defined with the aid of a Stokes RBB2 tablet machine instrumented to permit the simultaneous monitoring of tablet compression and ejection forces (10). The selection of this machine was based on the fact that it is routinely used in tablet production and the die-filling operation is dependent on the force of gravity and the flow properties of the material to be tableted. The press was fitted with standard concave punches 0.87 cm. ($^{11}/_{32}$ in.) in diameter and was set to operate at 1200 tablets/min.

[1] Foremost Dairies, Inc., San Francisco, Calif. In the case of the lactose USP (beadlets), only one lot of material was available for testing.

[2] Available as Celutab (Dextrose PAF 2011) from Penick and Ford, Ltd., Cedar Rapids, Iowa.

[3] Sheffield Chemical Co., Norwich, N. Y.

Table I—Physical Properties of Sugars for Direct Tablet Compression

Material	Tap Density, g./ml.	—Angle of Repose— Control[a]	After Exposure[b]	Particle-Size Range, μ
Lactose USP (beadlets)	0.63	39–41	46–48	15–300
Spray-dried lactose USP	0.64	44–46	48–50	15–300
Anhydrous lactose USP	0.60	53–55	58–60	15–450
Dextrose (PAF 2011)	0.67	39–41	54–56	75–350
Lactose USP	0.70	62–64	70–72	5–175

[a] Control angle of repose. [b] Angle of repose after exposure to 75% R.H. in open containers for 5 days.

The many samples of tablets required for evaluation of the physical and color stability of the various sugars were prepared with the aid of a Stokes Model F tablet machine using 1.27-cm. (0.5-in.) standard concave tooling.

Hardness—Tablet hardness was determined on a hardness tester[4] which was modified to operate from a compressed air line. All values were expressed as the average of the values obtained for 10 individual tablets.

Friability—Friability was determined in a Roche Friabilator (11). Samples of 10 tablets were weighed, subjected to rotation for 20 min. at 25 r.p.m., and then reweighed after careful dusting. The percentage of tablet weight lost was then calculated. Tablets that capped were taken as 100% loss, and the number capped was recorded.

Disintegration Time—Disintegration times were determined using the standard USP apparatus both with and without disks (12). These data were reported as the average time required for 12 tablets to disintegrate.

Bulk Density—The bulk density of each sugar was determined according to the tap method of Butler and Ramsey (13).

Particle Size—Particle size was determined by sieve analysis. Sizing was accomplished in an End Shake[5] sieve shaker using a series of 20- to 200-mesh stainless steel U. S. Standard sieves. The unit was operated for 15 min. The sample for each test was 100 g. The finite particle shape was determined by examination of each material under low power (100×) magnification.

Angle of Repose—The angle of repose for each substance was measured by a tilting box technique as previously reviewed by Train (14).

Color Stability Testing—Tests were carried out by exposing samples of 10 tablets, in open glass Petri dishes, to one of the following conditions: (*a*) heat storage at 56° for 10 days; (*b*) moisture storage at 75% R.H. for 30 days; (*c*) heat/moisture storage at 37°/75% R.H. for 10 days; or (*d*) light exposure to 600 foot candles (fc.) fluorescent illumination for 12 weeks (15).

Initial and Equilibrium Moisture Content—The initial moisture content of each material was determined by loss on drying in a vacuum oven after exposure for 16 hr. at 60° in open containers.

To determine the hygroscopicity of these agents for direct compression, tared samples of each were stored at various relative humidities in open containers in desiccators at 25° for a 7-day period. Samples were then weighed to determine the percentage of moisture picked up.

RESULTS AND DISCUSSION

Some of the physical properties of four sugars for direct compression are summarized in Table I. Data for lactose USP were also included for comparison.

The angle of repose of a powder is often regarded as providing a measure of the internal friction of the material. The determination of this angle, therefore, serves to quantify the relative degree of flowability of materials (16, 17). All of the agents for direct compression tested were found to have a low angle of repose, indicating excellent flow properties. It should be noted that, after exposure to 75% R.H. for 5 days in open containers, an increase in angle of repose resulted. Dextrose (PAF 2011) exhibited the greatest decrease in flowability. This material was found to be considerably more hygroscopic than the lactose sugars (Table II).

