where

A, B, and C have the previously noted connotations and

R = the average R value derived from the standard

E = ml. of oil sample taken for analysis

mg. ethinyl estradiol/Gm. =

$$\frac{(A)(C)}{(B)(R)} \times \frac{1}{(E)} \quad \text{(Eq. 2)}$$

where A, B, C, and R have the previously noted connotations and E = sample weight in Gm.

RESULTS AND DISCUSSION

Table I summarizes R values obtained in a typical calibration experiment. As can be seen, the standard deviation is approximately $\pm 1\%$. For comparison, peak height ratios were calculated, and the results indicate a standard deviation of $\pm 4.8\%$, illustrating the superior precision obtainable utilizing integrated areas. A typical chromatogram is reproduced in Fig. 1.

A solution was prepared of ethinyl estradiol in sesame oil to study the recovery of a sample subjected to this proposed procedure. The results of this experiment are shown in Table II.

Several samples of formulations prepared for clinical study have been analyzed by this technique. Data are summarized in Table III.

Although the authors have not encountered any examples of decomposition for ethinyl estradiol, the selectivity and sensitivity of the method appears adequate for stability studies. Certainly the method would be very sensitive to estrone, the most likely decomposition product.

SUMMARY

A quantitative gas liquid chromatographic procedure has been developed for the analysis of ethinyl estradiol using the internal standard technique. The precision of the gas chromatographic method is $\pm 1\%$, and the accuracy of the complete method is $100.2 \pm 1.7\%$. The method has been applied to oil solutions and solid granulations and permits a large number of replicate samples to be analyzed expeditiously with greater selectivity and sensitivity than previously reported methods.

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Technical Articles

Comparative Evaluation of Dextrose and Spray-Dried Lactose in Direct Compression Systems

By R. N. DUVALL, K. T. KOSHY, and R. E. DASHIELL

Many commercially available forms of dextrose have a distinct cost advantage over spray-dried lactose which is used extensively as a tablet excipient. The objective of this investigation was to compare the performance of a food grade dextrose with that of spray-dried lactose as an excipient in the direct compression of tablets. Several formulations were evaluated under accelerated stability conditions relative to changes in hardness, friability, disintegration time, and dissolution rate. Results indicated that dextrose can be partly or completely substituted for spray-dried lactose in some formulations. Dextrose was found to give less browning than spray-dried lactose in formulations containing no amines, whereas it gave more browning when amines were present.

IN RECENT years, interest in the direct compression of tablets has increased considerably. This technique is economical and enables one to tablet drugs which are not amenable to wet granulation procedures. The introduction of spray-dried lactose about 10 years ago and recent advances in tableting technology have lent considerable impetus toward the use of direct compaction methods. With today's potent medicinal agents, the active ingredient often makes up only

Received March 29, 1965, from the Corporate Pharmacy Research Laboratory, Miles Laboratories, Inc., Elkhart, Ind.
Accepted for publication June 2, 1965.
Presented to the Scientific Section, A.PH.A., Detroit meeting, March 1965.
The authors thank Mr. L. L. Shankle and Mr. D. D. Waterman for technical assistance.

TABLE I.—PARTICLE SIZE ANALYSIS OF RAW MATERIALS

Screen	60	80	120	140	170	200	Pan
			Material on Screen, %				
Lactose S.D.	0	4.5	24.5	16.0	18.0	12.0	25.0
Cerelose No. 2001	8.0	18.0	24.0	13.0	17.5	9.0	10.5
Cerelose No. 2401	3.5	32.5	33.0	13.0	9.0	5.0	4.0

a small percentage of the total bulk of the tablet. Therefore, a thorough understanding of the tableting properties of the fillers used in such tablets is important since they account for the main physical characteristics of the final product. Spray-dried lactose has been used extensively in such systems, and although discoloration of this material is a problem, it is still the standard to which other materials are referred.

Preliminary experiments in our laboratory with various forms of dextrose had indicated considerable potential in direct compression systems. Many of these forms are available at a distinct cost advantage over spray-dried lactose and have been reported in a company brochure[1] to be effective as dry binder additives in direct compression systems. Such information is lacking in details and no information relative to the direct compression tableting characteristics of dextrose has appeared in the scientific literature. The objective of this investigation was to compare the performance of a food grade dextrose[2] with that of spray-dried lactose as the major excipient in the direct compression of tablet formulations. Various formulations were evaluated relative to runability at various speeds, intertablet weight variation, and drug distribution. Stability of the formulas was evaluated following accelerated aging tests by measuring changes in hardness, friability, disintegration time, and dissolution rate. The browning tendency of dextrose and spray-dried lactose was also compared in the presence and absence of added amines following accelerated aging tests.

