

Each of the four methods used to assay calcium chloride gave results which were in satisfactory agreement. The low results obtained for the analysis of this salt may be attributed to the fact that the sample was taken from a stock bottle which had been in the laboratory for several years.

The standards specified by The United States Pharmacopœia XI for calcium bromide dihydrate, 84–94%  $\text{CaBr}_2$  (by theory 84.73%), and for calcium chloride dihydrate, 75–85%  $\text{CaCl}_2$  (by theory 75.49%), would indicate that these salts, as obtained on the market, contain less water of hydration than their formulas show. If the dihydrates are obtained as such, and in view of the fact that they are strongly deliquescent, the query is raised as to why their present standards should not be adjusted to agree with this fact.

In the assay of calcium gluconate, it appears that potassium permanganate gives results which are in somewhat better agreement with the theoretical composition of the salt, than does the use of ceric ammonium sulfate. Since calcium gluconate monohydrate is a stable salt, it appears that the present Pharmacopœial standard, 12.4–12.8%  $\text{CaO}$  (by theory 12.51%), might properly be adjusted to the mean of limits corresponding more closely to the theoretical composition.

#### SUMMARY

It has been shown in this study that ceric ammonium sulfate can be substituted for potassium permanganate as an oxidant in pharmaceutical assays; however, the cost of the cerate method is such that its general substitution for potassium permanganate does not appear to be warranted at the present time.

From the viewpoint of simplicity, speed and precision the Volhard method appears to be preferable to the methods now used in the United States Pharmacopœia for the assay of calcium chloride and of calcium bromide.

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## Adaptation of Assay Methods for Some N. F. Pastes\*

By Wm. B. Baker and D. I. Kutzly

There are six pastes in the Sixth Edition of the *National Formulary* for which there are no assay requirements. Since these pastes are contained in an official book, it is important that standards be adopted for them, fixing definitely the content limits of their active ingredients.

In some cases the assay methods used for certain drugs and chemicals can be adapted for use in the assay of official preparations containing these ingredients. This appears to be especially feasible in the case of four of the six pastes referred to.

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I. PASTE OF BISMUTH

The assay method for Bismuth Subnitrate, U. S. P. XI, may be successfully adapted for use in the assay of Paste of Bismuth, N. F. VI, as shown by the satisfactory results obtained in the experiments which follow. The bismuth subnitrate, which is the only therapeutically active ingredient in the paste, was determined as bismuth oxide, after proper separation of the former from the rest of the paste. Substantially the same procedure may be followed for the determination of bismuth subnitrate as is carried out in the assay of Compound Ointment of Resorcinol, N. F.<sup>1</sup>

EXPERIMENTAL

A sample of Paste of Bismuth was prepared in accordance with the directions given in the N. F. VI. The bismuth subnitrate used in the paste was examined for purity prior to the preparation of the sample.

*Assay of Bismuth Subnitrate.*—The method of the U. S. P. XI was followed in the assay of Bismuth Subnitrate.

Table I.—Results of Assay of Bismuth Subnitrate by the U. S. P. XI Method

Assay	No. 1	No. 2	No. 3	No. 4
Wt. of sample in Gm.	1.00	1.04	1.00	1.01
Wt. of residue in Gm.	0.79	0.83	0.80	0.81
Per cent of Bi <sub>2</sub> O <sub>3</sub>	79.51	80.23	80.10	80.00
Average per cent of Bi <sub>2</sub> O <sub>3</sub> = 79.96.				

*Assay of Paste of Bismuth.*—Accurately weigh about 2 Gm. of Paste of Bismuth in a tared crucible, heat it slowly until melted and carefully ignite to constant weight. The residue of Bi<sub>2</sub>O<sub>3</sub> is not less than 79 per cent of the amount of bismuth subnitrate in the paste taken for the assay.

Table II.—Results of Assay of Paste of Bismuth

Assay	No. 1	No. 2	No. 3	No. 4
Wt. of sample in Gm.	1.98	2.01	2.01	2.01
Wt. of residue in Gm.	0.46	0.47	0.47	0.47
Per cent of Bi <sub>2</sub> O <sub>3</sub>	23.67	23.72	23.60	23.71
Average per cent of Bi <sub>2</sub> O <sub>3</sub> found in sample	= 23.67			
Calculated per cent of Bi <sub>2</sub> O <sub>3</sub> in sample (30 × 79.96)	= 23.98			

Difference = 00.31  
 Percentage error (00.313 ÷ 23.988) × 100 = 1.30.

