Comparative Evaluation of Tablet Formulations Prepared from Conventionally-Processed and Spray-Dried Lactose

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Four tablet formulations made from two types of lactose were studied. The granulations were compared for particle size distribution, flow properties, and moisture content. The tablets made from them were evaluated for hardness, friability, disintegration time, weight control, and color development at room temperature, 40°, 50°, and 60° for 12 weeks. In general, it was found that spray-dried lactose produced harder, less friable tablets which, however, were more susceptible to color development following storage at elevated temperatures.

Since 1956, lactose suitable for use in tablets has been available in two types, depending upon the final manufacturing step. In the manufacture of lactose, the whey of milk is placed in vats where it is heated with dilute hydrochloric acid to coagulate the protein. The acidity is then neutralized with lime and the protein removed by filtration. The liquid portion is evaporated to produce a thick syrup containing 60–70% solids. Upon standing, the syrup crystallizes. After centrifuging the crystals are washed with water. This is crude lactose. The crude is dissolved in tap water at 180 to 200°F. and treated with carbon to decolorize it. It is again filtered and then sterilized by maintaining it at 210°F. for 25 to 35 minutes. It is reconcentrated to 60% solids in vats which then contain 10,000 to 14,000 pounds dry weight. It is at this point that the method of manufacture differentiates the two kinds of lactose discussed in this paper (1, 2). That which will be called conventionally-processed lactose is obtained by centrifuging first and then drying; the second kind is pumped into a spray dryer and becomes spray-dried lactose.

Spray-dried lactose contains about 8% of amorphous material; this is actually dried syrup which has not crystallized. Because the mother liquor becomes a part of the final material, spray-dried lactose contains larger amounts of impurities than the centrifuged product. Thus, it has about five times as much ash and protein, twice the heavy metals and "other sugars," and ten times the lipids (3).

In mesh size, spray-dried lactose has a small portion less than 100; over 94% passes through 100 mesh and 27 to 44% is finer than 200. Conventionally-processed lactose may be obtained in several mesh sizes. This article is mainly concerned with the fine material all of which passes through 100 and 40–50% through 200 mesh. The spray-dried lactose flows readily while the conventionally-processed has poor flow, except in the coarser mesh sizes.

Although spray-dried lactose is now also widely used in tablet formulations, literature about its tableting properties has not appeared in scientific journals. Accordingly, this study was undertaken to determine how the two kinds of lactose compared with each other as the major excipient in several representative tablet formulations.

The following aspects were evaluated: (*a*) particle size distribution in the granulations; (*b*) flow rate and angle of repose of the granulations; (*c*) changes in disintegration time, hardness, friability, and color, for several representative tablet formulations after storage at room temperature, 40°, 50°, and 60° (tests were made at 0, 4, 8, and 12 weeks); and (*d*) uniformity of tablet weight.

EXPERIMENTAL

Formulations

The first formulation (4) examined had the following composition

Formulation I

Lactose U.S.P.	88.5%
Tragacanth U.S.P.	2.0%
Polyethylene glycol 6000	4.0%
Confectioners sugar	2.0%
Talcum U.S.P.	3.0%
Magnesium stearate U.S.P.	0.5%
3A Alcohol 50%	*q.s.*

The polyethylene glycol was dissolved in the 50% alcohol and added to the mixture of the other components. The moist mass was passed through a No. 10 hand screen and dried with circulating, dehumidified air for a minimum of 16 hours. The granules were broken on a No. 16 hand screen and were then ready for compression.

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FORMULATION II

Lactose U.S.P.	94.5%
Cornstarch (dried)	4.5%
Stearic acid powder U.S.P.	1.0%
Purified water	*q.s.*

The lactose, stearic acid, and part of the starch were mixed together; the rest of the starch was converted to a paste with the water and used to wet down the powders. The moist mass was forced through a No. 8 hand screen and dried on trays at 100° F. for 16 hours. The material was then broken on a No. 16 hand screen.

FORMULATION III

Lactose U.S.P.	89.5%
Tragacanth U.S.P.	2.0%
Cornstarch	5.0%
Talcum U.S.P.	3.0%
Magnesium stearate U.S.P.	0.5%
3A Alcohol 50%	*q.s.*

The lactose and tragacanth were mixed and then moistened with the alcohol solution. The moist mass was screened through a 10-mesh sieve and dried with circulating dehumidified air for 16 hours. The dried material was then broken on a No. 16 hand screen and mixed with the cornstarch, talcum, and magnesium stearate.

