STABILITY OF HOMATROPINE HYDROBROMIDE SOLUTION.*

BY PAUL S. PITTENGER AND JOHN C. KRANTZ, JR.

In view of the fact that many oculists have noted different degrees of mydriasis with the same labeled strength solution of homatropine hydrobromide, it was thought advisable to determine whether this variation was due to deterioration or to variations in reaction of the pupils of different patients. It was necessary to determine if the solutions deteriorated with age and upon exposure to light of various wave-lengths. Also if these physical factors influenced these solutions chemically and to determine whether or not such changes are accompanied by changes in physiologic activity.

In order to determine the effects of various physical factors upon the solutions of homatropine hydrobromide, the following investigation was conducted.

METHOD OF STUDY AND RESULTS.

Physical Measurements.—A one per cent solution of homatropine hydrobromide U. S. P. was prepared for study of the isotonic value as compared with the tear. This solution showed a depression of the freezing point of 0.122° C. One and thirteen hundredths Gm. of sodium chloride added to 100 cc. of this one per cent solution yielded a product which gave a depression of the freezing point of 0.83° C. rendering the solution practically isotonic with the tear.

Solutions of homatropine hydrobromide were prepared in concentrations of 0.1 N., 0.01 N. and 0.001 N., the hydrogen-ion concentrations were measured electrometrically and the change in p_H upon standing and heating was determined.

Concn. of solution.	p_H when prepared.	p_H after 15 days.
0.1 *N*	3.172	3.65
0.01 *N*	3.875	5.835 Fungus growth
0.001 *N*	4.570	5.400
1.0% Isotonic with tear	4.387	4.42
		Boiled 5 min.
0.01 *N*	3.875	4.06

A solution containing one per cent of homatropine hydrobromide U. S. P. in plain distilled water and a solution rendered isotonic with the tear with sodium chloride were prepared and immediately physiologically tested by the Munch "Cat-Eye" method. After determining the physiologic activity of these solutions they were each divided into eight portions. One portion of each (A & A-1) was stored in flint ampuls without sterilizing. Another portion of each (B & B-1) was placed in flint ampuls and sterilized. Both portions were then placed on shelves in the laboratory to be tested at intervals of three months in order to determine the rate of deterioration under ordinary light conditions. In order to determine the effects of various wave-lengths of light upon these solutions five of the remaining six portions of each solution were placed in various colored quartz tubes while the sixth portion of each was placed in a plain pyrex tube. These twelve tubes were then irradiated with ultraviolet light by exposing for thirty minutes under an Alpine Sun Lamp and then retested in order to determine any changes in physiologic activity.

* Scientific Section, A. PH. A., Portland meeting, 1928.

Physiologic Measurements.—The solutions were tested by the "Munch Method for Biologic Assay of Miotics and Mydriatics."[1] This method consists in determining the smallest amount of a solution of the unknown required to produce the same degree of miosis or mydriasis as that produced by a standard solution of known strength.

As cats differ considerably in susceptibility to homatropine hydrobromide, each cat was first standardized by determining its susceptibility to the standard sample. A record was made of the minimum effective concentration for each cat, and used for comparison with the amounts of each unknown required to produce the same effects upon the same cat. In order to further eliminate variations in results due to variations in susceptibility five to nine cats were used for each test. Each animal received doses of concentrations ranging from 100 to 1000 mg. per liter. In order to conserve space only the minimum effective concentrations are given.

TEST NO. 1—SAMPLE A.

Ampul solution homatropine hydrobromide 1% in distilled water. Not sterilized. Original assay.

Cat. no.	Minimum effective concentration mg. per liter.
1	250
2	500
3	500
4	250
5	500
6	500
7	500
8	250
9	500

TEST NO. 2—SAMPLE A-1.

Ampul solution homatropine hydrobromide 1% isotonic with tear. Not sterilized. Original assay.

Cat. no.	Minimum effective concentration mg. per liter.
1	250
2	500
3	500
4	250
5	500
6	500
7	500
8	250
9	500

The above results show that the solution which was made isotonic with the tear and the solution prepared with plain distilled water were identical as to physiologic activity.

The ampuls containing the above solutions were then placed on a laboratory shelf and retested after three months with the following results.

TEST NO. 3—SAMPLE A.

Ampul solution homotropine hydrobromide 1% in distilled water. Not sterilized. Aged three months.

Cat. no.	Minimum effective concentration mg. per liter.
1	250
2	500
3	500
4	250
5	500
6	500
7	500
8	250
9	500

TEST NO. 4—SAMPLE A-1.

Ampul solution homatropine hydrobromide 1% isotonic with the test. Not sterilized. Aged three months.

Cat. no.	Minimum effective concentration mg. per liter.
1	250
2	500
3	500
4	250
5	500
6	500
7	500
8	250
9	500

[1] Munch, *Jour. A. O. A. C.*, 10 (1927), 383–386. "Pittenger's Biologic Assays," 2nd Edition, 158.

TEST NO. 5—SAMPLE B.

Ampul solution homatropine hydrobromide 1% in distilled water. Sterilized. Original assay.

