

# SCIENTIFIC SECTION

## THE CITRIC ACID "ASSAY" OF SOLUTION OF MAGNESIUM CITRATE, U. S. P.\*

BY H. V. ARNY<sup>1</sup> AND HUGO H. SCHAEFER.<sup>1</sup>

### INTRODUCTION.

Reference to the monograph on Solution of Magnesium Citrate, as given in the present (tenth) revision of the United States Pharmacopœia, indicates the presence of a test not found in U. S. P. IX. This is so-called "assay" for citric acid. The present monograph does not call it an assay but labels its two sentences "*minimum of acidity*" and "*minimum of total citric acid*," respectively. This phraseology was used because certain members of the sub-committee on inorganic chemicals of the U. S. P. Revision Committee considered the test too experimental and possibly too empirical to dignify with the word "assay."

The need of some sort of an assay showing the citric acid content of solution of magnesium citrate became apparent in connection with the work of the senior author as chemist of the Board of Pharmacy of the State of New York. This work (performed prior to 1920) included examination of the citrate of magnesia solution both for MgO and for citric acid content. Results showed that while most of the samples picked up in the drug stores of New York were up to requirements of U. S. P. IX as to magnesium oxide, in the case of samples manufactured by some of the large concerns specializing in this product, the citric acid content was twenty per cent below the 33 Gm. per bottle required by U. S. P. IX. This work performed in 1917 by H. J. Goeckel and the senior author using the Mayer method of "assay" (to be discussed later) gave the following results:

TABLE I.

Source of the Solution of Magnesium Citrate.	Total Citric Acid per 350-cc. bottle.	Source of the Solution of Magnesium Citrate.	Total Citric Acid per 350-cc. bottle.
Made by operators		Samples prepared	25.09 Gm. 1 sample
in exact accord with	34.447 Gm.; 34.939 Gm.	by one manu-	25.558 Gm. 1 sample
the recipe of U. S. P.		facturer	25.585 Gm. 3 samples
IX			26.07 Gm. 2 samples
One retail phar-			26.327 Gm. 1 sample
macy sample	33.46 Gm.		26.57 Gm. 4 samples
			26.79 Gm. 1 sample
			27.55 Gm. 1 sample
			28.049 Gm. 1 sample
			28.539 Gm. 1 sample
			29.02 Gm. 1 sample

The foregoing figures convinced the members of the sub-committee on inorganic chemicals of the U. S. P. Revision Committee (1920-1930) of the need of a proper control of citric acid in the official solution and the Mayer "assay" process (JOUR. A. PH. A., 9 (1920), 253) was chosen as the best test available. This test

\* Scientific Section, A. Ph. A., Baltimore meeting, 1930. No discussion.

<sup>1</sup> 115 W. 68th St., New York City.

after undergoing some modifications at the hands of some members of the Revision Committee finally appeared as tests for "minimum of acidity" and of "total citric acid" on page 219 of U. S. P. X. It can be condensed to the following concise statements:

Measure off 10 cc. of the solution; boil down to 5 cc.; titrate with  $N/2$  NaOH; indicator, phenolphthalein. It should require not less than 9.5 cc.  $N/2$  NaOH for neutralization (*free acidity*).

Evaporate the neutralized liquid to dryness, ash to a white residue, add 50 cc. of distilled water and titrate with  $N/2$   $H_2SO_4$ ; indicator, methyl orange. It should require not less than 28 cc.  $N/2$   $H_2SO_4$  (*total citric acid*).

#### THE OFFICIAL TEST.

The test as finally approved by the Revision Committee and as outlined above was the result of work performed in 1923 by the senior author and his pharmacopœial assistant Miss Elizabeth Kish. These experiments were performed upon three samples:

- A. Made in our laboratory by the recipe of U. S. P. IX;  
Magnesium carbonate, 15 Gm.; citric acid, 33 Gm. per 350-cc. bottle.
- B. Made in our laboratory by the recipe of U. S. P. X;  
Magnesium carbonate, 15 Gm.; citric acid, 35 Gm. per 350-cc. bottle.
- C. The commercial product cited above.

The results of assays of these three products are given below:

TABLE II.