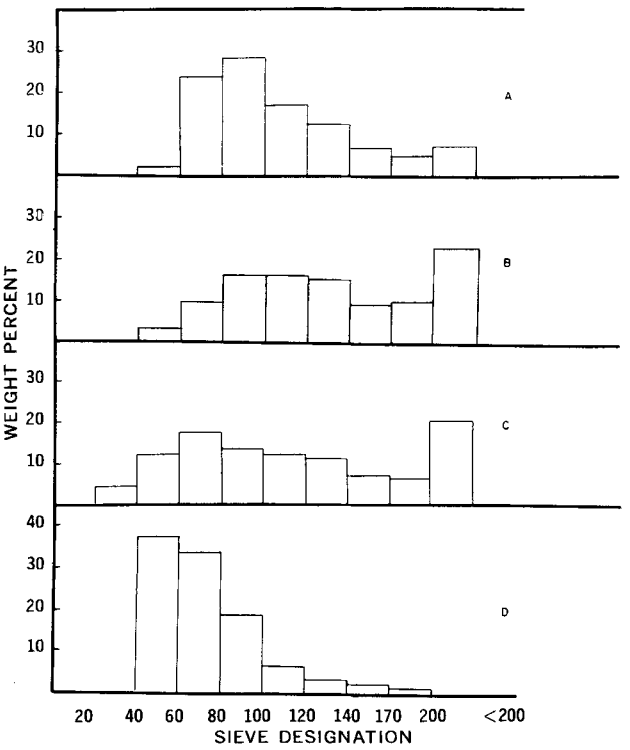

Figure 1—*Histograms displaying particle-size distribution of four materials for direct compression. Key: A, lactose USP (beadlets); B, spray-dried lactose USP; C, anhydrous lactose USP; and D, dextrose (PAF 2011).*

Sieve analysis indicated a wide range of particle size for each sugar tested. In general, when a material has a narrow particle-size distribution, it will exhibit less tablet-to-tablet weight variation than a material with a wider distribution of particle sizes. Dextrose (PAF 2011) was found to have not only the most narrow particle-size distribution, but it also contained the smallest percentage of "fines" (Fig. 1).

Color Stability—Several references indicate that tablets prepared from lactose tend to discolor upon storage (18, 19). This phenomenon is accelerated by the presence of amines and/or certain lubricants, and it is dependent upon the temperature, humidity, and illumination under which the tablet is stored. The mechanism governing this process has been previously elucidated (18, 20).

A study was undertaken to determine the degree of discoloration produced in the five sugars (four agents for direct compression plus a lactose USP control) when stored in open containers under four testing conditions—heat, moisture, heat/moisture, and light—in the presence of lubricants and selected amines. Results of visual observation are summarized in Table III. Samples stored at 37° at 75% R.H. for 10 days exhibited no more color change than those stored at either 56° or 75% R.H.

There is no evidence that stearic acid USP produces any less discoloration than magnesium stearate USP under these conditions. Control samples, which had been stored in a cool, dark environment (in closed containers) for a 12-week period, showed the same degree of discoloration as the test samples. Unlubricated control samples showed no color change after a 12-week storage period in closed containers. This indicates that the lubricants alone are capable of causing discoloration.

It was found that the incorporation of amines, such as *d*-amphetamine sulfate USP or phenylephrine hydrochloride USP, in the formulations both accentuated and accelerated the degree of darkening produced under all test conditions. In the presence of amines, magnesium stearate USP showed a greater tendency than stearic acid USP toward producing discolored sugar tablets.

Of the four materials tested for direct compression, only anhydrous lactose USP was able to withstand adequately the effects

[4] Strong-Cobb Arner Co.
[5] Newark Wire Cloth Co., Newark, N. J.