II. PASTE OF ZINC OXIDE

The zinc oxide contained in Paste of Zinc Oxide was determined by simple gravimetric means following its isolation from the other constituents of the paste.

<sup>1</sup> Wm. B. Baker and D. I. Kutzly, "Adaptation of Assay Methods for Some N. F. Ointments, III. Compound Ointment of Resorcinol," *Pharm. Arch.*, 10 (1939), 65.

EXPERIMENTAL

A sample of Paste of Zinc Oxide was prepared in accordance with the directions given in the N. F. VI. The zinc oxide used in the paste was examined for purity prior to the preparation of the sample.

*Assay of Zinc Oxide.*—The method of the U. S. P. XI was followed in the assay of zinc oxide.

Table III.—Results of Assay of Zinc Oxide by the U. S. P. XI Method

Assay	No. 1	No. 2	No. 3	No. 4
Wt. of sample in Gm.	1.50	1.50	1.50	1.53
Cc. of N/1 H <sub>2</sub> SO <sub>4</sub> added	52.65	52.65	52.65	52.65
Cc. of N/1 NaOH required	15.79	15.90	16.02	15.12
Cc. of N/1 H <sub>2</sub> SO <sub>4</sub> consumed	36.86	36.75	36.63	37.53
Per cent of ZnO	99.91	99.48	99.36	99.81
Average per cent of ZnO = 99.64.				

*Assay of Paste for Zinc Oxide.*—Place about 2 Gm. of Paste of Zinc Oxide, accurately weighed, in a crucible of about 30-cc. capacity. Heat the crucible and contents gently over a Bunsen flame until the paste is liquefied. Gradually increase the temperature and ignite to eliminate the base of the paste. Dry the residue to constant weight, and weigh the zinc oxide.

Table IV.—Results of Assay of Paste of Zinc Oxide

Assay	No. 1	No. 2	No. 3	No. 4
Wt. of sample in Gm.	2.00	2.00	2.00	2.00
Wt. of residue in Gm.	0.49	0.49	0.49	0.49
Per cent of ZnO	24.87	24.81	24.81	24.85
Average per cent of ZnO found in sample	= 24.84			
Calculated per cent of ZnO in sample (25 × 99.64)	= 24.91			

Difference = 00.07  
 Percentage error (00.07 ÷ 24.91) × 100 = 0.28.

III. PASTE OF ZINC OXIDE WITH SALICYLIC ACID

A sample of Paste of Zinc Oxide with Salicylic Acid was prepared in accordance with the directions given in the N. F. VI. The zinc oxide and the salicylic acid used in the paste were examined for purity prior to the preparation of the sample.

EXPERIMENTAL

*Assay of Zinc Oxide.*—The zinc oxide used was the same material as was used in the preparation of the sample of Paste of Zinc Oxide, above. The results of the assay are shown in Table III.

*Assay of Salicylic Acid.*—The method of the U. S. P. XI was followed in the assay of salicylic acid.

Table V.—Results of Assay of Salicylic Acid by the U. S. P. XI Method

Assay	No. 1	No. 2	No. 3	No. 4
Wt. of sample in Gm.	0.55	0.53	0.54	0.51
Cc. of N/10 Ba(OH) <sub>2</sub> used	40.25	38.58	39.53	36.78
Per cent of C <sub>7</sub> H <sub>6</sub> O <sub>3</sub>	99.51	99.05	99.58	98.90
Average per cent of C <sub>7</sub> H <sub>6</sub> O <sub>3</sub> = 99.26.				

*Assay of Paste for Zinc Oxide.*—The zinc oxide was determined by simple gravimetric means following its isolation from the other constituents of the paste.

Place about 5 Gm. of Paste of Zinc Oxide with Salicylic Acid, accurately weighed, in a 250-cc.

glass-stoppered Erlenmeyer flask. Add 50 cc. of ether to the flask and shake vigorously to dissolve the salicylic acid and the white petrolatum. Filter and continue the extraction with 40, 20, 20-cc. portions of ether. Combine the filtrates and set aside for the determination of salicylic acid as directed below under "Assay of Paste for Salicylic Acid." Place filter paper and contents into a tared crucible and wash the flask thoroughly with several small portions of dilute ammonia water, combining the washings with the contents of the crucible. Heat the crucible and contents carefully on a water-bath to evaporate to dryness, continue the heating with a Bunsen flame, ignite, dry to constant weight and weigh the zinc oxide.

