DOSAGE FORMS OF MELPHALAN

Melphalan Tablets

Identity Tests.—Transfer 2 ml. of the assay solution (5 mg. of melphalan in 100 ml.) into a glass-stoppered test tube and add 1 ml. of U.S.P. phthalate buffer, pH 4.0, 1 ml. of a 5 in 100 solution of 4-(*p*-nitrobenzyl) pyridine (NBP) in acetone, and 1 ml. of saline T.S. Heat on a water bath at 80° for 20 min. and cool the solution quickly. Add 10 ml. of alcohol and 1 ml. of 0.1 *N* potassium hydroxide: a violet to red-violet color is produced.

Assay.—*Standard Preparation.*—Transfer about 10 mg. of melphalan reference standard, accurately weighed, to a 100-ml. volumetric flask, dissolve in alcohol, dilute to volume with alcohol, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with alcohol, and mix.

Procedure.—Weigh and finely powder not less than 20 melphalan tablets. Transfer to a 100-ml. volumetric flask an amount of powdered tablets, accurately weighed, equivalent to about 5 mg. of melphalan. Add 10 ml. of water, swirl the sample, then add 10 ml. of alcohol. Warm on a steam bath for about 2 min. with intermittent shaking and cool the solution. Add alcohol to volume and mix. Centrifuge a portion of the mixture, transfer 10.0 ml. of the clear liquid to a 50-ml. volumetric flask, make to volume with alcohol, and mix. Concomitantly, determine the absorbance of this solution and that of the *Standard Preparation* in 1-cm. cells, at the maximum at about 260 mμ with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{13}H_{18}Cl_2N_2O_2$ in the portion of the tablets taken by the formula $0.5C\ (A_u/A_s)$, where C is the exact concentration, in mcg./ml., of melphalan in the *Standard Preparation*, calculated on the dried basis, A_u is the absorbance of the solution from the tablets, and A_s is the absorbance of the *Standard Preparation*. The amount of melphalan found is not less than 93.0% and not more than 107.0% of the labeled amount.

DISCUSSION

U.S.P. and N.F. terminologies for solubility, melting range, reagents, etc., have been used wherever feasible.

Melphalan,[1] synthesized by Bergel and Stock (1), is an orally active alkylating agent of the nitrogen mustard class which is useful in the treatment of multiple myeloma. Early literature references to this compound may be found under the synonym sarcolysin.

Identity Tests.—The colorimetric identification of melphalan is based on the procedure of Petering and Van Giessen (2) for the determination of alkylating agents. An additional identification test for melphalan drug is obtained by comparing the absorbances of the alcoholic solution at 226 mμ (minimum) and at 260 mμ (maximum). The ratio A_{226}/A_{260} is about 0.15.

Quantitative Methods.—Argentimetric determination of melphalan gave an average value of 95.7 ± 0.2%.[2] The titration was conducted using a silver electrode and a calomel electrode modified to contain saturated potassium sulfate solution. A rapid, precise measure of the chloride content may be determined by the oxygen flask method included for butyl chloride, N.F. XII, First Supplement. Analysis of commercial melphalan tablets by the spectrophotometric method gave an average value of 101.7 ± 1.5%.[2]

REFERENCES

(1) Bergel, F., and Stock, J. A., *J. Chem. Soc.*, **1954**, 2409.
(2) Petering, H. G., and Van Giessen, G. J., *J. Pharm. Sci.*, **52**, 1159(1963).

[1] Marketed as Alkeran by Burroughs Wellcome & Co. Inc., Tuckahoe, N. Y.
[2] Maximum deviation from the mean value.

Technical Articles

Anhydrous Lactose in Direct Tablet Compression

By NICHOLAS H. BATUYIOS

The use of anhydrous lactose U.S.P. XVII, tablet grade, as a diluent in direct tablet compression was investigated. It was found that it possesses excellent tableting properties and can be run on a high-speed tablet machine. The placebo and active tablets produced were not affected by elevated temperatures, high humidity, and direct sunlight.

IN TERMS of economics and product stability, direct tablet compression offers distinct advantages over double compression, known also as "slugging," and the wet granulating method (1). Also, direct compression should produce tablets of faster dissolution rates because no colloidal binders, (*e.g.*, starch and gelatin) are used to envelop the granules.