EXPERIMENTAL

Materials.—Spray-dried lactose U.S.P.,[3] Cerelose hydrous No. 2001 (8% water) and anhydrous 2401,[2] microcrystalline cellulose,[4] two hydrogenated soybean oils (*A* and *B*, respectively),[5] and either U.S.P. or N.F. grades of magnesium stearate, talc, phenobarbital, cornstarch, mannitol, amphetamine sulfate, and methamphetamine hydrochloride were used. Dimethylamphetamine hydrochloride was prepared by the procedure of Dirscherl *et al.* (1). The mesh analyses of the lactose and dextrose samples used are shown in Table I.

Tablet Formulations.—The compositions of the various formulations studied are shown in Tables II and III. The ingredients were mixed geometrically, passed through a No. 24 hand screen, blended for 5 min. in a twin-shell blender, and compressed directly on a single rotary 16 station Colton 216 tablet press operating at 820 tablets per minute using stainless steel $^{7}/_{16}$-in. flat-faced punches with beveled edge and stainless steel dies.

The high-speed runability experiments were conducted on a Colton 243–225 tablet press operating at 2700 tablets per minute using $^{5}/_{16}$-in. deep cup punches and $^{7}/_{16}$-in. flat-faced punches with beveled edge. The Colton 260–60 press operating at 1600–2000 tablets per minute using 1-in. flat punches with beveled edges was also used for runability trials.

EVALUATION PROCEDURES

Particle Size Analysis.—Particle size was determined with a Ro-Tap testing sieve shaker, using U. S. Standard sieves in series 60, 80, 120, 140, 170, and 200 mesh sizes. A 200-Gm. sample was tested in the sieve shaker for 5 min.

Accelerated Stability Conditions.—Comparative data were obtained following storage of tablets at 25°, 25°—70% R.H., 50°, and 50°—70% R.H.

Hardness.—Hardness of tablets was determined using a Stokes hardness tester.

Friability.—Friability was ascertained using the Roche Friabilator after 100 revolutions at 25 r.p.m.

Disintegration.—Disintegration times were determined using simulated gastric juice and the U.S.P. apparatus without disks.

Drug Content Uniformity.—Intertablet distribution data for phenobarbital formulations were determined by assaying 10 tablets individually as follows. One tablet was dissolved in 100 ml. of 0.02 *N* sodium hydroxide, filtered, 5.0 ml. of filtrate diluted to 100 ml. with 0.02 *N* sodium hydroxide, and the absorbance of this solution measured at 240 mμ.

Dissolution Rate.—Dissolution of phenobarbital was measured by taking 10-ml. aliquots of fluid from the U.S.P. disintegration apparatus at 5-min. intervals, filtering, diluting 4.0 ml. of filtrate to 100 ml. with 0.02 *N* sodium hydroxide, and measuring the absorbance of the resulting solution at 240 mμ.

Browning Reaction.—The relative browning of lactose and dextrose formulations in the absence of added amines was evaluated visually and by measuring the absorbance maximum in the ultraviolet using a Beckman DB spectrophotometer. Six tablets were dissolved in 25 ml. of water, filtered, and

[1] F. J. Stokes Corp., Philadelphia, Pa.
[2] Marketed as Cerelose by Corn Products Co., New York N. Y.
[3] Foremost Dairies, Inc., Appleton, Wis.
[4] Marketed as Avicel by American Viscose Corp., Philadelphia, Pa.
[5] Marketed as Sterotex and Durkex 500 by Capital City Products Co., Columbus, Ohio, and Durkee Famous Foods, Chicago, Ill.

TABLE II.—PHYSICAL TESTS ON DEXTROSE AND LACTOSE TABLETS STORED AT ROOM TEMPERATURE[a]