Solution.	Free.	Total.	Solution.	Free.	Total.
A.	10.10	32.62	C.	10.00	29.20
	10.10	32.62		10.00	29.60
	10.10	32.71		10.00	29.56
B.	11.88	34.80	10.00	29.50	
	11.88	34.33	10.00	29.60	
	11.88	34.58			
	11.88	34.58			

In anticipation of litigation in which the accuracy of the "assay" was likely to be attacked, in 1928, with the assistance of Mr. C. H. Soren, we ran a series of MgO and citric acid determinations on four samples of solution of magnesium citrate made in our laboratory from three different samples of citric acid and two samples of magnesium carbonate. These chemicals were assayed prior to using them in preparing the several batches of solution and their percentage strengths are given below:

Magnesium Carbonate.		Citric Acid.	
Sample No.	MgO Content	Sample No.	$H_2C_6H_7O_7 \cdot H_2O$ Content.
1	40.8%	1 (efflorescent)	107.3%
2	39.9%	2	100.1%
		3	99.8%

The five samples of finished solution at the time of preparation gave the assay figures in Table III.

The effect of aging was studied in connection with the work; four of the samples being opened at intervals during four weeks, carefully stoppered after each opening and the contents assayed for both MgO and citric acid.

TABLE III.\*

Solution.	Solution (350 cc.) made from		Assay figures 350 cc. solution.		
	15 Gm. MgO.	35 Gm. Citric Acid.	H <sub>2</sub> C <sub>2</sub> H <sub>3</sub> O <sub>7</sub> . Free.	H <sub>2</sub> O. Total.	MgO.
A	No. 1	No. 2	12.63	35.5	1.88
B	No. 2	No. 1	14.97	37.2	1.81
C	No. 2	No. 3	14.7	34.07	1.85

As expected the MgO content remained practically stable. The citric acid figures are given below:

TABLE IV.\*

Sample No.	Gms. total Citric Acid per 350-cc. bottle.			
	Fresh.	After 1 week.	After 2 weeks.	After 4 weeks.
A	35.5	34.8	35.0	34.8
B	37.2	36.5	36.0	34.2

\* The work reported in Tables III and IV, being somewhat hurried, will be repeated in more extended fashion by one of us (H. H. S.) during the coming year.

The foregoing table indicates that while deterioration occurs when solution of magnesium citrate is kept for four weeks in a partially filled bottle at room temperature, this deterioration is less than ten per cent.

There have been some questions raised as to the effect of heat during ashing upon the ash titration and upon the subsequent calculation of citric acid content. As all of our ashing operations are carried on in a muffle oven and as the differentiation between dull red heat, red heat and white heat is easily discernable, in such ovens, we assayed the batches of the same sample both at "dull red heat" prescribed by the Pharmacopœia and also at white heat. The sample, purchased from a high-grade prescription pharmacy, assayed for MgO, on three runs gave 1.80, 1.80 and 1.78 per cent; the free acid titrations ran (for 10 cc.) 11.0, 11.2 and 11.0 cc. of *N*/2 NaOH. The figures for the titrations of the ash follow:

TABLE V.

Dull red heat 1 hour.	Expressed in terms of Gm. per 350-cc. bottle.		
	White Heat 1/2 hour.	White Heat 1 hour.	White Heat 2 hours.
36 Gm.	35.4 Gm.	31.6 Gm.	31.0 Gm.

This indicates that the "dull red heat" direction of the Pharmacopœia must be observed but that even white heat for one-half hour does not produce more than a 2 per cent discrepancy.

## COMMENTS ON THE TEST.

The work on aging and on heat of ashing were performed in preparation of litigation involving one of the manufacturers of solution of magnesium citrate who defied the citric acid assay of U. S. P. X. Prosecutions based upon six sub-standard samples (total citric acid content of 350-cc. bottles being 29.75, 30.5, 30.5, 31.0, 31.0 and 31.0 Gm., respectively) were instituted and the defense put up a vigorous fight based upon:

- (a) Value of the "assay" in general.
- (b) Possible blunders in manipulations of the chemist.

(c) Possibility of deterioration between the time the samples were purchased and the time the chemist began the actual assay (some three days interval having elapsed between time of purchase and beginning of assay).

(d) Difficulty in establishing the variable factor "dull red heat."

All of these points were successfully met by the two chemists appearing for the State and a verdict of "guilty" was brought in by the jury. It is true the "guilty" verdict was applied only to the three lowest samples while "acquittal" was registered for the three 31-Gm. samples but the split verdict represented a question of equity and the outcome of the trial was a complete victory for the "assay" itself.

