SCIENTIFIC SECTION

THE CONSTANTS OF CHLOROFORM LINIMENT.*

BY L. E. WARREN.†

More than a year ago the writer was informed by the chief control chemist of a pharmaceutical manufacturing establishment that the determination of chloroform in chloroform liniment in production control was causing trouble, the results obtained always coming below theory. Inquiry established that the method of assay employed was similar to one that had been used in coöperative trials by the Association of Official Agricultural Chemists several years ago.[1] The literature was searched to ascertain what had been the results reported in the analysis of chloroform liniment by other analysts. Only one complete analysis of the preparation was found,[2] although several methods for the determination of chloroform in pharmaceuticals have been published, some of which have been applied to the analysis of the liniment.[3,4,5,6,7,8]

Chloroform liniment is described in several foreign pharmacopœias but the composition of the product in the various countries differs considerably from that of the U. S. Pharmacopœia X article. This paper deals only with the U. S. Pharmacopœia preparation. The Pharmacopœia gives directions for the preparation of chloroform liniment by mixing chloroform and soap liniment, but it does not provide any standards for the finished product. Further, an examination of the available literature indicates that but very little information concerning the physical constants and standards for the liniment could be found. Because of this dearth of knowledge concerning such a well known and widely used product it seemed desirable to ascertain the constants of an authenticated specimen.

Soap liniment was prepared strictly according to the U. S. Pharmacopœia. The powdered castile soap used was labeled as of U. S. Pharmacopœia quality. On drying it lost 1.7% of its weight, whereas the U. S. Pharmacopœia permits 10% loss. The chloroform used had a specific gravity of 1.4759 at 25/25° C. The U. S. Pharmacopœia limits for the specific gravity of chloroform are 1.4740 to 1.4780. The camphor used had an optical rotation of +41° (angular) at 20° C. in a 10% solution in alcohol in a 100-mm. tube. The soap liniment pre-

* Scientific Section A. PH. A., St. Louis meeting, 1927.

† Drug Control Laboratory, Food, Drug and Insecticide Administration, Washington, D. C.

[1] A. G. Murray, "Report on the Determination of Chloroform in Drug Products," *Jour. A. O. A. C.*, 5, 539 (1922).

[2] J. W. E. Harrisson, "Rate of Volatility of Chloroform from Chloroform Liniment," JOUR. A. PH. A., 12, 333 (1923).

[3] L. de Saint Marten, *Compt. rend.*, 106, 492 (1888).

[4] W. A. Puckner, "The Estimation of Chloroform," PROC. A. PH. A., 49, 294 (1901).

[5] J. L. Mayer, "A Rapid, Accurate Method for the Quantitative Estimation of Chloroform in Chloroform Liniment," JOUR. A. PH. A., 1, 1155 (1912).

[6] E. B. Putt, "Determination of Chloroform in Cough Syrups," *Am. Food J.*, 10, 467 (1915).

[7] Schlicht and Austen, "Estimation of Chloroform and Other Volatile Substances," *Z. öffentl. Chem.*, 26, 55 (1920).

[8] O. Sasse, "Estimation of Chloroform," *Pharm. Ztg.*, 65, 559 (1920).

pared as above described had a specific gravity of 0.8873 at 25/25° C. It gave a residue of 6 Gm. per 100 cc. on drying on sand at 100° C. Its optical rotation was +1.80° (direct angular reading) at 20° C.

Three lots of chloroform liniment were prepared by mixing 700 cc. of soap liniment with 300 of chloroform as directed by the Pharmacopœia. Three other lots of liniment were prepared, two of which contained somewhat less chloroform than the Pharmacopœia prescribes and the other slightly more. The formulas for these six lots of liniment are given in Table I.

TABLE I.

COMPOSITION OF SEVERAL SPECIMENS OF CHLOROFORM LINIMENT PREPARED FOR ANALYSIS.

Sample no.	Chloroform volumes.	Soap liniment volumes.
I	30	70
II	30	70
III	27	73
IV	29	71
V	31	69
VI	30	70

Each of these samples was analyzed by the writer with particular reference to the specific gravity, optical rotatory power and yield of solids on drying. Chloroform and alcohol were determined in some of the specimens. After preliminary trials the following tentative methods were selected for use.

SPECIFIC GRAVITY.

Determine the specific gravity at 25/25° C. by means of a pycnometer.

TOTAL SOLIDS.

Place about 1 Gm. of sand and a small stirring rod in a beaker of about 150-cc. capacity, dry the apparatus at 110° for 1 hour, cool and weigh. Add 10 cc. of chloroform liniment by means of a pipette. Evaporate the mixture on the steam-bath with occasional stirring until the odor of camphor has disappeared. Dry the residue in an oven at 110° to constant weight.

