Determination of Nitroglycerin in Concentrated Triturations

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Nitroglycerin for medicinal use is commonly supplied to manufacturing pharmacists either as a trituration with sugar of milk or chalk or as a solution in 95% ethanol. The concentration may vary with individual orders but is usually specified as 10% by weight. From time to time controversies have arisen between this Laboratory and the manufacturing pharmacists as to the exact percentage of nitroglycerin present in these sugar of milk triturations, in spite of the great care taken to assure a definite and uniform concentration. In view of the care used in weighing and blending the ingredients, it appears that shortages cannot ordinarily be attributed to errors on the part of the supplier.

Experience in filling orders for these ingredients over a period of years has led to the conviction that the complaints are caused chiefly by the assay methods used by the purchasers. It is conceivable that methods suitable for assay of tablets, containing $^1/_{100}$ grain each, would not be accurate for a trituration containing 10% nitroglycerin. The object of this paper is to present data supporting this statement and to propose a more practical method for assay of concentrated triturations of nitroglycerin.

The *Pharmacopœia of the United States*, 11th Revision, 1935, gives methods of assay for spirit of nitroglycerin and tablets of nitroglycerin, but offers no specific method for the concentrated mixtures. This is also true of *Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists*, 4th Edition, 1935, and *Pharmaceutical Standards, Including Tolerances and Methods of Analysis* of the American Drug Manufacturers' Association and the American Pharmaceutical Manufacturers' Association, Revised Edition, 1935.

There are few references in the literature to the determination of nitroglycerin in concentrated medicinal preparations. Several attempts have been made to use saponification with alcoholic potash as a quantitative method, but the consensus is that it is unreliable because of various side reactions. This was reviewed by Majrich (1), who presented data on the saponification of organic nitrates, indicating that they have a peroxide-type formula. However, Hay (2) found that saponification of nitroglycerin produced a uniform quantity of nitrite, determined colormetrically, even when conditions were widely varied. Heyl and Staley (3) obtained good precision in the analysis of concentrated (10%) triturations and alcoholic solutions by the Kjeldahl method, using the usual modification for nitrates. They found that the colorimetric method of Scoville (4), using phenoldisulfonic acid, was also satisfactory but considered it better adapted to small amounts, as in tablets.

Murray (5) recommended the colorimetric methods of Hay and of Scoville for assay of nitroglycerin tablets. In collaborative work by twenty laboratories (6) both methods gave good results in most cases. Sykes (7) extracted tablets with glacial acetic acid and compared colors obtained with diphenylamine, while Meek (8) used a similar extraction but depended on the color produced by phenoldisulfonic acid.

The method of the A. O. A. C. (9) depends on extraction with ether, followed by a reduction of the nitrate with Devarda's alloy and distillation of the ammonia into standard acid, using a special scrubber. It is the same as the method of the *U. S. Pharmacopœia* (10) and the preferred method of the *Pharmaceutical Standards* (11), except that they both saponify the nitroglycerin in the presence of potassium permanganate after the ether extraction.

The use of the Devarda method with the preliminary saponification was proposed by Grantham (12). It was later studied by Hanson (13, 14) who claimed that results were more nearly quantitative if the saponification was omitted. Caron and Raquet (15) also recommended the Devarda method without saponification and considered it more accurate than colorimetric methods. Popov (16) used aluminum instead of De-

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varda's alloy. Anderson (17) substituted an acid distillation for the ether-extraction step, collecting the distillate in 5% NaOH and subjecting this to the usual Devarda procedure. He noted a high blank on the alkaline distillation, even though an efficient scrubber was used. This is one of the serious defects of the Devarda method for nitrates. Kenworthy (18) obtained 98.9% to 103.1% recovery of nitroglycerin by Anderson's method in the presence of other medicinal ingredients when these were added singly. Smith (19) used a similar method but substituted reduced iron for Devarda's alloy and determined ammonia in the final distillate by means of Nessler's reagent instead of by titrating the excess of standard acid.

The method which we have found most satisfactory when high concentrations of nitroglycerin are to be determined consists of extraction with pure, dry ether in a Wiley apparatus, evaporating the ether at room temperature and weighing the dried ether extract. It is similar to the method recommended by the U. S. Bureau of Mines for determination of nitroglycerin in dynamite (20). Murray (5, 6) mentioned ether extraction as a method for assay of nitroglycerin tablets and Engelhardt (21) recommended it. The details of our method are as follows:—

EXPERIMENTAL

Apparatus and Reagents.—Wiley Extraction Apparatus, complete as described in Arthur H. Thomas Company's catalog No. 5020. The Gooch crucible should be prepared in the usual way with a fairly thin asbestos mat and dried at 100° C.