Table VI.—Results of Assay of Paste of Zinc Oxide with Salicylic Acid for Zinc Oxide Content

Assay	No. 1	No. 2	No. 3	No. 4
Wt. of sample in Gm.	4.85	5.03	5.00	5.02
Wt. of residue in Gm.	1.18	1.23	1.22	1.23
Per cent of ZnO	24.42	24.50	24.50	24.54
Average per cent of ZnO found in sample				= 24.49
Calculated per cent of ZnO in sample ( $25 \times 99.64$ )				= 24.91

Difference = 00.42

Percentage error  $(00.42 \div 24.91) \times 100 = 1.68$ .

*Assay of Paste for Salicylic Acid.*—Evaporate the filtrate, collected in the preceding assay, by means of a current of dry air. Dissolve the residue in 50 cc. of neutral diluted alcohol. Titrate the alcoholic solution with *N*/10 sodium hydroxide, using phenolphthalein T.S. as the indicator. If the white petrolatum in the solution congeals before the titration is complete, warm on a water-bath, and continue the titration until a permanent pink color is obtained. Each cc. of tenth-normal sodium hydroxide is equivalent to 0.01381 Gm. of  $C_7H_6O_3$ .

Table VII.—Results of Assay of Paste of Zinc Oxide with Salicylic Acid for Salicylic Acid Content

Assay	No. 1	No. 2	No. 3	No. 4
Wt. of sample in Gm.	4.85	5.03	5.00	5.02
Cc. of <i>N</i> /10 NaOH used	6.90	7.20	7.00	6.95
Per cent of $C_7H_6O_3$	1.97	1.98	1.94	1.92
Average per cent of $C_7H_6O_3$ found in sample				= 1.95
Calculated per cent of $C_7H_6O_3$ in sample ( $2 \times 99.26$ )				= 1.98

Difference = 00.028

Percentage error  $(00.028 \div 1.985) \times 100 = 1.41$ .

#### IV. HARD PASTE OF ZINC OXIDE

The zinc oxide in Hard Paste of Zinc Oxide was determined titrimetrically following its isolation from the benzoined lard in the paste.

#### EXPERIMENTAL

A sample of Hard Paste of Zinc Oxide was prepared in accordance with the directions given in the N. F. VI. The zinc oxide used in the paste was examined for purity prior to the preparation of the sample.

*Assay of Zinc Oxide.*—The zinc oxide used was the same material as was used in the preparation of

the sample of Paste of Zinc Oxide, above. The results of the assay are shown in Table III.

*Assay of Paste for Zinc Oxide.*—Place about 2 Gm. of Hard Paste of Zinc Oxide, accurately weighed, in a crucible of about 30-cc. capacity. Heat the crucible and contents gently over a Bunsen flame until the paste is liquefied. Gradually increase the temperature and ignite to free of carbonaceous material. Digest the residue remaining in the crucible after ignition with 50 cc. of normal sulfuric acid until solution is complete. Then titrate the excess of sulfuric acid with normal sodium hydroxide, using methyl orange T.S. as the indicator. Each cc. of normal sulfuric acid corresponds to 0.04069 Gm. of ZnO.

Table VIII.—Results of Assay of Hard Paste of Zinc Oxide for Zinc Oxide Content

Assay	No. 1	No. 2	No. 3	No. 4
Wt. of sample in Gm.	2.08	1.98	2.04	2.03
Cc. of <i>N</i> /1 $H_2SO_4$ added	53.07	52.76	52.18	54.86
Cc. of <i>N</i> /1 NaOH required	40.31	40.52	40.62	42.40
Cc. of <i>N</i> /1 $H_2SO_4$ consumed	12.76	12.24	12.56	12.46
Gm. of ZnO per 100 Gm. of paste	24.90	25.00	24.98	24.86
Average per cent of ZnO found in sample				= 24.94
Calculated per cent of ZnO in sample ( $25 \times 99.64$ )				= 24.91

Difference = 00.03

Percentage error  $(00.03 \div 24.91) \times 100 = 0.12$ .

#### DISCUSSION

For the most part, the determinations of the active ingredients in the pastes studied were carried out without difficulty after proper isolation from their respective bases. The actual separation of the active ingredients from their bases presented little difficulty.