	Tablet Compn.	Hardness, Kg.			Friability, % Loss			Disintegration Time					
		Orig.	8 wk.	8 wk. 70%	Orig.	8 wk.	8 wk. 70%	Orig. min.	Orig. sec.	8 wk. min.	8 wk. sec.	8 wk. 70% min.	8 wk. 70% sec
1.	Dextrose hydrous	5.4	6.9	6.8	0.72	0.73	0.53	6	30	6	13	8	38
2.	Lactose S.D.	5.3	5.9	6.6	0.80	0.79	0.75	4	22	5	40	10	58
3.	Dext. hyd. + dext. anhyd. (1:1)	6.1	8.4	10.3	0.64	0.58	0.61	6	50	7	38	9	33
4.	Dext. hyd. + lact. S.D. (1:1)	5.9	6.7	6.3	0.81	0.97	0.62	3	25	3	22	11	45
5.	Dext. hyd. + cornstarch 5%	6.0	7.2	5.0	0.86	0.87	1.15	3	31	8	27	9	45
6.	Lact. S.D. + cornstarch 5%	6.5	8.4	9.5	0.88	0.61	1.05	1	33	1	32	2	35
7.	Dext. hyd. + lact. S.D. (1:1) + cornstarch 5%	5.2	6.0	4.5	0.89	0.85	1.24	1	51	2	07	5	15
8.	Dext. hyd. + microcrystalline cellulose 10%	6.0	6.4	3.9	0.70	0.70	1.10	0	23	0	22	3	10
9.	Lact. S.D. + microcrystalline cellulose 10%	6.5	7.2	6.6	0.43	0.40	0.75	0	53	0	40	2	45
10.	Dext. hyd. + phenobarbital[b]	6.6	8.7	9.5	0.71	0.55	0.62	11	23	11	25	12	15
11.	Lact. S.D. + phenobarbital[b]	6.6	7.5	9.7	0.78	0.72	0.59	16	23	18	52	17	45
12.	Dext. hyd. + anhyd. (1:1) + phenobarbital[b]	5.8	6.7	6.6	0.74	0.83	0.75	14	41	12	12	9	52

[a] All tablets contained 1% magnesium stearate as the lubricant. [b] Thirty milligrams of phenobarbital per tablet.

TABLE III.—PHYSICAL TESTS ON DEXTROSE AND LACTOSE TABLETS STORED AT ACCELERATED CONDITIONS[a]

	Tablet Compn.	Hardness, Kg.			Friability, % Loss			Disintegration Time					
		Orig.	4 wk. 50°	4 wk. 50°, 70%	Orig.	4 wk. 50°	4 wk. 50°, 70%	Orig. min.	Orig. sec.	4 wk. 50° min.	4 wk. 50° sec.	4 wk. 50°, 70% min.	4 wk. 50°, 70% sec.
1.	Dextrose hydrous	5.4	10.9	13.3	0.72	0.51	0.51	6	30	9	15	8	33
2.	Lactose S.D.	5.3	8.0	6.9	0.80	0.77	0.72	4	22	10	32	10	25
3.	Dext. hyd. + dext. anyd. (1:1)	6.1	10.0	10.0	0.64	0.49	0.74	6	50	8	08	8	01
4.	Dext. hyd. + lact. S.D. (1:1)	5.9	4.6	5.1	0.81	0.51	0.62	3	25	12	25	11	40
5.	Dext. hyd. + cornstarch 5%	6.0	6.4	6.2	0.86	0.80	1.01	3	31	8	30	6	58
6.	Lact. S.D. + cornstarch 5%	6.5	7.4	9.1	0.88	0.72	0.87	1	33	1	21	1	38
7.	Dext. hyd. + lact. S.D. (1:1) + cornstarch 5%	5.2	4.9	3.5	0.89	1.06	1.74	1	51	9	12	7	05
8.	Dext. hyd. + microcrystalline cellulose 10%	6.0	4.8	4.7	0.70	1.06	1.02	0	23	9	12	9	45
9.	Lact. S.D. + microcrystalline cellulose 10%	6.5	8.2	7.5	0.43	0.70	0.67	0	53	1	27	2	15
10.	Dext. hyd. + phenobarbital[b]	6.6	12.0	14.4	0.71	0.36	0.41	11	23	10	11	10	33
11.	Lact. S. D. + phenobarbital[b]	6.6	8.6	10.1	0.78	0.62	0.66	16	23	15	00	17	40
12.	Dext. hyd. + dext. anhyd. (1:1) + phenobarbital[b]	5.8	15.0	11.2	0.74	0.50	0.74	14	41	15	15	12	15

[a] All tablets contained 1% magnesium stearate as the lubricant. [b] Thirty milligrams of phenobarbital per tablet.

the absorbance measured at 276 mμ. Browning in the presence of added amines—amphetamine, methamphetamine, and dimethylamphetamine—was estimated only visually.

DISCUSSION

Results of the physical tests on the various formulations are summarized in Tables II and III. All tablets weighed approximately 450 mg., were compressed to similar hardness values, and met U.S.P. tablet weight variation tolerances.

Comparing formulations *1* and *2*, dextrose tablets had more of a tendency to harden with a slight decrease in friability than did lactose tablets under similar accelerated conditions. There was an increase in disintegration times for both materials under stress, the increase being greater for lactose than for dextrose.