OPTICAL ROTATORY POWER.

Determine the optical power at 20° in a 100-mm. tube and report the findings in angular degrees. If the material be too dark for direct reading, dilute it with one or more volumes of alcohol at 20°.

CHLOROFORM.[1]

By means of a pipette place 10 cc. of chloroform liniment in a 100-cc. graduated flask and fill to the mark with methyl alcohol. Mix thoroughly. By means of a pipette place 10 cc. of the diluted solution (equivalent to 1 cc. of chloroform liniment) in a 200-cc. volumetric flask containing 40 cc. of 30% potassium hydroxide in methyl alcohol. Shake the mixture occasionally for one or two hours and allow to stand over night. Fill to the mark with water. Mix thoroughly, and use 50-cc. aliquot portions for the determination of chloride either gravimetrically or volumetrically.

Gravimetric Determination.—Place 50 cc. of the dilution in a beaker and add an equal volume of water. Heat on the steam bath, add a drop of methyl red test solution as indicator and add 5 cc. of nitric acid with stirring, or a sufficient quantity to render the mixture distinctly pink. Add 25 cc. of silver nitrate test solution with stirring, heat for half an hour on the steam-bath with occasional stirring, collect the silver chloride in a tared Gooch crucible, dry the precipitate at 100° and weigh in the usual way. A blank should be carried through with the reagents and a correction applied if necessary.

[1] This method is still under investigation by the A. O. A. C. because of the suspicion that it gives low results. This will be mentioned again.

$$AgCl \times 0.27764 = CHCl_3$$

Volumetric Determination.—Place 100 cc. of the alkaline solution in a 200-cc. volumetric flask, add 10 cc. of nitric acid and 60 cc. of 0.1 *N* silver nitrate, make up to the mark with water, stopper the flask and shake well. Filter through a dry filter, reject the first 20 cc. of the filtrate, collect 100 cc. of the filtrate and titrate the excess silver in the solution with 0.1 *N* potassium sulphocyanate, using 5 cc. of ferric ammonium sulphate test solution as indicator.

$$1 \text{ cc. } 0.1\ N\ AgNO_3 \text{ solution} = 0.00398 \text{ Gm. of } CHCl_3$$

ALCOHOL.

Place 50 cc. of saturated salt solution, 25 cc. of petroleum benzin, and 25 cc. of the liniment in a separator. Agitate gently and allow to separate. Draw off the aqueous layer into a second separator, shake the solution thoroughly[1] with 25 cc. of petroleum benzin and after separation draw the aqueous layer into a distilling flask. Shake the chloroform-petroleum benzin mixture in the first separator with 2 successive portions of 20 cc. each of saturated salt solution and after settling draw off the aqueous solutions into the second separator. Wash each portion of the salt solution in the second separator with fresh petroleum benzin and draw off the aqueous solution into the distilling flash. Add 50 cc. of water and a few glass beads and distil off about 45 cc., collecting the distillate in a 50-cc. graduated flask. Make up to the mark with water, determine the specific gravity of the distillate in a pycnometer and calculate the alcohol in the usual way by reference to the U. S. Pharmacopœia X Alcohol tables.[2]

TABLE II.

ANALYSES OF CHLOROFORM LINIMENT.

Sample no.	Specific gravity.	Solids (soap) Gm. per 100 cc.	Optical rotation.	Chloroform Gm. per 100 cc.	Alcohol.
		4.28	+1.28°	41.88	...
I	1.0561	4.29	+1.21°	41.88	41.71
			.....	41.55	...
		4.38	.....	...	...
II	1.0598	4.39	+1.32°	...	43.25
			.....	37.74	...
		4.41	.....	37.51	...
III	1.0400	4.41	+1.2°	38.20	51.06
			.....	38.62	...
			.....	39.95	...
	1.0538	4.30	.....	41.67	...
IV	1.0502	4.28	+1.71°	41.18	45.82
			.....	41.37	...
			.....	41.26	...
	1.0661	4.17	.....	44.25	...
V	1.0611	4.17	+1.38°	44.17	45.44
			.....	44.26	...
			.....	43.78	...
			.....	42.01	...
VI	1.0557	4.25	.....	42.18	43.82
		4.25	+1.41°	42.97	...
			.....	42.52	...
Theory for normal		4.20	+1.31°	44.05	46.65

[1] Unless care is exercised the determination of alcohol may give low results, owing to the fact that the petroleum benzin-chloroform mixture retains a considerable proportion of alcohol, necessitating *thorough washing* with the salt solution.

[2] U. S. Pharmacopœia X p. 528.

The findings for the several analyses are given in Table II. For comparison the theoretical composition of chloroform liniment as near as may be calculated is also included.