Table II—Sorption of Water Vapor in Humidity Chambers

Sample	Initial Moisture, %	% Moisture Present[a] 11	31	51	75	84	93	100
Lactose USP (beadlets)	0.22	0.22	0.22	0.22	0.22	0.22	1.0	17.0
Spray-dried lactose USP	0.20	0.50	0.50	1.0	1.0	1.0	1.5	21.5
Anhydrous lactose USP	0.24	0.24	0.24	0.24	1.0	1.5	3.0	27.0
Dextrose (PAF 2011)	8.50	9.0	9.0	9.5	10.5	27.0	60.0	76.0
Lactose USP	0.16	0.16	0.16	0.16	0.16	0.16	0.16	17.5

[a] After exposure to specified humidity for 7 days at 25° in open containers.

Table III—Color Stability of Sugar Tablets after Exposure to Different Storage Conditions in Open Containers

Sugar	Lubricant	Degree of Discoloration (Visual Observation) 56° for 10 Days	75% R.H. R.T. for 7 Days	600 fc. for 12 Weeks
Lactose USP (beadlets)	Mg stearate	Slight	Slight	Slight
	Stearic acid	Slight	Slight	Slight
Spray-dried lactose USP	Mg stearate	Slight	Slight	Slight
	Stearic acid	Slight	Slight	Slight
Anhydrous lactose USP	Mg stearate	None	None	None
	Stearic acid	None	None	None
Dextrose (PAF 2011)	Mg stearate	Slight	Slight	None
	Stearic acid	Slight	Slight	None
Lactose USP	Mg stearate	None	Slight	None
	Stearic acid	None	Slight	None

of high temperature, humidity, and exposure to light. These findings agree with those of Batuyios (21). Neither lactose USP (beadlets) nor dextrose (PAF 2011) represents a substantial improvement over spray-dried lactose USP with regard to overall physical and color stability.

Compression Characteristics—The compression characteristics of the four sugars for direct compression were defined with the aid of a rotary tablet machine instrumented with strain gauges. Compression and ejection forces were monitored continuously and correlated with the tablet parameters of hardness, friability, tablet-to-tablet weight variation, and disintegration time.

Figure 2, illustrating waveforms resulting from compression and ejection events, is included for comparative purposes. The top tracing is a series of typical compression responses, the mean value for which was about 1200 lb. force (each major division is equivalent to 786 lb.). The lower tracing represents the response obtained from ejection-force measurements using an ejection cam instrumented with metal foil strain gauges (10). A mean value of about 22 lb. force was obtained in this instance (each major division is equivalent to 12.5 lb.).

Tablets were prepared from each of the four materials for direct compression at two levels of pressure: a "normal" pressure level (approximately 2200 lb.) to simulate typical production conditions and a "high" pressure level (approximately 4100 lb.) to encourage compressional difficulties. The physical specifications of the tablets prepared are listed in Table IV.

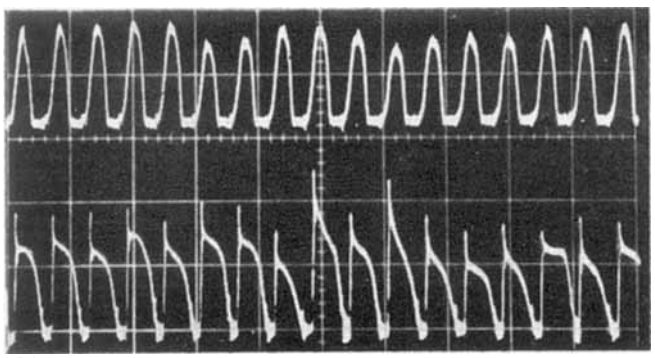

Figure 2—*Oscilloscopic tracing of force waveforms obtained from Stokes RBB2 tablet press. See text for explanation.*