The moisture content of dextrose could be a

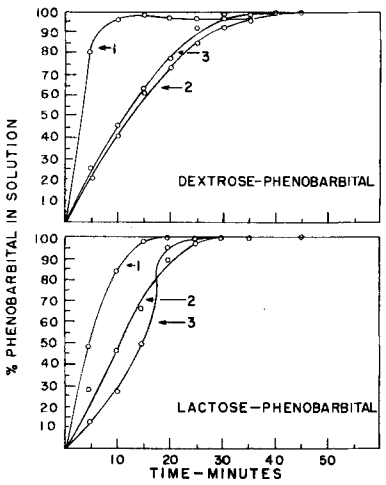

Fig. 1.—Dissolution rate of phenobarbital tablets following aging tests. Key: 1, original; 2, RT—8 weeks; 3, 50° + 70% R. H.—8 weeks.

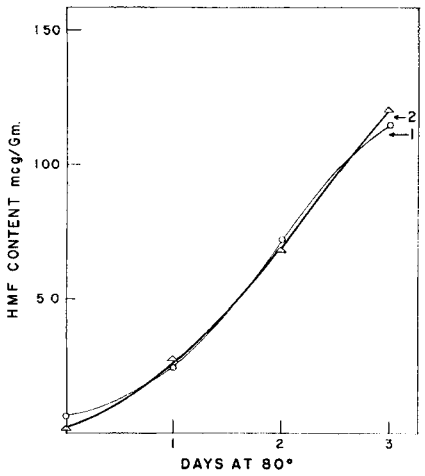

Fig. 2.—5-Hydroxymethylfurfural (HMF) content of a 10% dextrose solution stored at 80° by the TBA and U.V. methods. Key: 1, U.V. method; 2, TBA method.

problem with some drugs. Consequently, the use of an anhydrous form was investigated. This material did not have adequate binding properties and could not be compressed directly, even though the particle size data looked promising. However, a 1:1 mixture of anhydrous and hydrous dextrose could be tableted directly (formulation *3*) and gave results comparable to those with hydrous dextrose alone. Attempts to reduce the moisture content further by increasing the proportion of anhydrous dextrose resulted in poor tablets.

In view of cost advantages, the feasibility of substituting part of the lactose with dextrose was explored. Anhydrous dextrose and spray-dried lactose 1:1 resulted in poor tablets, whereas the hydrous form in the same ratio had good tableting characteristics (formulation *4*). With one exception, friability actually decreased somewhat, even though the tablets did not harden in storage. The increase in disintegration time compared to that occurring with spray-dried lactose alone.

Lubrication requirements for dextrose and lactose in these systems were found to differ mainly in the amount of lubricant required. Talc, hydrogenated soybean oil *A*, hydrogenated soybean oil *B*, and magnesium stearate were evaluated, and only magnesium stearate gave satisfactory results with both materials. Dextrose required approximately 1% magnesium stearate, whereas spray-dried lactose gave satisfactory results at the 0.5% level.

Two disintegrants, cornstarch and microcrystalline cellulose, were studied in dextrose and lactose systems (formulations *5–9*). In general, the use of microcrystalline cellulose resulted in superior direct compression characteristics. Dextrose tablets containing cornstarch showed a significant increase in friability and disintegration time on storage under accelerated conditions, although no changes in hardness were observed. The only change in the corresponding lactose tablets was a slight increase in hardness. Tablets containing dextrose and lactose 1:1 with 5% cornstarch softened on storage with an accompanying increase in friability and disintegration time. Increased disintegration times were found with dextrose tablets containing 10% microcrystalline cellulose, whereas disintegration times of lactose–microcrystalline cellulose tablets remained much shorter. In addition, dextrose–microcrystalline cellulose tablets softened on storage resulting in higher friability losses. From the foregoing discussion, it appears obvious that the addition of either cornstarch or microcrystalline cellulose to dextrose is unnecessary and, in fact, deleterious to formulation quality, whereas the same disintegrants improved the physical characteristics of lactose formulations.

High-speed runability experiments with 1% magnesium stearate as the lubricant indicated that dextrose compared favorably with lactose except when deep cup punches were used. In this case, capping problems were encountered with dextrose if tablets were compressed harder than 3–4 Kg., whereas no capping or other problems were evidenced with flat-faced punches at hardness in excess of 10 Kg.

