

# THE FLASK COMBUSTION TECHNIQUE IN PHARMACEUTICAL ANALYSIS: MERCURY-CONTAINING SUBSTANCES

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A method has been developed for the assay of mercury in organic samples using the flask combustion method followed by complexometric titration with a visual end point. The method has been applied to a wide range of mercury-containing materials used in pharmacy and agriculture.

THE determination of mercury in organic compounds making use of decomposition by the flask combustion technique has received scant attention. Southworth, Hodecker and Fleischer (1958) successfully analysed some mercury compounds in this way finishing with a complexometric titration. Their attempts to use a visual end point were unsuccessful and they found it necessary to resort to an amperometric method. The method is not directly applicable to chlorine-containing compounds since these, on combustion, give mercurous chloride which must be oxidised before titration. If a visual end point method of titration could be developed, free from interference by halides the flask combustion assay should then be applicable to the many commercially important mercury-containing materials used in pharmacy and agriculture.

## EXPERIMENTAL

Southworth, Hodecker and Fleischer (1958) found that the oxides of nitrogen produced when the combustion products dissolve in nitric acid, destroyed the indicators used in the complexometric titration. Attempts to eliminate this interference were unsuccessful. By analogy with the Rupp (1905) method of determining mercury, bromine water should prove a suitable absorbing liquid, even for those compounds giving rise to mercurous chloride on combustion, and this was found to be so. Attempts made to remove the excess bromine using either phenol or formic acid led to unsatisfactory end points when these solutions were titrated complexometrically. Removal of the bromine was finally achieved by simply drawing air through the solution. Sharper end points were thus obtained, with no increase in operator time over the formic acid method.

The choice of a suitable complexometric titration of the mercury was next considered. Although Southworth and his colleagues (1958) titrated with (ethylenedinitrilo) tetra-acetic acid solution, we preferred the more widely used EDTA. As an indicator solochrome black or 1-(2-pyridylazo)-2-naphthol (PAN) was satisfactory, the latter being preferred because the colour change was more easily seen at the end point.

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In addition to simple titration with standard zinc solution a second method was considered. This involved back-titration with standard zinc solution, liberation of EDTA from the mercury complex by addition of potassium iodide and titration of the EDTA with standard zinc solution.

**TABLE I**  
**RESULTS OBTAINED ON PHENYLMERCURIC ACETATE (M.A.R. STANDARD)**

	No. of determinations	Mean result	Range	Results by alternative procedure*
<i>Sample No. 1—</i>				
Platinum .. ..	8	59.3	59.1–59.4	59.4
Silica .. ..	2	59.3	59.2–59.4	—
<i>Sample No. 2—</i>				
Platinum .. ..	8	59.4	59.2–59.8	59.5
Silica .. ..	2	59.4	59.3–59.4	59.5

\*The material is decomposed by refluxing with 4M sulphuric acid for 1 hr. Dilute potassium permanganate solution is added until the solution is just pink. After cooling hydrogen peroxide is added to remove the excess permanganate and the solution titrated with 0.1N ammonium thiocyanate solution using ferric ammonium sulphate solution as indicator.

This is the recommended method of the Microchemistry Group of the Society for Analytical Chemistry (1961).