After careful examination of the compression curves and evaluation of the physical properties of the tablets, those prepared from dextrose (PAF 2011) were found to be the hardest and least friable of the four agents tested. At "normal" pressure and speed, tablets prepared from spray-dried lactose USP began capping after 6 hr. This was not the case with the other three materials. Figure 3A shows a waveform resulting from the ejection of spray-dried lactose USP tablets 15 min. after commencement of operation. Figure 3B is a similar photograph taken 6 hr. later. The twin peak effect is indicative of capping insofar as the materials tested in this study are concerned. The initial peak is representative of the force required to overcome die wall–tablet adhesion. Under ordinary conditions, this force is rapidly dissipated as the tablet emerges from the die. However, when capping and/or lamination occur, the rapid expansion of the tablet results in an increase in force which manifests itself as the second peak in the ejection waveform. The possibility that these second peaks were the result of buildup of material in the dies or on the lower punch tips was minimized because both these sites were checked for cleanliness at regular intervals throughout the run.

At the higher pressure, tablets prepared from anhydrous lactose USP began capping as depicted by the ejection waveforms shown in Fig. 4. The secondary peaks in this figure are not as pronounced as those in Fig. 3B. However, when one compares the waveforms in Fig. 4 with those seen in a typical noncapping situation (Fig. 2), the secondary peak becomes more apparent. A secondary peak of this type indicates a latent tendency toward capping; the tablets do not cap as they come off the machine but cap during handling

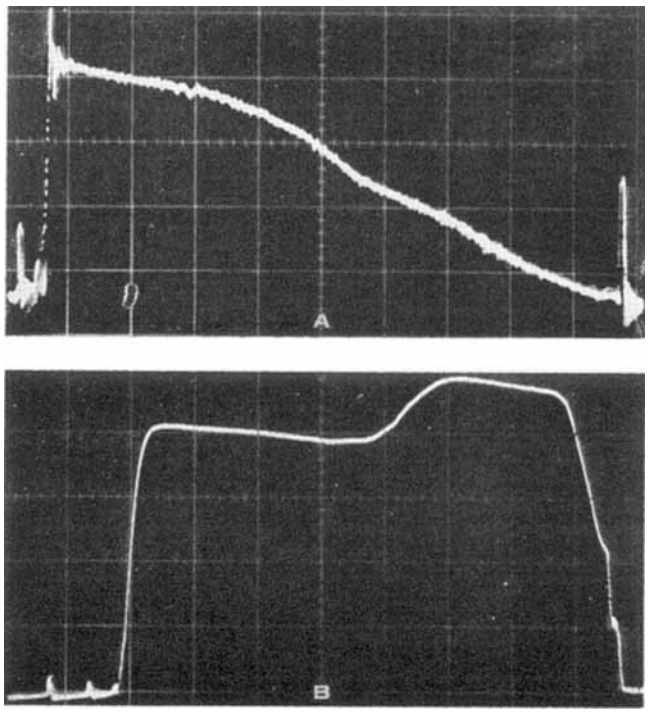

Figure 3—*Oscilloscopic tracing resulting from the ejection of spray-dried lactose USP tablets; each large division represents 6.27 lb. Key: A, no capping; and B, capping.*

Table IV—Compression Specifications of Four Sugars for Direct Tablet Compression[a]

Materials	Compression Force, lb.[b]	Weight, g.[c]	Thickness, cm. (in.)[c]	Hardness[c]	Friability (% Loss)[d]	No. of Capped Tablets
Lactose USP (beadlets)	2230	0.200	0.337 (0.133)	11.3	1.2	0
	4108	0.198	0.314 (0.124)	15.8	11.8	1
Spray-dried lactose USP	2219	0.201	0.337 (0.133)	7.0	1.8	0
	4083	0.201	0.314 (0.124)	14.0	60.9	5
Anhydrous lactose USP	2231	0.204	0.337 (0.133)	8.1	1.6	0
	3974	0.203	0.314 (0.124)	16.2	21.9	2
Dextrose (PAF 2011)	2153	0.201	0.337 (0.133)	12.3	0.7	0
	4120	0.201	0.314 (0.124)	19.8	1.0	0

[a] All tablets lubricated with 0.5% each magnesium stearate USP and stearic acid USP. [b] Average of 20 consecutive events. [c] Average of 10 readings. [d] Capped tablets taken as 100% loss.

and packaging. Tablets prepared from lactose USP (beadlets) also exhibited, to a lesser degree, a latent tendency toward capping at high pressure when run with standard concave punches.