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TABLE I.—WEIGHT VARIATION

Random Sample Size	Target Wt.	Sample Mean	S. D.	Coeff. of Variation
100	175.0	174.5[a]	1.1	0.63

[a] The mean ±3 standard deviations included every tablet weight of the sample.

The materials were mixed in a Twin-Shell blender for approximately 15 min. Then the blend was compressed at a weight of 125 mg. on a Stokes 551 tablet machine at various speeds using $^{9}/_{32}$-in. special flat-faced beveled edge, engraved punches. At a speed up to 3500 tablets/min., tablets of excellent quality were produced. When 100 tablets were weighed collectively and individually, it was found that no tablet varied more than ±4.5% from the mean.

TABLE II.—ANALYTICAL DATA

Compression Period	Time Interval Tablets Removed During Compression Run, hr.	Assay Results of Single Tablets, % of Label Claim					Av. of Single Tablets Assay	Assays from Powder of 10 Crushed Tablets
1st day	2	101.5	102.1	101.5	102.9	100.2	101.6	100.8
	4	97.1	96.2	95.2	94.3[a]	102.9	97.1	99.1
	6	97.7	98.9	96.0	99.0	97.5	97.8	96.6
2nd day	2	100.9	102.9	102.7	101.7	99.9	101.6	100.1
	4	99.2	101.2	99.2	97.3	99.8	99.3	98.5
	6	99.2	101.6	101.6	100.0	99.0	100.3	98.9
3rd day	2	102.1	101.5	97.7	102.5	102.5	101.3	96.9
	4	103.5	102.5	102.9	105.5	105.9[b]	104.1	98.6
	6	99.9	98.7	103.3	102.1	100.1	100.8	97.0

[a] Low. [b] High.

There are several tablet diluents commercially available that can be compressed directly (1–3). Because of high cost, physical and chemical properties, and poor tableting characteristics, they have only limited use.

In this laboratory, it was found that anhydrous lactose[1] U.S.P. XVII, tablet grade, possesses excellent flow and compression properties. It produces highly elegant tablets on a high-speed rotary tablet machine without requiring induced feeding and/or metered hoppers. It contains no more than 1.0% free and bound moisture, and its price is comparable to spray-dried lactose.

EXPERIMENTAL

Anhydrous Lactose Particle Size

	Sieve Analysis Mesh Size	%
Retained on:	40	0
	60	13.3–14.1
	80	22.2–24.5
	100	15.4–16.7
	200	26.5–28.7
Through:	200	16.7–21.6

Formulations

Several small experimental batches indicated that anhydrous lactose U.S.P. XVII, tablet grade, has good tableting characteristics. Therefore, in order to fully determine its tableting properties, a placebo batch of approximately 500,000 tablets of the following composition was made:

Formulation I

	%
Anhydrous lactose U.S.P., tablet grade	89.25
Starch U.S.P.	10.00
Calcium stearate U.S.P.	0.75

[1] Marketed by Sheffield Chemical.

Samples of tablets were placed at 50°, 80% R. H. at R. T. and sunlight for 6 weeks. No significant change with respect to color, hardness, and disintegration time was found.

When results indicated that a satisfactory placebo tablet could be made, then the following active formulations of 200,000 tablets each were made:

Formulations II, III, IV, and V

	per tablet, mg. II	III	IV	V
McN-JR-2498[2] hydrochloride	0.5	1.0	2.0	5.0
Anhydrous lactose U.S.P. XVII	155.7	155.2	154.2	151.2
Starch U.S.P.	17.5	17.5	17.5	17.5
Calcium stearate U.S.P.	1.3	1.3	1.3	1.3
	175	175	175	175

The active ingredient was passed through a 100-mesh screen and mixed with the inert materials in a 2-cu. ft. Twin-Shell blender for 30 min. The blend was compressed on a Stokes B-2 tablet machine at a speed of 44 r.p.m. A set of four special, flat oval, engraved punches was used (only four punches were available). No attempt was made to control the humidity during the compression of the four formulations which was done over a period of 2 months.

In all formulations tablets of excellent quality were obtained. All formulations were subjected to various tests, and the results were satisfactory. Formulation III, containing 1 mg. active ingredient per tablet, was tested more extensively, and the results are reported below. The solubility of McN-JR-2498 hydrochloride in water is 5 mg./ml.