The fourth formula is a simple mixture of the ingredients which are

FORMULATION IV

Lactose U.S.P.	94.5%
Cornstarch	5.0%
Magnesium stearate U.S.P.	0.5%

These materials were passed through a 20-mesh screen and then mixed.

Granulations were prepared in batches of 20,000 tablets, ten batches with conventionally-processed lactose, ten batches with spray-dried lactose. They were manufactured in a model A-200 Hobart planetary mixer. For each series, the mixing time, mixing speed, and amount of granulating liquid were the same. The granulations were compressed into 150-mg. tablets on a single rotary, 16-station press set to operate at 27,000 tablets per hour. The punches were $^{9}/_{32}$ in. diameter standard concave, uppers bisected and lowers monogrammed. Plain steel dies were used.

The results of the various tests to be described are the average of ten determinations.

Test Methods

Moisture Content.—Moisture content of the granulations was determined on a Cenco moisture balance operating at 120 v. with a 125-w. infrared lamp. The test was continued until the granulation changed color or until three consecutive readings at 1-min. intervals were the same.

Hardness.—Hardness was read on the hardness tester manufactured by the Strong-Cobb Arner Company. This unit was modified to operate from a compressed air line.

Friability.—Friability was measured with a Roche Friabilitor using a 4-min. cycle.

Disintegration Time.—Disintegration times were taken on the U.S.P. apparatus; no disks or holders were used.

Particle Size Analysis.—Sieve sizing was done on a Ro-Tap testing sieve shaker using stainless steel U.S. Standard sieve series in 20, 30, 40, 50, 60, and 80 mesh sizes and operating for 15 minutes. Each sample tested weighed 100 Gm.

Angle of Repose.—Angle of repose was measured by the cone method using a cathetometer and a 4-in. diameter tripod.

Flow Rate.—Flow rate was determined by timing the passage of 250 Gm. of granulation through a stainless steel funnel with a 1-in. orifice.

TABLE I.—INFLUENCE OF STORAGE ON DISINTEGRATION TIMES, IN MINUTES[a]

	R.T.		40° C.		50° C.		60° C.	
	A	B	A	B	A	B	A	B
Initial	12'25"	11'05"	...	...	...	...	...	...
4 Weeks	10'50"	10'40"	11'10"	10'50"	12'00"	10'40"	9'00"	9'25"
8 Weeks	11'15"	10'10"	11'05"	9'45"	12'40"	9'55"	6'10"	7'55"
12 Weeks	11'10"	9'30"	10'50"	9'25"	12'30"	9'35"	4'45"	7'20"

[a] A, conventionally-processed lactose; B, spray-dried lactose.

TABLE II.—INFLUENCE OF STORAGE ON HARDNESS, KG./SQ. IN.[a]

	R.T.		40° C.		50° C.		60° C.	
	A	B	A	B	A	B	A	B
Initial	5.9	8.5	...	...	...	...	...	...
4 Weeks	6.2	8.9	6.2	7.5	5.9	7.7	5.5	7.7
8 Weeks	6.1	8.4	6.2	8.0	6.1	7.6	4.5	7.6
12 Weeks	5.9	8.4	6.3	8.4	5.8	7.9	4.1	7.0

[a] A, conventionally-processed lactose; B, spray-dried lactose.

TABLE III.—INFLUENCE OF STORAGE ON FRIABILITY, % LOSS[a]

	R.T.		40° C.		50° C.		60° C.	
	A	B	A	B	A	B	A	B
Initial	0.34	0.20	...	...	...	...	...	...
4 Weeks	0.28	0.17	0.33	0.23	0.37	0.28	0.44	0.23
8 Weeks	0.28	0.18	0.34	0.20	0.37	0.21	0.36	0.21
12 Weeks	0.34	0.16	0.39	0.21	0.39	0.22	0.34	0.20

[a] A conventionally-processed lactose; B, spray-dried lactose.

RESULTS AND DISCUSSION

Formulation I.—As is evident from the data in Tables I, II, and III, the tablets were physically satisfactory. At the end of the 12-week test period, disintegration times were lower than initially at all temperatures. The tablets of spray-dried lactose disintegrated a little more rapidly except at 60°. Times for both types of tablets were well within U.S.P. limits.

Both sets of tablets exhibited good hardnesses with the conventional lactose always associated with the lower results. With time and temperature, there were changes downward from the initial figures but all the tablets were satisfactory except those of conventional lactose at 60°.