A comparison of the findings for the three specimens of genuine chloroform liniment (I, II and VI) indicates that chloroform liniment should have a specific gravity at 25/25° C. of not far from 1.056 and an optical rotation (direct angular reading) of about +1.3° and should contain about 4.3 Gm. of solids per 100 cc.

The writer asked several collaborators to determine the physical constants of one or more of the specimens of chloroform liniment which he had prepared.

Those submitting reports were:

N. T. Chamberlin, Western Reserve University School of Pharmacy, Cleveland, Ohio.

G. F. Harvey Co., Saratoga Springs, N. Y.

Eli Lilly & Co., Indianapolis, Ind.

Joseph L. Mayer, of the Louis K. Liggett Co., N. Y.

Margaret C. Moore and Cassius L. Clay, State Board of Health, New Orleans, La.

The findings reported by the several investigators are given in Table III.

TABLE III.

CONSTANTS FOR CHLOROFORM LINIMENT.

Investigator.		N. T. C.	Harvey.	Lilly.	J. L. M.	C. & M.
Sample I (normal)	Sp. gr.	1.0505	1.0525	1.0507	1.0488	1.0453
	Rotation	+1.14°		+1.32°	+0.997°	
	Solids	4.29		3.90	4.15	4.56
Sample II (Normal)	Sp. gr.	1.0550	1.0535	1.0538		
			1.0529			
				+1.27°		
	Rotation	+1.14°		+1.31°		
	Solids	4.29		3.73		
			1.0370			
Sample III	Sp. gr.		1.0365			
$CHCl_3$ 27	Rotation					
S. Lin. 73	Solids					
Sample IV	Sp. gr.	1.0560		1.0423	1.0504	
$CHCl_3$ 29				+1.25°		
S. Lin. 71	Rotation	+1.10°		+1.22°	+0.967°	
	Solids	4.28		4.00	4.12	
Sample V	Sp. gr.	1.0658		1.0640	1.0643	
$CHCl_3$ 31				+1.18°		
S. Lin. 69	Rotation	+1.10°		+1.11°	+0.974°	
	Solids	4.10		3.76	3.86	

In a further attempt to obtain information concerning the physical constants of chloroform liniment several workers in schools of pharmacy were asked to prepare chloroform liniment from known materials and to determine the physical constants of the finished preparations. Manufacturers also were asked to report their control findings.

Those reporting were:

N. T. Chamberlin, Western Reserve University School of Pharmacy.
Samuel Shkolnik, University of Illinois, School of Pharmacy.
Parke, Davis & Co., Detroit, Michigan.

The findings are given in Table IV. For comparison the findings as reported by Harrisson[1] and those obtained on one sample by the writer are included.

TABLE IV.

ANALYSES OF CHLOROFORM LINIMENT.

Observer.	Sp. gr. 25/25° C.	Rotation (angular degrees).	Solids.
	1.0600	+1.56	4.22
N. T. C.	1.0570	+1.38	4.03
	1.0620	+1.87	4.45
S. S.	1.0600	+1.23	4.16
J. W. E. H.	.....	+1.3	3.73
L. E. W.	1.0557	+1.41	4.25
P. D. & Co.	1.060	+1.57	3.43

CONCLUSIONS.

From a comparison of all of the information obtainable it would appear reasonable to conclude that chloroform liniment of good quality should have the following properties:

Color—pale yellow
Odor—like chloroform, camphor and faintly of oil of rosemary
Specific gravity at 25/25° C.—1.050 to 1.060
Optical rotation $\left\{\begin{matrix}\text{direct reading} \\ \text{angular degree}\end{matrix}\right\}$ — + 1.14 to +1.6
Solids (residue at 110°)—3.90 to 4.50 Gm. per 100 cc.
Alcohol—43% to 45% by volume
Chloroform—no standard suggested

No standards are suggested for the limits of chloroform in chloroform liniment because the methods for its determination are not sufficiently elaborated and standardized. According to Moraw[2] it would appear that both heat and pressure are necessary to convert chloroform into chloride quantitatively. The directions and specimens for collaborative work upon the results of which this paper is based were sent out before Moraw's report was made public and most of the work had been completed. Consequently there has been no opportunity to employ a method for the determination of chloroform in the liniment involving the use of a pressure bottle.

The writer wishes to acknowledge his appreciation to the several pharmaceutical manufacturers and to others who have aided in this study, either by contributing material or by collaborative work.

[1] J. W. E. Harrisson, "Rate of Volatility of Chloroform from Chloroform Liniment," JOUR. A. PH. A., 12, 333 (1923).

[2] Moraw, "Report on Chloroform and Carbon Tetrachloride," *Jour. A. O. A. C.*, 10, 351 (1927).