Test Methods

Moisture Contents.—Moisture content was determined on a Cenco moisture balance operating at

[2] A No. code designation for trifluperido

120 v. with a 125-w. infrared lamp. The test was continued until a constant weight was reached at 50°.

Hardness.—Hardness was determined by the Strong-Cobb Arner hardness tester.

Friability.—Friability was measured with a Roche Friabilator using a 4-min. cycle and at least a 6.0-Gm. tablet sample.

Disintegration.—Disintegration time was determined using water and the U.S.P. apparatus; no disks were used.

Dissolution Rates.—The dissolution rate was determined in a 1-L. three-necked round-bottom flask fitted with a mechanical stirrer and a 7.5-cm. Teflon stirring paddle. The stirring paddle was adjusted to 2.5–3.5 cm. above the bottom of the flask and the stirring rate was maintained at 50 r.p.m. The flask contained 750 ml. of fluid and was immersed in a constant-temperature water bath maintained at 37° ± 0.1°. Each run consisted of 15 tablets and a Swinny hypodermic adapter filter was used for sampling. The fluids used were U.S.P. simulated gastric fluid without pepsin and U.S.P. simulated intestinal fluid without pancreatin.

Sieve Analysis.—Sieve analysis was done on a Cenco-Meinzer sieve shaker operating at 115 v. 50/60 cycles and at a setting of No. 5. Harshaw Scientific 5-in. diameter sieves were employed. A 100-Gm. sample per determination was used, and the range reported represents three determinations.

Table III.—Dissolution Rates

% McN-JR-2498 Released in Modified, Simulated Gastric Fluid			
Time, min.	Initial	3 Mo. at R. T.	3 Mo. at 60°
1	...	10.1	14.5
2	...	24.1	26.1
4	...	43.3	39.8
6	...	63.5	66.4
8	...	78.3	81.5
10	...	88.4	91.6
15	...	96.4	100.6
20	...	98.7	102.2
25	...	97.9	102.4
30	100.0	99.2	103.9

% McN-JR-2498 Released in Modified, Simulated Intestinal Fluid	
Time, hr.	Initial
1/2	25.3
1	31.9
2	42.0
2 3/4	47.4
5	61.8
7	72.0

DISCUSSION

The placebo batch showed that this anhydrous lactose formulation can be run on a high-speed tablet machine, using 9/32-in. special, flat-faced beveled edge, engraved punches, producing excellent tablets. Also, the four batches containing up to 5 mg. of active ingredient per tablet produced tablets

Table IV.—Chemical and Physical Stability Data

	Time, wk.							
	Initial	1	2	3	4	5	6	12
Chemical								
(McN-JR-2498, %)								
R.T.	100.2	...	...	...	...	...	...	102.4
	100.6	...	...	...	...	...	...	100.5
40°	...	...	...	...	101.8	...	...	100.0
	...	...	...	...	102.0	...	...	99.2
60°	...	...	...	...	100.0	...	...	98.0
	...	...	...	...	103.0	...	...	97.2
80°	...	...	...	...	98.7	...	...	...
	...	...	...	...	99.3	...	...	...
Physical								
R.T.								
Moisture, %	0.9	...	...	...	...	...	...	...
Color	White	...	...	...	...	...	White	White
Disint. time, min.	3–4	...	...	...	...	...	3–4	3–4
Hardness	9–10	...	...	...	...	...	9–10	9–10
Friability, %	0.08	...	...	...	...	...	0.08	0.08
50°[a]								
Color change	...	...	...	...	NSC[b]	...	NSC	NSC
Disint. time, min.	...	...	...	...	3–4	...	3–4	3–4
Hardness	...	...	...	...	8–9	...	8–9	9–10
Friability, %	...	...	...	...	0.08	...	0.07	0.0
80% R.H., R.T.[a] (open container)								
Color change	...	NC[c]	NC	NC	NC	...	...	...
Disint. time, min.	...	3–3.5	2–3	2–3	2–3.5	...	...	...
Hardness	...	8–9	8–9	8–9	8–9	...	...	...
Friability, %	...	...	...	0.21	0.20	...	...	...
Weight increase, %	...	...	...	1.5	1.5	...	...	...
Sunlight (color change)								
Amber glass	...	NC	NC	NC	NC	...	...	...
Flint glass	...	NC	NC	NC	NC	...	...	...