Cat. no.	Minimum effective concentration mg. per liter.
1	250
2	500
3	500
4	250
5	500
6	500
7	500
8	250
9	500

TEST NO. 6—SAMPLE B-1.

Ampul solution homatropine hydrobromide 1% isotonic with tear. Sterilized. Original assay.

Cat. no.	Minimum effective concentration mg. per liter.
1	250
2	500
3	500
4	250
5	500
6	500
7	500
8	250
9	500

It will be noted from the above that sterilization at 15 lbs. for 15 minutes has no effect upon the activity of the homatropine, either in plain distilled water or in isotonic solution.

TEST NO. 7—SAMPLE B.

Ampul solution homatropine hydrobromide 1% in distilled water. Sterilized. Aged three months.

Cat. no.	Minimum effective concentration mg. per liter.
1	250
2	500
3	500
4	250
5	500
6	500
7	500
8	250
9	500

TEST NO. 8—SAMPLE B-1.

Ampul solution homatropine hydrobromide 1% isotonic with tear. Sterilized. Aged three months.

Cat. no.	Minimum effective concentration mg. per liter.
1	250
2	500
3	500
4	250
5	500
6	500
7	500
8	250
9	500

Both solutions are, therefore, effective in the same concentrations as when originally prepared showing that no deterioration occurred during the three-month aging period.

Samples of the sterilized ampuls B & B-1 were again tested after six months' aging and were found to be as active as when originally prepared. A fresh solution of the standard was prepared at the end of the three- and nine-month period and used to check the susceptibility of each cat. No change in the reaction of the animals to the drug could be noted as the minimum effective concentration for each cat was the same after three and nine months, respectively, as in the original assays. (Tests 1 & 2.)

The effects of exposure to various wave-lengths of light are shown by the following chart:

EFFECT OF VARIOUS WAVE-LENGTHS OF LIGHT UPON SOLUTION HOMATROPINE HYDROBROMIDE 1%.

Sample.	How prepared.	Container.	Original assay.	Assay after exposure for 30 minutes under an Alpine sun lamp.
C	In distilled water	Yellow quartz tube	Same as Test No. 5	Same as Test No. 5
C-1	In isotonic solution	Yellow quartz tube	Same as Test No. 6	Same as Test No. 6

D	In distilled water	Plain quartz tube	Same as Test No. 5	Same as Test No. 5
D-1	In isotonic solution	Plain quartz tube	Same as Test No. 6	Same as Test No. 6
E	In distilled water	Red quartz tube	Same as Test No. 5	Same as Test No. 5
E-1	In isotonic solution	Red quartz tube	Same as Test No. 6	Same as Test No. 6
F	In distilled water	Green quartz tube	Same as Test No. 5	Same as Test No. 5
F-1	In isotonic solution	Green quartz tube	Same as Test No. 6	Same as Test No. 6
G	In distilled water	Purple quartz tube	Same as Test No. 5	Same as Test No. 5
G-1	In isotonic solution	Purple quartz tube	Same as Test No. 6	Same as Test No. 6
H	In distilled water	Pyrex tube	Same as Test No. 5	Same as Test No. 5
H-1	In isotonic solution	Pyrex tube	Same as Test No. 6	Same as Test No. 6

These results indicate that exposure to ultraviolet radiation in the various types of containers employed has no deleterious influence upon the mydriatic action of solution of homatropine hydrobromide.

CONCLUSIONS.

(1) Certain physical measurements of solution of homatropine hydrobromide have been made.

(2) Sterilization or exposure to ultraviolet radiation has no apparent deleterious effect upon the mydriatic action of homatropine hydrobromide in either distilled water in sodium chloride solution isotonic with the tear.

(3) Homatropine hydrobromide in distilled water or isotonic solution preserved in ampuls shows no apparent loss in mydriatic action during a period of nine months.

RESEARCH LABORATORIES,
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MERCURIC IODIDE DETERMINATION IN TABLETS.*

BY H. O. MORAW.

Mercuric iodide as a medicinal agent is available in the U. S. P. form, in tablet triturates of one-eighth or one-fourth grain, in potassium iodide oil suspension in ampuls and in ointments. From the standpoint of pharmaceutical manufacturing as well as the Government regulatory work, tablets and ampuls are probably the more important forms of dispensing this drug. Since, in the case of tablets the usual builders, disintegrators and lubricants, such as sugar, starch and talc, might interfere in the electrolytic determination which is specified for the assay of the U. S. P. product, it is necessary to adapt a method to the assay in the presence of interfering substances. This has been done by Bender[1] who effected solution of interfering substances other than talc by free chlorine treatment and subsequent estimation as mercuric sulphide. Morgan[2] has adapted this method to calomel tablets and suggests it for other mercurials. Since the electrolytic apparatus is not available in the average laboratory, consideration was given to the practicability of other methods employing the usual laboratory equipment. The time

* Work performed while employed in the U. S. Food & Drug Laboratory, 1625 Transportation Bldg., Chicago, Ill.

[1] *Ind. & Eng. Chem.*, 6, No. 9 (1914), 753.

[2] *J. Assocn. Official Agr. Chem.*, 10 (1927), 367-9; cf. Spencer, *C. A.*, 20, 3210.