**TABLE II**  
**RESULTS OBTAINED ON VARIOUS COMMERCIAL ORGANO-MERCURY COMPOUNDS BY THE FLASK AND OTHER METHODS**

Substance	Mercury content per cent				
	Calculated from formula	By flask method			By alternative method
		No. of detns.	Mean result	Range	
Phenylmercuric nitrate B.P. ..	63.2	4	62.9	62.9–63.0	63.6 <sup>1</sup> ; 63.5 <sup>2</sup> 63.0; 62.8 <sup>1</sup>
Mersalyl sodium B.P.C. ... ..	39.7	4	39.2	39.1–39.3	39.4 <sup>1</sup>
Mercurochrome B.P.C. 1954 (1)	26.7	3	26.7	26.7–26.7	27.0 <sup>1</sup> ; 26.6 <sup>4</sup>
"    "    "    "    (2)	—	4	26.1	26.0–26.2	26.2 <sup>1</sup>
Chlormerodrin B.P.C. ... ..	54.6	4	54.5	54.4–54.5	54.6 <sup>1</sup>
Tolylmercuric acetate (1) ..	57.2	4	60.5	60.4–60.6	60.8; 60.9 <sup>2</sup> 61.9 <sup>2</sup>
"    "    (2) ..	—	2	61.5	61.4–61.6	62.0 <sup>2</sup>
"    "    (3) ..	—	2	61.4	61.3–61.4	63.0; 63.3 <sup>2</sup> 61.8 <sup>2</sup>
Ethylmercuric chloride (1) ..	75.7	3	71.7	71.5–72.0	74.5; 72.4 72.3 <sup>2</sup>
"    "    (2) ..	—	3	74.7	74.5–75.0	75.6; 74.9 <sup>2</sup>
"    "    (3) ..	—	4	75.1	75.0–75.2	75.1 <sup>2</sup> 74.2 <sup>2</sup>
Phenylmercuric <i>p</i> -hydroxybenzoate .. ..	48.4	5	45.8	45.1–46.1	45.7; 45.3 <sup>2</sup>
Phenylmercuric acetate .. ..	59.6	4	59.4	59.2–59.5	59.6; 59.5 <sup>2</sup> 59.6 <sup>2</sup>
Phenylmercuric chloride ..	64.1	4	64.5	64.4–64.6	64.0 <sup>2</sup>
Ethylmercuric phosphate ..	72.6	4	71.2	71.2–71.3	73.0; 72.0 <sup>2</sup>
Ethylmercuric methyl phenyl dithiocarbamate .. ..	48.7	3	52.1	52.0–52.2	52.0 <sup>2</sup>

<sup>1</sup> Official method of the B.P. or B.P.C.

<sup>2</sup> Sulphide precipitation after destruction of organic matter with hydrogen peroxide and sulphuric acid. Method of Tabern and Shelberg (1932).

<sup>3</sup> Titration with thiocyanate after destruction as in 2. Method of Tabern and Shelberg (1932).

<sup>4</sup> Method of Brookes and Solomon (1959).

The second method was preferred since it is specific for mercury and needs only one standard solution which can be prepared from pure zinc.

The recommended reagents and general method are as follows.

### Reagents

*Bromine water.* A saturated solution of bromine in water. *EDTA solution, 0.005M.* A solution of disodium ethylenediamine tetra-acetate (approximately 1.86 g.) in water (1 litre). This solution need not be accurately standardised. *Zinc solution, 0.01M.* A solution containing pure zinc (0.6538 g.) dissolved in the minimum quantity of hydrochloric

TABLE III  
RESULTS OBTAINED ON VARIOUS PILL AND TABLET FORMULATIONS

Preparation	Mercury content					Results expressed as
	Calculated from formula	By flask method			By alternative method	
		No. of detns.	Mean result	Range		
Tab. Calomel B.P.C. . . . .	0.25	4	0.237	0.234-0.238	0.24 <sup>1</sup>	gr. HgCl per tablet
Tab. Calomel, Rhubarb and Colocynth Co. . . . .	2.0	4	1.99	1.96-2.01	1.92 <sup>2</sup>	gr. HgCl per tablet
Tab. Calomel, Jalap and Santonin . . . . .	1.33	4	1.28	1.28-1.28	1.30 <sup>3</sup>	gr. HgCl per tablet
Tab. Mersalyl Co. . . . .	31.8	4	29.6	29.4-29.7	30.2 <sup>4</sup>	mg. Hg per tablet
Pil. Calomel and Colocynth B.P.C. 1949 . . . . .	63.0	4	62.0	61.5-62.5	60.9 <sup>1</sup>	mg. HgCl per pill
Pil. Calomel, Colocynth and Hyoscyamus B.P.C. 1949 . . . . .	63.0	4	60.6	59.4-61.8	60.9 <sup>1</sup>	mg. HgCl per pill
Pil. Mercury B.P. 1948 . . . . .	1.33	3	1.37	1.37-1.38	1.33 <sup>1</sup>	gr. Hg per pill
Pil. Calomel and Menthol . . . . .	0.25	3	0.225	0.223-0.226	0.218; 0.214 <sup>3</sup> 0.224; 0.223	gr. HgCl per pill
Pil. Red Mercuric Iodide . . . . .	0.0625	3	0.058	0.057-0.058	0.058; 0.055 <sup>4</sup>	gr. HgI <sub>2</sub> per pill

<sup>1</sup> The official method of the B.P. or B.P.C.