[a] The 50° sample and the 80% R. H. sample were tested immediately upon removal from their respective stations and after standing at R. T. for approximately 2 hr. The results were the same. [b] NSC, no significant change. [c] NC, no change.

of excellent quality using special, flat oval, engraved punches.

The criteria used in evaluating the tablets were appearance, distribution of active ingredient, weight uniformity, friability, binding, sticking, capping, hardness, disintegration time, dissolution rates, and the effects of elevated temperatures, high humidity, and sunlight. No attempt was made to control the relative humidity during compression which took place over a period of approximately 2 months.

The data in Table I show excellent tablet weight uniformity. Table II shows that the active material was uniformly distributed and that no separation occurred during a 3-day compression period. Table III shows that the dissolution rates in simulated gastric fluid were not affected by high temperature. In simulated intestinal fluid the tablets disintegrated in 3–4 min., but the dissolution rates were slow due to poor solubility of the active compound at pH 7.5 (0.06 mg./ml.). Table IV shows that the tablets were not affected chemically or physically by high temperature, high humidity, and direct sunlight. Assays not reported here on tablets exposed to sunlight and high humidity showed good stability. The tablet color did not change significantly after 12 weeks at 50°. A very slight off-white color developed which could be detected only when the room temperature and the 50° samples were observed together.

SUMMARY

1. Placebo and active tablets were made by direct compression using anhydrous lactose U.S.P. XVII, tablet grade, as a diluent.

2. A placebo batch of approximately 500,000 tablets was run at a speed of 3500 tablets/min. on a Stokes 551 tablet machine resulting in excellent tablets. Special $^{9}/_{32}$-in. flat beveled edge, engraved punches were used.

3. Four batches of 200,000 tablets each, containing 0.5, 1, 2, and 5 mg. active material per tablet, were made using a set of four special, flat oval, engraved punches, on a stokes B-2 tablet machine at a speed of 44 r.p.m.

4. The placebo and active tablets were excellent as shown by the elegance, small tablet weight variation, uniform distribution of the active ingredient, fast disintegration and dissolution rates, good hardness, low friability, and lack of binding, sticking, and capping.

5. No induced feeding and/or metered hoppers were required.

6. Physical and chemical stability studies showed that high temperature, high humidity, and direct sunlight had no effect on the formulations.

REFERENCES

(1) Milosovich, G., *Drug Cosmetic Ind.*, **92**, 557(1963).
(2) Fox, C. D., *et al.*, *ibid.*, **92**, 161(1963).
(3) Brownley, C. A., and Lachman, L., *J. Pharm. Sci.*, **53** 452(1964).

Notes

Quantitative Determination of Iodochlorhydroxyquin by Infrared Analysis

By T. URBÁNYI, D. SLONIEWSKY, and F. TISHLER

A quantitative infrared procedure for the determination of iodochlorhydroxyquin and its intermediates is described. The method is based on measurements of absorption in the 14.4 and 14.9 μ regions of a carbon disulfide solution of the compound. By measurements at other wavelengths in the infrared region, 5,7-diiodo-8-hydroxyquinoline, 5-chloro-8-hydroxyquinoline, and 5,7-dichloro-8-hydroxyquinoline, present as impurities, can also be quantitatively determined.

THE OFFICIAL U.S.P. XVII procedure (1) for the determination of iodochlorhydroxyquin, based on halogen content, suffers from the fact that the method frequently does not distinguish between the parent compound and its intermediates, which may occur as contaminants. The thin-layer chromatographic procedure of Korzun, Brody, and Tishler (2) offers a semiquantitative method for the determination of iodochlorhydroxyquin; however, 5,7-dichloro-8-hydroxyquinoline, which was found in many of the commercial samples examined, cannot be separated from iodochlorhydroxyquin by this method. Until now, phase solubility has been the only quantitative technique available for determining the absolute purity of iodochlorhydroxyquin. This procedure, although accurate and specific, is time consuming.

Bigeard *et al.* (3) have recently developed an infrared spectrophotometric method for the semiquantitative determination of iodochlorhydroxyquin

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