In friability the tablets containing spray-dried lactose suffered losses approximately one-half those of the conventional lactose regardless of time or temperature. The results for both sets of tablets remained quite constant under all storage conditions. It may be noted from the tables that even for those tablets which had a relatively poor hardness, the friability was not adversely affected.

A visible color change appeared in the spray-dried lactose tablets at 50° and 60°, a change confirmed by reflectance readings. However, the set of tablets from conventionally-processed lactose retained its original whiteness. The flow rates of the two granulations were very much alike, a fact confirmed by the similarities in the angles of repose. Spray-dried lactose gave slightly better results. On sieve analysis, both granulations contained mostly fine material, 78% of the conventional type and 89% of the spray-dried passing through a No. 60 sieve. Moisture content ranged between 3.3% and 5.3% but a correlation between moisture content and other physical characteristics was not apparent.

Formulation II.—Table IV shows that disintegration times were very rapid at room temperature throughout the test period. They rose gradually with storage at 40° and 50° with a severe increase at 60°. At this temperature, the tablets of spray-dried lactose disintegrated more rapidly than those of conventionally-processed lactose. Melting of the stearic acid or some change in the starch may have produced this effect.

Both types of tablets behaved similarly in the hardness test as evidenced by the data in Table V. At room temperature, there was a progressive softening of the tablets; this did not occur at the other temperatures. The tablets of conventionally-processed lactose were generally harder than those of spray-dried lactose.

Friability results shown in Table VI indicated that the conventionally-processed lactose produced better tablets initially but the losses became almost identical in all the later tests except the one at 60° for 12 weeks. These losses represented a large increase over the initial levels.

In flow rate and angle of repose, the conventional lactose averaged slightly better than the spray-dried. Moisture content averaged 0.7% higher in the granulations made from conventionally-processed lactose. A comparison of individual batch results gave no apparent correlation of moisture with hardness, with friability, or with disintegration time.

On sieve analysis, the granulations from spray-dried lactose had almost equal amounts caught on all screens with the No. 20 having the least. On the other hand, the granulations from the conventionally-processed lactose had a 43% cut passing through the 80-mesh screen with the second largest (19%) caught on the No. 80. Nevertheless, tableting characteristics of the two were very similar.

TABLE IV.—INFLUENCE OF STORAGE ON DISINTEGRATION TIME, IN MINUTES[a]

	R.T.		40° C.		50° C.		60° C.	
	A	B	A	B	A	B	A	B
Initial	0'15"	0'40"	...	...	...	...	...	...
4 Weeks	0'15"	0'50"	0'20"	1'05"	0'40"	2'05"	8'15"	10'30"
8 Weeks	0'15"	0'55"	0'20"	1'20"	2'30"	5'30"	22'30"	19'00"
12 Weeks	0'15"	0'50"	0'25"	1'40"	4'10"	7'25"	28'15"	22'40"

[a] A, conventionally-processed lactose; B, spray-dried lactose.

TABLE V.—INFLUENCE OF STORAGE ON HARDNESS, KG./SQ. IN.[a]

	R.T.		40° C.		50° C.		60° C.	
	A	B	A	B	A	B	A	B
Initial	5.2	5.2	...	...	...	...	...	...
4 Weeks	5.1	5.1	5.1	5.1	5.2	5.2	5.5	5.3
8 Weeks	4.9	4.7	5.2	5.1	5.4	5.2	5.2	5.1
12 Weeks	4.5	4.4	4.9	5.1	5.1	5.2	5.4	5.1

[a] A, conventionally-processed lactose; B, spray-dried lactose.

TABLE VI.—INFLUENCE OF STORAGE ON FRIABILITY, % LOSS[a]

	R.T.		40° C.		50° C.		60° C.	
	A	B	A	B	A	B	A	B
Initial	0.18	0.32	...	...	...	...	...	...
4 Weeks	0.45	0.51	0.46	0.47	0.56	0.55	0.53	0.51
8 Weeks	0.49	0.48	0.46	0.51	0.56	0.56	0.57	0.59
12 Weeks	0.52	0.55	0.48	0.49	0.57	0.62	0.60	0.73

[a] A, conventionally-processed lactose; B, spray-dried lactose.

By reflectance measurement, the tablets of spray-dried lactose were darker even when freshly made and became more so at 60°, the change being 7.3% whereas the tablets of conventionally-processed lactose changed only 2%. The difference between the two initially was 8.4% and increased to 13.7%.