Ether, Free from Alcohol and Peroxides.—It is most important that the ether be of the best quality, particularly that it be free from the impurities mentioned. Alcohol is objectionable because it is difficult to remove by evaporation after the extraction. If peroxides of ether are present some of the nitroglycerin may be decomposed toward the end of the evaporation and, in fact, when this impurity is considerable, the entire residue of nitroglycerin may decompose with evolution of brown fumes.

The formation of peroxides is caused by exposure to light, so that a freshly opened can should not show such impurities. The following test is recommended by the Institute of Makers of Explosives: Add 1 cc. of a solution of 5% cadmium iodide, 5% potassium iodide and 90% water to 10 cc. of ether in a glass-stoppered bottle. Shake several times during a period of one hour, keeping bottle in the dark. Orange color in the solution indicates peroxide.

If this test is positive, the ether may be purified by the method of Gatterman and Wieland (22) as follows: Shake in a separatory funnel with about one-tenth its volume of a solution consisting of 100 Gm. $FeSO_4.7H_2O$ and 50 cc. H_2SO_4 (96%) in a liter of water. Repeat this extraction twice, then wash three times with water, add anhydrous calcium chloride to the ether layer and distil. If peroxides are absent, the ether need only be freed from alcohol by washing three times with water in a separatory funnel, shaking with anhydrous calcium chloride and distilling.

Nitroglycerin Remover.—Dissolve 7 parts by weight of sodium sulfide (fused chips, 60% Na_2S) in 23 parts water. Add 54 parts denatured alcohol and 16 parts acetone. Mix thoroughly.

Procedure.—Weigh 4 Gm. of the concentrated trituration of nitroglycerin into the Gooch crucible, suspend it in the Wiley extractor and add 40 cc. purified ether. Pass cold water through the condenser and immerse the tube of the extractor in a water-bath heated with a steam coil. The ether should boil at such a rate that the condensate covers the sample but does not flow over the side of the crucible.

Continue the extraction for five hours, then raise the apparatus from the bath and allow the crucible to drain. Remove the glass tube from the apparatus, pour the solution into a tared 150-cc. beaker and rinse the tube with three or four 10-cc. portions of ether, adding them to the beaker. Let the beaker stand at room temperature for about sixteen hours in a place not unduly exposed to dust. If there is no odor of ether, weigh the beaker and contents and, after standing several hours longer, repeat the weighing.

To obtain results more quickly, an optional method of evaporation may be carried out by placing the beaker on the steam-bath, but care must be taken to remove the beaker when about 10 to 15 cc. remain to be evaporated. Otherwise, loss may occur because of the volatility of nitroglycerin at a temperature above that of the normal room. Moreover, heating on the steam-bath after all ether is removed may cause complete decomposition, with evolution of fumes of nitrogen peroxide.

The residue weighed represents nitroglycerin, which is calculated to per cent of the sample taken.

Disposal of Nitroglycerin.—When final weight of beaker and contents has been obtained the nitroglycerin should be disposed of at once. Add to the beaker 25 cc. of "nitrolgycerin remover," prepared as described above under "Apparatus and Reagents." Allow the beaker to stand 10 to 15 minutes and pour the solution into the sink. The sodium sulfide decomposes the nitroglycerin completely so that it no longer has explosive properties.

A comparison of this method with that recommended by the A. O. A. C. for tablets gave the results set forth in Table I.

Table I.—Results Obtained by Weighing Ether Extract and by A. O. A. C. Method

Sample No.	3	4	8	9
Weighing ether extract	10.10	9.25	11.00	9.92
	10.08	9.40	11.00	9.87
	...	...	10.99	...
A. O. A. C. method	8.81	8.28	6.76*	8.50
	8.76	8.53	10.14*	8.70
	...	...	9.30	...
	...	...	9.43	...

While it appears that the variation in the determinations marked with asterisks may have been caused by faulty manipulation, they have been included for the sake of completeness. If these are eliminated, duplicates obtained by the A. O. A. C. method are in agreement, but only show from 84.5% to 91.5% of the mean of the values obtained by weighing the ether extract. The scrubber used was an exact reproduction of one of those depicted in the reference (9) and all details were strictly observed.

Another method, which has been quoted by purchasers of medicinal nitroglycerin more than any other, is that designated as "alternate" in the *Pharmaceutical Standards* (11). In this method, the crushed tablets are heated strongly with milk sugar, aluminum sheet and 1:1 KOH solution in a copper distilling flask and boiled until the dense white fumes cease. The ammonia formed is absorbed in excess of standard acid and back titrated. We have not been able to find any data on this method in the literature. In subsequent discussion it will be referred to as the "alternate method."

