

Statistical Study of the Disintegration Time of Tablets.—An average (7) gives considerable information about numerical data, but it does not show how the data varies or how much they differ from the average. A measure of dispersion or variance is therefore of considerable aid in summarizing the data.

To get a measure of dispersion from the deviation one must use the mean squares of the deviation. This quantity is called the variance of the set of variates. The variance however is not of the same dimension as the variates. The square root of the variance is measured in the same units as the variates and it is the measure of the dispersion which will be used in this report. It is called the standard deviation and is denoted by the symbol σ_x expressed symbolically as:

$$\sigma_x = \sqrt{\frac{\sum x_i^2}{n} - M_x^2}$$

The standard deviation as a means of measuring dispersion for a bell-shaped distribution curve is contained in the following:

A. Approximately two-thirds of the variates lie in the range of M equals $\pm \sigma$. B. Approximately 1% of the variates lie outside of the range of M plus or minus 3σ .

The mean square deviation of the disintegration time in seconds of *A* and *B* batches of sodium bicarbonate and calcium gluconate tablets is given in Table III.

TABLE III.—MEAN SQUARE DEVIATION OF THE DISINTEGRATION TIME IN SECONDS OF *A* AND *B* BATCHES OF SODIUM BICARBONATE AND CALCIUM GLUCONATE TABLETS

	Sodium Bicarbonate		Calcium Gluconate	
	A-Batch	B-Batch	A-Batch	B-Batch
CMC®	83	54	102	46
Methocel®	51	45	14	33
Kelgin®	65	63	49	32
Gelloid®	28	32	32	55

The range of deviation for tablets of both soluble and slightly soluble medicaments containing the same granulating agent shows that the experimental error ranges from 4 to 13%.

DISCUSSION

The effective concentrations of the granulating solutions were 1% excepting methylcellulose which was used in 5% concentration. The quantities of solution used in each case to effect granulation should not be considered as a critical value for it is possible to effect granulation with smaller or larger amounts depending upon such conditions as the manner of mixing, the medicinal agent, and the diluent.

The sodium bicarbonate tablets compressed from the Methocel® and Gelloid® granulations were white, nonporous, smooth, and possessed a slight sheen characteristic of the talc and mineral oil lubricant. The sodium bicarbonate tablets compressed from the starch, Kelgin®, and CMC granulations possessed a like appearance but had a tendency to split when shaken in the bottle or between the palms of the hands.

The calcium gluconate tablets compressed from the CMC, starch, and sodium alginate granulations were white, nonporous, and smooth and possessed a slight sheen characteristic of the talc heavy mineral oil lubricant. The calcium gluconate tablets compressed from the Gelloid® and Methocel® granulations were white but were slightly porous and did not possess the slight sheen characteristic of the talc mineral oil lubricant.

The results of this study are in general agreement with previous studies (1, 4, 5). The applicability of any granulating agent to a specific medicinal should be ascertained by experimentation with the medicinal in question. The agents discussed here have proven themselves suitable for sodium bicarbonate as representative of a soluble medicinal and calcium gluconate as representative of a slightly soluble medicinal.

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A Note on the Alkaloids of *Rauwolfia micrantha* Hook. f.*

By D. S. RAO and S. B. RAO

IN VIEW of the current therapeutic interest in *Rauwolfia*, *R. micrantha*, a commonly growing species of South Travancore was subjected to a detailed systematic analysis. The oleoresin fraction prepared by the method of J. C. Gupta, *et al.* (1) on paper chromatography (circular, with butanol-

hydrochloric acid-water (50, 7.5, 17.5) showed the following fluorescent bands: deep yellow, R_f 0.80, greenish-yellow, R_f 0.86, and yellowish-green R_f 0.92.

The oleoresin was further fractionated by adsorption ultra-chromatography on alumina. Valuable information regarding the distribution of the fluorescent bases which was of great use in their fractionation could be gathered by circular paper

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chromatography of the fractions. In this way we were able to isolate the following bases from the oleoresin fraction:

Base A	m. p. 264-266°
Base B	m. p. 247-248°
Base C	m. p. 157-159°

Base A had the characteristic yellowish fluorescence of reserpine. On circular paper chromatograms run with authentic reserpine (R_f 0.98) it gave only a single band (R_f 0.98). Keller's color reaction was positive, blue changing to greenish-yellow. The m. p. of Base A was not depressed by the addition of pure reserpine isolated from *Rauwolfia serpentina* oleoresin.