To compare the performance of dextrose and lactose with a typical medicinal agent in a direct compression system, tablets containing 30 mg. of phenobarbital were prepared with dextrose, lactose, and a 1:1 mixture of hydrous and anhydrous dextrose (formulations *10–12*). These tablets were evaluated relative to tablet weight variation, intertablet drug distribution, dissolution rate, and changes in physical characteristics following accelerated aging tests. All tablets were in the same weight and hardness ranges. No problems were encountered concerning tablet weight variation. For 450-mg. tablets, the standard deviations were 3.9, 2.7, and 6.8 mg. for lactose, dextrose, and the dextrose mixture, respectively. Intertablet drug distribution was determined for each formulation by assaying 10 tablets individually. Excellent distribution was indicated by standard deviations of 0.21, 0.22, and 0.36 mg. for lactose, dextrose, and the dextrose mixture, respectively. All formulations easily met U.S.P. content uniformity requirements since all 10 results in each test were well within the 85–115% limits. Hardness and friability changes followed the same pattern evidenced in similar tablets containing no phenobarbital (formulations *1–3*). The addition of phenobarbital imparted a

TABLE IV.—BROWNING TENDENCY OF DEXTROSE AND LACTOSE TABLETS[a] IN THE ABSENCE OF ADDED AMINES STORED AT 50°

	A_{276} mμ				Relative Degree of Browning[b]			
	Orig.	2 wk.	4 wk.	8 wk.	Orig.	2 wk.	4 wk.	8 wk.
Dextrose	0.142	0.207	0.219	0.265	0	+1	+2	+3
Lactose	0.395	0.650	0.660	0.789	0	+2	+3	+4

[a] Tablets contained 1% magnesium stearate. [b] From 0 to +4 indicates relative increases in browning.

significant increase in disintegration time, although the tablets were in the same hardness range.

The three formulations were also studied relative to changes in dissolution rate of phenobarbital following aging tests. Representative data for the dextrose and lactose formulations are shown in Fig. 1. The dissolution curves for the dextrose mixture—phenobarbital tablets were similar to the dextrose—phenobarbital curves. Results indicated a decrease in dissolution rate for both dextrose and lactose at all accelerated conditions which corresponded quite closely to room temperature data at the same time period. However, there appeared to be no significant difference in the dissolution rate of phenobarbital in formulations containing dextrose or lactose.

The browning tendency of lactose has been the subject of many investigations. Brownley and Lachman (2) have shown that the browning of lactose was related to the amount of free 5-hydroxymethylfurfural (HMF) as determined colorimetrically using 2-thiobarbituric acid (TBA). In a previous communication (3) the relationship between the browning of lactose, the free HMF content, and the ultraviolet absorbance of aqueous solutions was reported. This relationship between free HMF and ultraviolet absorbance was also found to exist for dextrose as shown in Fig. 2. The data are from a 10% aqueous solution of dextrose stored at 80° and analyzed periodically for HMF by the TBA method and by measuring the absorbance at 276 mμ. Consequently, the relative browning of dextrose and lactose formulations was studied by measuring the absorbance at 276 mμ and also by visual comparison. Results are shown in Table IV. Both the ultraviolet absorbance readings and visual observation ratings indicated that lactose was more susceptible to browning than dextrose.

The browning of lactose in the presence of added amines, amphetamine, methamphetamine, and dimethylamphetamine was shown by Duvall *et al.* (4) to be predominantly a primary amine–carbonyl reaction. Ten-milligram tablets of each of the above amines were prepared with both dextrose and lactose, all containing 1% magnesium stearate as lubricant. A relative visual comparison of these tablets under all accelerated conditions indicated that amine browning was worse with dextrose than with lactose. Dextrose browning was extensive even with the secondary and tertiary amine, whereas reaction of lactose with these latter two amines was minimal.

SUMMARY

1. The tableting characteristics of a commercial form of dextrose were evaluated in comparison to spray-dried lactose in direct compression systems.

2. Although slightly more lubrication was necessary, dextrose was comparable to lactose in high-speed runability experiments except when deep cup punches were used.

3. The addition of starch or microcrystalline cellulose was deleterious to dextrose, whereas these disintegrants improved the physical characteristics of lactose tablets.

4. In general, tablets containing dextrose had a greater tendency to harden along with a decrease in friability. There were increases in disintegration times following accelerated aging tests, the increase being greater for lactose than for dextrose. The dissolution rate of phenobarbital from both materials was found to decrease on aging.

5. Tablet weight variation and intertablet distribution of phenobarbital for both systems were well within U.S.P. limits.

6. Dextrose exhibited less tendency toward browning than lactose in formulations containing no amines. In the presence of amines, however, dextrose browning was more extensive than lactose browning.

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