It was decided to subject the two best performers [lactose USP (beadlets) and dextrose (PAF 2011)] to a more severe test. Each material was run on the same tablet machine at 1200 tablets/min., using extra deep concave (modified ball) tooling at the high pressure level. Under these conditions, pronounced capping was evident in the case of the lactose USP (beadlets). In contrast, tablets prepared from dextrose (PAF 2011) did not cap under these same test conditions (Fig. 5).

Weight Variation—Extremely close weight tolerances were obtained with all agents except anhydrous lactose USP. To determine the magnitude of tablet-to-tablet weight variation, each material was run for 1 hr. on the instrumented RBB2 tablet press. The presence of a blank station in the die table served to index the compression forces at each individual station. It was, therefore, possible to determine if fluctuations in compression force levels were due to tablet-to-tablet weight variation or to tooling variation (*i.e.*, the combined length of the upper and lower punches was either more or less than the norm for the particular set of tooling). Figure 6 shows a series of waveforms resulting from the compression of dextrose (PAF 2011) in which a pattern of variable peak heights is evident. Since this pattern recurs in successive revolutions, one may assume that it is due to tooling variation. Hence, the dextrose (PAF 2011) exhibited remarkably close weight tolerances. In comparison, the waveforms for anhydrous lactose USP depicted in Fig. 7 showed a considerable degree of fluctuating peak heights. Since the pattern obtained in this case does not recur at regular intervals, the force variations cannot be attributed to tooling variations.

Samples were taken from the machine at 10-min. intervals. Twenty tablets were selected, at random, from these samples and weighed individually on a semimicro balance. The statistical data obtained are tabulated in Table V.

Table V—Weight Variation of Four Sugar Tablets Prepared by Direct Compression

Sample	Mean Weight[a]	Standard Deviation
Lactose USP (beadlets)	201.94	±0.7466
Spray-dried lactose USP	197.77	±0.9177
Anhydrous lactose USP	199.41	±1.4949[b]
Dextrose (PAF 2011)	195.63	±0.9652

[a] Average of 20 tablets and expressed in mg. [b] $p = 0.0165$. Significant at 95% confidence limits.

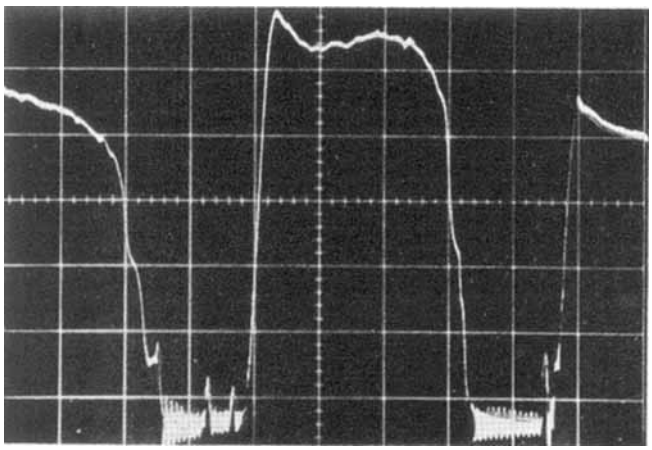

Figure 4—*Oscilloscopic tracing resulting from the ejection of anhydrous lactose USP tablets; each large division represents 12.5 lb.*