<sup>2</sup> The method described for Pills of Calomel, Colocynth and Hyoscyamus in the B.P.C. 1949.

<sup>3</sup> The method for Tab. Calomel B.P.C.

<sup>4</sup> The method for Mercuric Iodide B.P.C. 1949.

acid and diluted to 1 litre with water. *Ammonia buffer solution.* Ammonium chloride (13.5 g.) in strong solution of ammonia (114 ml.) diluted to 200 ml. with water. *Potassium iodide.* PAN indicator solution. A 0.1 per cent solution of 1-(2-pyridylazo)2-naphthol in ethanol (95 per cent). This solution is stable for several weeks.

### Method

Accurately weigh a suitable quantity of the sample containing about 25 mg. of mercury, transfer to a strip of filter paper (Whatman No. 1 of a suitable size according to the sample) and burn by the method previously described by Johnson and Vickers (1959). Use bromine

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solution (5 ml.) in water (20 ml.) as the absorbing liquid. When combustion is complete shake the flask vigorously for about 5 min., and then open in the usual manner. Remove the excess bromine from the solution by drawing a stream of air through it until colourless and then for a further 5 min. Rinse the aspiration tube with a little distilled water, and add 0.005M EDTA solution (30 ml.), 5 ml. of ammonia buffer solution and 0.3 ml. PAN indicator solution to the flask. Titrate with 0.01M zinc solution to the first pink colour using a magnetic stirrer. Add potassium iodide (2 g.), stir the solution for 2 min., and continue the

TABLE IV  
RESULTS OBTAINED ON VARIOUS OINTMENTS

Preparation	Mercury content per cent				
	Calculated from formula	By flask method			By alternative method
		No. of detns.	Mean result	Range	
Ointment Mercury Strong B.P.C.	30.0	4	30.2	30.2-30.2	28.9 <sup>1</sup>
Ointment Mercury Compound	12.0	4	12.4	12.4-12.5	11.7; 12.0 <sup>1</sup>
" " (2) .. ..		3	12.7	12.5-12.8	
Ointment Mercury Dilute B.P.C.	10.0	4	9.72	9.67-9.74	9.55; 9.40 <sup>1</sup>
Ointment Mercuric Nitrate, Strong B.P.C. .. ..	not less than 6.7	4	7.06	7.02-7.08	6.92 <sup>1</sup>
Oleated Mercury B.P.C. . . .	20.0 per cent HgO	4	20.6	20.6-20.7	20.4 <sup>1</sup> per cent HgO

<sup>1</sup> Official method of the B.P. or B.P.C.

titration, again to the pink colour. Each ml of 0.01M zinc solution required after addition of the potassium iodide is equivalent to 0.0020061 g. of Hg.

With ointments, the sample is weighed on to a small square of grease-proof paper which is folded so as to completely enclose the material: this is then itself folded in filter paper as usual.

### RESULTS AND DISCUSSION

The method was first applied to phenylmercuric acetate of micro-analytical reagent grade (theoretical mercury content 59.57 per cent) and gave satisfactory recoveries (Table I). Table II lists results obtained on some organo-mercury compounds used in pharmacy and agriculture, both by the proposed flask combustion method and other methods. Table III shows the results obtained on a number of pill and tablet formulations and Table IV those obtained on ointments. The method described is applicable only to materials with a mercury content  $\geq 5$  per cent: attempts are being made to extend the method to materials of lower mercury content.

It was necessary to investigate whether some alloying of mercury and platinum could occur during combustion. A spiral of silica was used as a sample holder and assays were again carried out on phenylmercuric

acetate (micro-analytical reagent grade). The results obtained were identical with those using the conventional platinum holder (Table I).

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