Formulation III.—From Table VII it may be seen that both sets of tablets were almost identical in disintegration time at each storage condition. There were decreases with time and with temperature. All test results were low.

On the average, the spray-dried lactose produced the superior hardnesses as is indicated by the data in Table VIII. These increased from the fourth to the twelfth week at all temperatures with the room temperature samples increasing about half a unit while the 40°, 50°, and 60° samples ended up almost equal with each other and slightly below the initial level. The conventionally-processed lactose tablets softened under all conditions with the room temperature samples falling one unit and the other temperature results dropping slightly less.

In the friability tests, the conventionally-processed lactose tablets were very poor, two of the batches capping in the initial test and continuing to do so under the various storage conditions as shown in Table IX. Most of the other batches capped also but in a random pattern. Only two batches did not cap at all. As a consequence at all times and conditions, average friabilities were 0.9% or worse. On the other hand, the spray-dried lactose gave very good results at room temperature and satisfactory results at 50°, but rather poor at 40° and at 60°.

Tablets of spray-dried lactose darkened slightly more than those of conventionally-processed lactose at the accelerated conditions. There were small differences in flow rate and angle of repose. Both granulations contained many fines, the spray-dried lactose having more—93.6% passing through a No. 80 screen as against 81.7% for the conventional.

Formulation IV.—It was impossible to make adequate tablets from conventionally-processed lactose even when it was in the form of coarse (60–80 mesh) free-flowing granules. The tablets would not hold together. Therefore, the following data refer only to spray-dried lactose.

Disintegration times decreased with time at room temperature and reached their lowest points after 4 weeks at the other three storage conditions. These

Table X.—Influence of Storage on Disintegration Time, In Minutes

	R.T.	40° C.	50° C.	60° C.
Initial	7'50"	...	...	...
4 Weeks	7'45"	2'45"	1'45"	2'25"
8 Weeks	5'40"	2'50"	2'20"	4'50"
12 Weeks	4'30"	2'55"	3'30"	7'20"

Table XI.—Influence of Storage on Hardness, Kg./sq. in.

	R.T.	40° C.	50° C.	60° C.
Initial	5.7	...	...	...
4 Weeks	6.4	6.0	6.5	6.3
8 Weeks	6.1	6.3	6.4	6.0
12 Weeks	5.9	6.1	6.3	5.9

Table XII.—Influence of Storage on Friability, % Loss

	R.T.	40° C.	50° C.	60° C.
Initial	0.07	...	...	...
4 Weeks	0.18	0.27	0.25	0.29
8 Weeks	0.30	0.29	0.26	0.29
12 Weeks	0.34	0.30	0.26	0.29

Table VII.—Influence of Storage on Disintegration Time, In Minutes[a]

	R.T.		40° C.		50° C.		60° C.	
	A	B	A	B	A	B	A	B
Initial	2'05"	2'05"	...	...	...	...	...	...
4 Weeks	1'50"	1'30"	1'20"	1'05"	0'50"	1'00"	0'30"	0'45"
8 Weeks	1'45"	1'20"	1'10"	0'55"	0'45"	0'55"	0'30"	0'35"
12 Weeks	1'40"	1'30"	1'05"	1'00"	0'45"	0'50"	0'30"	0'35"

[a] A, conventionally-processed lactose; B, spray-dried lactose.

Table VIII.—Influence of Storage on Hardness, Kg./sq. in.[a]

	R.T.		40° C.		50° C.		60° C.	
	A	B	A	B	A	B	A	B
Initial	4.7	5.0	...	...	...	...	...	...
4 Weeks	4.3	4.9	4.2	4.6	4.0	4.4	4.1	4.6
8 Weeks	4.0	5.0	4.0	4.7	4.1	4.8	3.9	4.8
12 Weeks	3.7	5.4	3.9	4.8	3.8	4.9	3.8	4.9

[a] A, conventionally-processed lactose; B, spray-dried lactose.

Table IX.—Influence of Storage on Friability, % Loss[a]

	R.T.		40° C.		50° C.		60° C.	
	A	B	A	B	A	B	A	B
Initial	0.96	0.16	...	...	...	...	...	...
4 Weeks	0.95	0.21	1.05	0.71	1.43	0.36	0.72	0.71
8 Weeks	0.91	0.20	1.31	0.76	1.33	0.32	1.49	0.44
12 Weeks	1.03	0.26	1.23	0.42	0.95	0.39	1.14	0.60

[a] A, conventionally-processed lactose; B, spray-dried lactose.

latter then rose during the next 8 weeks until the 60° samples approached the initial result at room temperature (Table X).