Base B had a greenish-yellow fluorescence (R_f 0.90) which could be easily distinguished from a yellowish-green fluorescent band of Base A.

Base C also showed a pale greenish-yellow fluorescence (R_f 0.86).

The main alkaloidal fraction prepared by the method of A. Furlenmier (2) after adsorption ultrachromatography on alumina, yielded several fractions. Paper chromatography indicated the presence of at least four bases. Of these we have been able to get only one in crystalline form. Base D m. p. 257° gave a HCl salt, m. p. 278°. This was

homogeneous paper chromatographically, and showed a greenish-yellow fluorescent band (R_f 0.92). On running with reserpine, separation could be clearly noted. Base D, melting point 257°, did not depress the melting point of an authentic sample of ajmalicine (kindly kept at our disposal by Messrs. Riker Laboratories Inc., Los Angeles California). On running mixed paper chromatograms in butanol-hydrochloric acid-water (50, 7.5, 17.5) only one spot could be noted. Further work bearing on its constitution is in progress.

We have also studied the paper chromatographic pictures of *R. serpentina*, *R. canescens*, *R. bad-domei*, and *R. densiflora*. Of these the presence of reserpine could be clearly seen in the first two. Characteristic differences of diagnostic importance have also been noted. In view of the easy paper chromatographic separation and characterization of reserpine, a quantitative method for its estimation on similar lines is being worked out. Details with respect to the above will be published elsewhere.

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A Note on Stability of the B Vitamins in Solutions—Crystalline Vitamin B₁₂*

By THOMAS J. MACEK and BEATE A. FELLER

IN A RECENT REPORT (1) it is concluded that vitamin B₁₂ is not stable in B complex solution containing thiamine and niacinamide as constituents. For the most part this conclusion appears to be based upon analysis of solutions exposed to elevated temperatures.

Investigations conducted in this laboratory support these findings in a general way, even though we have not encountered as rapid a rate of destruction at elevated temperatures as reported. On the other hand our data also show that under ordinary storage conditions crystalline vitamin B₁₂ is stable in aqueous B vitamin solutions for long periods of time.

In this regard, microbiological assay data on parenteral solutions containing other B vitamins showed not more than 10% loss of vitamin B₁₂ at pH 3.5 and pH 4.5 after storage for one year at room temperature. These solutions maintained at 120° for ninety minutes, however, showed losses of vitamin B₁₂ amounting to 55% and 65%, respectively. The solutions contained per cc.: crystalline vitamin B₁₂, 15 µg.; thiamine hydrochloride, 10 mg.; riboflavin, 0.5 mg.; niacinamide, 25 mg.; calcium pantothenate dextrorotatory, 5 mg.; pyridoxine hydrochloride, 5 mg.; benzyl alcohol, 15

mg.; and sodium chloride, 9 mg. Dilute hydrochloric acid was used to adjust pH. The solutions were sterilized by filtration through microporous porcelain and were subdivided into flame-sealed ampuls.

Microbiological assays for vitamin B₁₂ in a flavored B vitamin-iron elixir at pH 4.2 indicated only 5% loss of B₁₂ after six months' storage at room temperature and 11% loss after six months at 40°. The composition of the elixir per 4 cc. was: Crystalline vitamin B₁₂, 10 µg.; thiamine hydrochloride, 2 mg.; niacinamide, 15 mg.; pyridoxine hydrochloride, 1 mg.; calcium pantothenate dextrorotatory, 0.64 mg.; ferrous sulfate, 20 mg.; glycerin, 0.8 cc.; alcohol, 0.8 cc.; syrup, 0.8 cc.; cherry and lemon-lime flavors and water *q. s.*

Based on our findings, we conclude that solutions of the B vitamins can be prepared in which crystalline vitamin B₁₂ is stable for prolonged periods of time at normal storage temperatures. The large losses of vitamin B₁₂ encountered when such solutions are stored at elevated temperatures is not unexpected. A paper showing the effect of thiamine hydrochloride on stability of solutions of vitamin B₁₂ is in preparation and will be published soon.

REFERENCE

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* Received February 2, 1955, from Merck & Co., Inc., Rahway, N. J.