In obtaining the residue of bismuth oxide, during the assay of Paste of Bismuth, the ignition should be carried out carefully, in order to prevent fusion and subsequent formation of metallic bismuth.

The methods described above give accurate and consistent results. Therefore, it is recommended that they be adopted for admission to the *National Formulary*, and that the following standards be prescribed:

*Paste of Bismuth.*—Paste of Bismuth contains not less than 28 per cent and not more than 32 per cent of bismuth subnitrate, equivalent to not less than 22.12 per cent and not more than 25.28 per cent of  $Bi_2O_3$ .

*Paste of Zinc Oxide.*—Paste of Zinc Oxide contains not less than 23 per cent and not more than 27 per cent of ZnO.

*Paste of Zinc Oxide with Salicylic Acid.*—Paste of Zinc Oxide with Salicylic Acid contains not less than 23 per cent and not

more than 26 per cent of ZnO, and not less than 1.8 per cent and not more than 2.2 per cent of  $C_7H_6O_3$ .

*Hard Paste of Zinc Oxide.*—Hard Paste of Zinc Oxide contains not less than 23 per cent and not more than 27 per cent of ZnO.

## Assays for Iodine and Iodide in Iodine Solutions\*

By *Bert S. Alstodt*

The iodine solutions considered in this study are the U. S. P. XI preparations: Tinctura Iodi, Tinctura Iodi Mitis and Liquor Iodi Compositus. The proposed assays are applicable also to other iodine-iodide solutions, such as Tinctura Iodi Fortior, N. F. VI.

The United States Pharmacopœia XI directs that the iodine of iodine solutions be determined by titrating a 5-cc. portion with  $N/10$  sodium thiosulfate. To determine the iodide, the Pharmacopœia directs that another 5-cc. portion be evaporated on a water-bath to dryness, that it be repeatedly moistened until a white residue remains, which is weighed and calculated as potassium iodide for Tinctura Iodi and Liquor Iodi Compositus, or as sodium iodide for Tinctura Iodi Mitis.

The British Pharmacopœia, 1932, directs that the iodine be determined by titrating a 10-cc. portion of the iodine solution with  $N/10$  sodium thiosulfate; and the potassium iodide by treating another 10-cc. portion according to the method of Andrews (1).

The thiosulfate titration for determining iodine is generally regarded as satisfactory and requires no further discussion. The iodide assay according to U. S. P. XI, although simple, is definitely unsatisfactory for several reasons. First, the method does not determine the iodide only, but rather total solids on evaporation. This was pointed out by Schaefer (2). Second, the method is time-consuming, requiring as many as twenty to thirty moistenings, over a period of three to five hours. Schaefer, in his article, states that very often it is

difficult to obtain a white residue, due to impurities present. Third, the method invariably leads to high results. From Table II (see Experimental Part) it can be seen that the potassium iodide by the U. S. P. XI method exceeds the theoretical amount by four to six parts per thousand; and exceeds the iodate method by about four parts per thousand. In the case of sodium iodide, by the U. S. P. method, the theoretical amount is exceeded by about one hundred and thirty parts per thousand; and with the iodate method, it is exceeded by about one hundred and twenty parts per thousand. Fourth, the use of a 5-cc. portion in the assay of Tinctura Iodi Mitis results in decreased accuracy, since only about 7 cc. of the standard solution are used in the titration, and only about 110 mg. of the difficultly weighable sodium iodide are obtained.

The high results in the iodide content when determined by U. S. P. XI method led to the belief that not all of the water which is added in order to volatilize the iodine to obtain a white residue is removed by heating on the water-bath. The white residue obtained by the pharmacopœial method was therefore dried for two hours in an electric oven at  $110^\circ C$ . Table II (see Experimental Part) shows that the amounts of potassium iodide and sodium iodide were considerably decreased. This, obviously, must be due to water not removed by heating on the water-bath only. The potassium iodide content by the official method is about six parts per thousand higher than the potassium iodide content obtained after drying at  $110^\circ C$ . for two hours.

As previously indicated, the sodium iodide assay in Tinctura Iodi Mitis is even less satisfactory. The deliquescent nature of sodium iodide renders the attainment of close checks almost impossible. This is indicated by the relative average deviation of fifty-one parts per thousand, for the series of determinations of sodium iodide made by the U. S. P. XI method. Table II (see Experimental Part) shows the diversity of results which may be expected when the sodium iodide is determined by weighing the residue from a 5-cc. sample of the mild tincture.

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