Because of its wide acceptance as a method of analyzing concentrated nitroglycerin triturations, more time was spent on this than the other methods studied. The results obtained are shown in Table II, in comparison with those obtained by weighing the ether extract.

In analysis of Sample 1, five out of seven determinations by the "alternate method" agreed closely with the ether extract method; also, for Sample 2 the agreement between the two methods was satisfactory. However, this agreement was not found on later samples, all of which gave lower results by the "alternate method," ranging from 86.7% to 93.3% of the mean of the ether extracts. (Sample 7 was a trituration with chalk instead of sugar of milk.) In analysis of some of the later samples, connections of the apparatus were renewed and all details of the procedure carefully checked without improvement in the results.

In addition to the analyses shown in Table II, Sample 1 was analyzed by what may be called the preferred method of the *Pharmaceutical Standards* (11), which is essentially the same as the method of the U. S. Pharmacopœia. This gave 9.29% and 9.44%.

The "alternate method" and the ether extract method were then checked against known samples. For the "alternate method," samples of dry nitroglycerin in the approximate amount specified by the method, 0.06 Gm., were weighed by difference and dropped directly into the copper flasks containing 0.6 Gm. sugar of milk. The analysis was then conducted as usual.

For the ether extract method, 3 Gm. dry nitroglycerin, nitrogen content 18.39% by nitrometer, were weighed into a beaker containing 27 Gm. sugar of milk. The mixture was stirred in the beaker with a hard rubber spatula for some time after it appeared to be thoroughly uniform, or about ten minutes in all. It was transferred to a bottle and stored for one week with occasional shaking. Duplicate samples of 4 Gm. each were then weighed out and analyzed by the method detailed above.

Table II.—Results Obtained by Weighing Ether Extract and by the "Alternate Method"

Sample No.	1	2	3	4	5	6	7
Weighing ether extract	10.22	10.04	10.10	9.25	9.23	10.07	9.92
	10.17	10.10	10.08	9.40	9.25	10.08	10.07
"Alternate method"	9.30	10.16	9.00	8.58	8.57	8.73	9.18
	9.16	10.14	8.97	8.70	8.59	8.91	8.92
	10.05	...	...	..	..	...	8.90
	10.03	...	...	..	..	...	8.88
	10.13	...	...	..	..	...	8.91
	10.06	...	...	..	..	...	...
	10.03	...	...	..	..	...	...

The results on known amounts of nitroglycerin are shown in Table III.

Table III.—Results with Known Amounts of Nitroglycerin

	Grams Nitroglycerin Added	Found	% Found
Ether extract	0.4000	0.3935	98.4
	0.4000	0.3941	98.5
"Alternate"	0.0670	0.0614	91.6
	0.0863	0.0783	90.7
	0.0560	0.0509	90.9
	0.0563	0.0537	95.4

It is believed that ether extraction actually gives results more nearly quantitative than shown by the two analyses given in the table. A slight loss may have occurred in mixing this small quantity because of nitroglycerin adhering to the beaker and spatula. The results are sufficient to show that the method is superior to the others investigated here. In addition to the data appearing in the above tables, many other analyses have been made over a period of years. This experience with the ether extraction

method has likewise indicated that it is precise and accurate.

The deficiency of nitroglycerin found in known samples by the "alternate method" is in line with most of the analyses given in Table II. Incidentally, it is about the same as reported by purchasers who complained of shortage and based their complaint on assay by the "alternate method." The data indicate that the method cannot be sufficiently controlled to produce reliable results.

CONCLUSIONS

This investigation has been limited to those methods of assay of nitroglycerin tablets which have official status in the United States and which have been applied to the assay of concentrated triturations. It has been shown that, with a few exceptions, the official methods give low results on the concentrated triturations in comparison with the ether extract. On known samples the ether extract gave results which approached the known value more closely than results obtained by the "alternate method."

In view of these comparisons, it would seem desirable for manufacturers of nitroglycerin tablets to assay their purchases of concentrated triturations by the ether-extraction method. It appears that less error will be introduced in compounding tablets when this is done than when the concentrated product is analyzed by one of the official methods recommended for the assay of tablets.

Since many substances are soluble in ether, objection may be raised to a mere weighing of ether-soluble material as an assay for nitroglycerin. Yet the "alternate method," which has been widely used, is open to a similar criticism, because an equivalent amount of any nitrate, saltpeter, for example, would be determined as nitroglycerin. If there is doubt as to the composition of the ether extract, qualitative tests for nitrate can be made. If further confirmation is desired, the nitrogen content can be determined by the nitrometer or by Becker's method (23). Commercial nitroglycerin ordinarily contains 18.30% to 18.45% nitrogen (theoretical 18.51%).

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