As mentioned in the beginning of this paper the citric acid "assay" should at its best be considered as a test for limits of free and total acidity. As to "free acidity" our experience is that standard set (10 cc. of the official solution should require not less than 9.5 cc. of  $N/2$  NaOH) is a trifle severe. The extremely broad standard set for magnesium carbonate (not less than 39.2 per cent of MgO) plus the fact that much of the pharmacopœial carbonate runs considerably over 40 per cent is reflected in the high MgO content of samples of solution of magnesium citrate. Thus results shown in Table III

MgO Content of the Carbonate.	MgO Content of the Citrate Solution (per 100 cc.).	
40.8%	1.88	1.88
39.9%	1.81	1.85

indicate not only that the 1.50 Gm. MgO content per 100 cc. is markedly low but furthermore that when a carbonate of high MgO content is employed the degree of free acidity will fall, at times below the U. S. P. limit.

*We therefore recommend that in the monograph in U. S. P. XI the words "minimum of acidity" be omitted and that the test stands as indicating "minimum of total citric acid" only.*

Dr. Joseph L. Mayer, deviser of the original "assay," has publicly protested against certain pharmacopœial modifications, which he claims lessen the value of the test. In Dr. Mayer's main objection, the present writers concur. The wording of the "assay" on page 219 of U. S. P. X provides for the evaporation and ashing of the neutralized fluid and then states "proceed as directed under the assay for alkali salts of organic acids, page 431." Reference to page 431 shows that the residue is to be treated with water and then titrated with  $N/2$   $H_2SO_4$ , using methyl orange as indicator. Dr. Mayer's original procedure was to dissolve this residue in an excess quantity of  $N/2$   $H_2SO_4$  and then titrate the fluid (after removal of  $CO_2$  by boiling) with  $N/2$  NaOH, using phenolphthalein as indicator. We agree with Dr. Mayer that his procedure is better than that of the Pharmacopœia; we actually follow this more accurate procedure in our routine analyses of this pharmaceutical; and we hope that the next Revision Committee will direct this vastly superior "residual titration" method for the direct titration now provided.

There has been much (and just) criticism of the action of the U. S. P. Revision Committee in increasing the amount of citric acid in Solution of Magnesium Citrate from the 33 Gm. per 350 cc. standard provided in U. S. P. IX to the 35 Gm. standard of U. S. P. X. While this phase of the magnesia situation is beyond

the limits of this paper, we have no hesitation in saying that as yet no explanation from advocates of the change have appeared valid to us. The argument most frequently stressed, the argument that the addition of another two grams of citric acid prevents precipitation, is, in our opinion, based upon faulty reasoning. The true solution of the precipitation problem is solved by two factors: (a) complete sterilization of the finished solution (including bottles and stoppers) and (b) proper sealing of the bottle. We therefore express the hope that the next Revision Committee will direct the lessening of the citric acid content of the solution to 33 Gm. per 350 cc.

#### CONCLUSIONS.

1. The test for limit of total acid in Solution of Magnesium Citrate has stood the scrutiny of hundreds of analyses and has withstood the fires of the rigidly critical cross examination of litigation.
2. That part of the test relating to "minimum of acidity" is somewhat too severe, is unnecessary and should not be mentioned in the monograph of U. S. P. XI.
3. Statements as to the rapid loss of citric acid by decomposition after the bottle is opened are not borne out by data given in this paper.
4. The pharmacopœial requirement as to ashing *at dull red heat* should be observed. However, heating to white heat for one-half hour does not seriously affect the "assay."
5. The alkalinity of the resultant ash should be determined by residual titration rather than by the direct titration method given on page 431 of U. S. P. X.
6. It is our opinion that the increase of the citric acid content of the 350-cc. bottle of Solution of Magnesium Citrate from the 33 Gm. of U. S. P. IX to the 35 Gm. of U. S. P. X was inadvisable and unnecessary.

#### ACKNOWLEDGMENTS.

Our thanks are due to our assistants (1917-1929), H. J. Goeckel, Elizabeth Kish Schaefer, C. H. Soren and Harry Koslowsky, for their valuable aid in obtaining much of the analytical data upon which this paper is based.

COLLEGE OF PHARMACY, COLUMBIA UNIVERSITY,  
April 30, 1930.

---

## EXPERIMENTAL INVESTIGATIONS CONCERNING THE STANDARDIZATION AND THE PHARMACOLOGY OF HEART TONICS.\*

(With a New Assay Method.)

BY WILLIAM NYIRI, M.D., AND LOUIS DUBOIS.

During the last two years we have carried out research work on heart tonics at the Rutgers College of Pharmacy in Newark, N. J., and we take the liberty to report, briefly, on the results of our investigations, giving you the principal points

---

\* Scientific Session, A. Ph. A., Baltimore, Md., 1930.