Table XI indicates that all hardness results were greater than the initial one. For room temperature, 50°, and 60° they reached a peak at 4 weeks and then declined. Although the hardness readings decreased at 50° and 60° during the last 8 weeks, the disintegration times increased.

Friability was remarkably low at the beginning of the study but it increased with time, the highest level being at room temperature (See Table XII). All results were satisfactory however. Color change was very strong, being 13.5% darker after 12 weeks at 60° than initially.

An inconvenience with spray-dried lactose is that on aging it darkens appreciably more than the conventionally-processed material. This fact has been indicated in the discussion of each formulation. Table XIII compares the reflectance values of the tablets at the beginning and the end of the study along with the values for samples of the two types of lactose.

TABLE XIII.—EFFECT OF STORAGE ON COLOR STABILITY OF LACTOSE AND LACTOSE TABLETS ACCORDING TO REFLECTANCE MEASUREMENTS

Formulation[a]	Zero Time	12 Weeks' Storage at— R.T.	40° C.	50° C.	60° C.
88.5% lactose					
I A	63.0	62.0	63.0	63.0	62.0
I B	62.0	62.0	59.7	54.3	50.3
94.5% lactose					
II A	67.0	67.0	66.0	66.0	65.0
II B	59.4	58.6	57.0	54.7	51.3
89.5% lactose					
III A	59.8	59.4	58.0	57.7	55.9
III B	57.8	57.8	57.0	53.3	51.9
94.5% lactose					
IV B	57.2	56.8	52.2	46.7	43.3
100% lactose					
A	99.0	99.0	89.0	91.0	89.0
B	88.0	88.0	62.0	63.0	38.0

[a] A, conventionally-processed lactose; B, spray-dried lactose.

Why spray-dried lactose discolors more than conventionally-processed lactose has not been specifically elucidated. However, it does contain larger amounts of impurities because the mother liquor is included in it. It is exposed to high heat while passing through the spray dryer but, theoretically, the evaporation of the moisture cools the crystals and prevents them from overheating. However, the other ingredients in the formulation afford some protection and indicate one method of attack on the problem.

A seeming paradox occurred between the data on flow and on weight control of the tablets (Table XIV).

The formulation with the slowest flow rate (Formulation III) produced the tablets with the most accurate weight control while the formulation with the most rapid flow (Formulation II) had the greatest weight variance.

Reference has been made several times to sieve sizing. The complete results are available in Table XV.

SUMMARY AND CONCLUSIONS

1. In three out of four formulations examined, tablets made from spray-dried lactose exhibited better physical qualities than those made from conventionally-processed lactose.

2. Spray-dried lactose is particularly useful because tablets can be made from it without wet granulating or slugging.

3. Spray-dried lactose darkens much more readily than conventionally-processed lactose.

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TABLE XIV.—FLOW PROPERTIES AND WEIGHT VARIATION

Tests	Formulation[a] I A	I B	II A	II B	III A	III B	IV B
Flow rate (seconds)	8.57	8.44	7.60	8.14	10.48	11.21	8.35
Angle of repose	36°29′	34°45′	36°10′	37°29′	36°55′	37°39′	36°08′
Mean weight (mg.)	151.16	150.33	148.84	148.78	148.47	150.34	149.36
Standard deviation (mg.)	±1.10	±1.14	±1.50	±1.72	±0.55	±0.58	±0.70

[a] A, conventionally-processed lactose; B, spray-dried lactose.

TABLE XV.—SIEVE ANALYSIS, %

% Found On	Formulation[a] I A	I B	II A	II B	III A	III B	IV B
20 mesh	1.08	2.06	1.76	5.82	0.12	0.33	...
30 mesh	4.23	4.16	5.91	14.78	0.81	1.13	...
40 mesh	3.88	1.95	7.10	14.24	0.67	0.55	...
50 mesh	7.01	1.63	13.72	19.48	2.32	0.95	...
60 mesh	5.50	0.90	9.30	11.78	2.36	0.72	...
80 mesh	19.17	4.16	19.25	17.57	12.04	2.71	...
Through 80 mesh	59.13	85.13	42.96	16.33	81.68	93.61	100.00

[a] A, conventionally-processed lactose; B, spray-dried lactose.