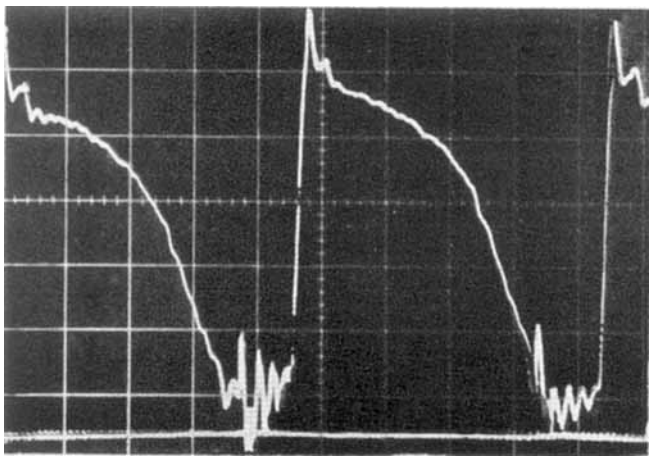

Figure 5—*Oscilloscopic tracing resulting from the ejection of dextrose (PAF 2011) tablets; each large division represents 6.27 lb.*

Disintegration—To obtain disintegration information, samples were prepared from each of the four agents for direct compression according to the following formula:

Ingredients	g./Tablet
Material for direct compression	0.190
Starch USP	0.010
Magnesium stearate USP	0.001
Stearic acid USP	0.001
	0.202

Tablets were compressed on the instrumented RBB2 tablet

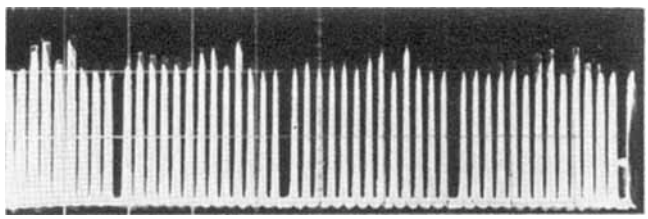

Figure 6—*Oscilloscopic tracing resulting from the compression of dextrose (PAF 2011); each large division represents 786 lb.*

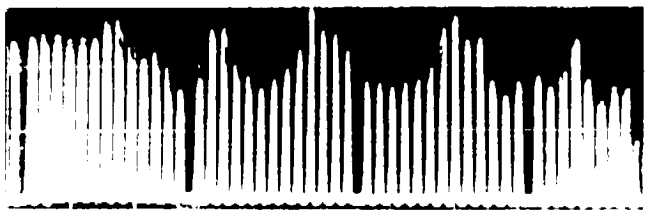

Figure 7—*Oscilloscopic tracing resulting from the compression of anhydrous lactose USP; each large division represents 786 lb.*

machine. The uniformity of the compression force, weight, and tablet thickness was maintained within narrow limits. Disintegration times, as determined by the official USP method (12), are recorded in Table VI.

Although all samples had disintegration times of less than 9 min., those prepared from dextrose (PAF 2011) exhibited the shortest and most uniform times. This observation could well have been predicted in view of the difference in solubility between dextrose and lactose.

SUMMARY AND CONCLUSIONS

Lactose USP (beadlets) and dextrose (PAF 2011) have been evaluated and compared with two commonly used agents for direct compression, namely, spray-dried lactose USP and anhydrous lactose USP, as to their relative physical properties and stability for tableting by direct compression.

The physical properties, *i.e.*, bulk density, angle of repose, and particle-size distribution, of all four agents were determined. The effects of heat, moisture, and light, as well as the presence of selected amines and lubricants, on the physical properties and color stability of tablets prepared from the materials were compared with a lactose USP control. The compression characteristics of all four materials were defined with the aid of an instrumented rotary tablet machine. Compression and ejection forces were monitored continuously and correlated with tablet hardness, friability, weight variation, and disintegration time.

Both dextrose (PAF 2011) and lactose USP (beadlets) exhibited excellent flow characteristics, as evidenced by minimal tablet-to-tablet weight variation. The hygroscopic nature of the dextrose (PAF 2011) detracts considerably from its overall physical stability. Neither new agent represented a significant improvement over the older materials with regard to color stability. Of the four agents tested, only anhydrous lactose USP was able to withstand adequately the exposure to heat, light, and moisture.

The compressional characteristics of dextrose (PAF 2011) were superior to those of the lactose sugars. When identical formulations were tested, dextrose (PAF 2011) produced the hardest and least friable tablets. The compression characteristics of lactose USP (beadlets) were superior to those of spray-dried lactose USP and anhydrous lactose USP.

It is felt that both dextrose (PAF 2011) and lactose USP (beadlets) warrant serious consideration for use as agents for direct compression in the pharmaceutical industry.

Table VI—Disintegration Time for Four Sugar Tablets Prepared by Direct Compression

Sample	Weight, g.[a]	Thickness, cm. (in.)[a]	Compression Force, lb.[b]	Disintegration Time, sec. With Disks[c]	Disintegration Time, sec. Without Disks[c]
Lactose USP (beadlets)	0.202	0.337 (0.133)	2257	310	440
Spray-dried lactose USP	0.198	0.235 (0.132)	2201	190	320
Anhydrous lactose USP	0.199	0.337 (0.133)	2237	400	510
Dextrose (PAF 2011)	0.196	0.235 (0.132)	2187	130	160

[a] Average of 10 tablets. [b] Average of 10 consecutive events. [c] Average of 12 tablets.

REFERENCES

(1) G. Milosovich, *Drug Cosmet. Ind.*, **92**, 557(1963).

(2) M. W. Scott, H. A. Lieberman, D. Maher, and F. Chow, paper presented to the Eastern Regional Meeting, Industrial Pharmacy Section, APhA, 1961.

(3) C. D. Fox, M. D. Richman, G. E. Reier, and R. Shangraw, *Drug Cosmet. Ind.*, **92**, 161(1963).

(4) J. Jaffe and N. E. Foss, *J. Amer. Pharm. Ass., Sci. Ed.*, **48**, 26(1959).

(5) A. M. Raff, M. J. Robinson, and E. V. Svedres, *J. Pharm. Sci.*, **50**, 76(1961).

(6) K. P. Perlman, *Diss. Abstr.*, **23**, 603(1962).

(7) R. N. Duvall, K. T. Koshy, and R. E. Dashiell, *J. Pharm. Sci.*, **54**, 1196(1965).

(8) G. M. Kovac, paper presented to the Industrial Pharmacy Section, APhA, Las Vegas, Nev., 1962.

(9) G. E. Reier, Ph.D. thesis, University of Maryland, College Park, Md., 1964.

(10) P. E. Wray, J. G. Vincent, F. W. Moller, and G. J. Jackson, paper presented at annual meeting, APhA, Dallas, Texas, 1966.

(11) E. G. E. Shafer, E. G. Wollish, and C. E. Engel, *J. Amer. Pharm. Ass., Sci. Ed.*, **45**, 114(1956).

(12) "United States Pharmacopeia," 17th rev., Mack Publishing Co., Easton, Pa., 1965, pp. 919–920.

(13) A. Q. Butler and J. C. Ramsey, *Drug. Stand.*, **20**, 222(1952).

(14) D. Train, *J. Pharm. Pharmacol.*, **10**, 127T(1958).

(15) L. Lachman, C. J. Swartz, and J. Cooper, *J. Amer. Pharm. Ass., Sci. Ed.*, **49**, 213(1960).

(16) A. C. Todd, paper presented at Particle Characteristics Conference, Union, N. J., 1968.

(17) B. S. Neuman, in "Flow Properties of Disperse Systems," J. J. Hermans, Ed., Interscience, New York, N. Y., 1953, chap. 10.

(18) R. A. Castello and A. M. Mattocks, *J. Pharm. Sci.*, **51**, 106(1962).

(19) W. C. Gunsel and L. Lachman, *ibid.*, **52**, 178(1963).

(20) C. A. Brownley and L. Lachman, *ibid.*, **53**, 452(1964).

(21) N. H. Batuyios, *ibid.*, **55**, 727(1966).

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