A—Stirred for 30 minutes with mechanical stirrer.
B—Stirred vigorously for 5 minutes, then stirred at 5 minute intervals for 1 hour, and let stand until clear.
C—Stirred vigorously for 10 minutes, then as in B.

The assay for sodium bromide showed the presence of 7.898 Gm. of sodium bromide per 100 cc. of Elixir (average of results) which is 98.7 per cent of the theoretical, and is equivalent to 6.134 Gm. of bromine. The assay for ammonium bromide showed the presence of 7.984 Gm. of ammonium bromide per 100 cc. of Elixir (99.8 per cent of theoretical), equivalent to 6.513 Gm. of bromine. The total bromine content per 100 cc. of Elixir was found to be 18.038 Gm. of bromine. Bromine present as potassium bromide = 18.038 Gm. − (6.134 + 6.513) Gm., or 5.391 Gm. of bromine; which is equivalent to 8.027 Gm. of potassium bromide. The value found for this salt is 100.3 per cent of the theoretical.

DISCUSSION.

In the determination of sodium the stirring must be quite vigorous at all times to obtain a quantitative precipitation of the complex. The employment of the first filtrate as a transferring agent minimizes the use of alcohol. In the official assay the National Formulary provides 50 cc. of N/10 silver nitrate to assay an aliquot containing a maximum of 0.250 Gm. of mixed bromides equivalent to 23.6 cc. of the silver solution. As this is an excess greater than 100 per cent, the amount of N/10 silver nitrate employed was reduced to 30 cc.

The estimation of potassium bromide yields results in good agreement with the theoretical.

SUMMARY.

A procedure is recommended for the determination of ammonium bromide and sodium bromide and the estimation of potassium bromide in the Elixir of Three Bromides National Formulary VI.

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A STUDY OF MASTIC IN THE PREPARATION OF ENTERIC MEDICAMENTS.*[1]

BY F. S. BUKEY[2] AND C. J. KLEMME.[3]

The object of this study was to determine the efficiency of mastic-talc and mastic-magnesium stearate as enteric coating materials. The use of talc as a drying agent is of common commercial practice in the application of an enteric coating. In one part of this study, magnesium stearate was used in place of talc, as it was

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believed that it would serve the same purpose and in addition be directly useful in the enteric coating, since it would be converted in the stomach to stearic acid. Careful attention was paid to possible commercial adaptation of the coating methods used in this study. The efficiency of these coatings was determined by radiographic methods similar to those previously reported by Bukey and co-workers.

A pill of barium sulfate, $^{9}/_{32}$ inch in diameter, was the form of medicament used. The mastic was of pharmaceutical grade and in order to insure a clean product was dissolved in ether, filtered and the ether removed by evaporation on a steam-bath. The mastic solution used for coating was 25 per cent dissolved in methyl propyl ketone. A laboratory size coating pan was used.

In preparing the pills with the mastic-talc coating, a desired number were placed in a rotating pan and then thoroughly wet with the mastic solution. The rotating pills were prevented from massing as the solvent evaporated by the addition of small amounts of finely powdered talc. Five coats of the resin applied in this way were necessary before tests in 0.3 per cent hydrochloric acid indicated sufficient durability to warrant a radiographic examination. It was found on weighing lots of twenty-five pills that they had increased in total weight 0.40 Gm.

The application of the mastic-magnesium stearate was similar to that just described. Considerable care must be taken not to add too much magnesium stearate to the rotating pills when they begin to mass in the pan, otherwise they will become lumpy. Since this combination does not dry as rapidly as mastic-talc, it was necessary to thoroughly dry the pills before the application of the next coat. Six coats were necessary before the hydrochloric acid test indicated sufficient durability. It was found in the case of this coating that the average for lots of twenty-five pills was an increase in total weight of 0.26 Gm.

The radiographic study was first made on the mastic-talc and then the mastic-magnesium stearate coating. The results were based on one hundred experiments in each case. Fifty subjects were selected and duplicate experiments were conducted for both coatings. These individuals ingested 400 pills and in making the radiographic study, 936 radiographs were taken.

In making the radiographic study of the mastic-talc coating, the experiments were conducted, in most cases, over a period of fifteen hours. Some pills had shown no signs of disintegration by the end of this time so they were located and listed as undetermined. It will be noted in the tables that the most of these pills were well advanced in the alimentary tract at this hour. Table I gives, in a condensed form, the results obtained for this coating. The calculation of percentage was based on the total number of pills ingested. These values were determined for the

TABLE I.

Pills Which Disintegrated.

Stomach	15 pills	7.5 per cent
Small Intestine	26 pills	13.0 per cent
Ascending Colon	71 pills	35.5 per cent
Transverse Colon	11 pills	5.5 per cent
Descending Colon	13 pills	6.5 per cent
Total	136 pills	68.0 per cent

Pills of Undetermined Location at Time of Disintegration.

Stomach	8 pills	4.0 per cent
Small Intestine	5 pills	2.5 per cent
Ascending Colon	28 pills	14.0 per cent
Transverse Colon	14 pills	7.0 per cent
Descending Colon	8 pills	4.0 per cent
Lost	1 pill	0.5 per cent
Total	64 pills	32.0 per cent

various locations, both for the pills that disintegrated and for those for which the location of the point of disintegration was undetermined when the last radiograph was taken.

If one considers the efficiency of an enteric coating as the percentage disintegration in the intestinal tract, then the efficiency of the mastic-talc coating would be 60.5 per cent. Since the highest percentage, 35.5 per cent, disintegrated in the ascending colon, and only 13.0 per cent in the stomach, one might consider this mixture as a relative efficient material. On the other hand, 27.5 per cent of the pills remained undetermined in the intestinal tract for a period too long for proper medication. If one assumed that the bulk of any medicament is absorbed through the small intestine or ascending colon, then the enteric efficiency of a coating should be based on disintegration in these two regions. Applying this theory of efficiency to the mastic-talc coating, it was found to have a value of 48.5 per cent. Although this idea of determining percentage efficiency has not been used, it would seem to be the logical approach to the problem.

Table II was compiled from the data collected on the mastic-magnesium stearate experiments over the fifteen hour period.

TABLE II.

Pills Which Disintegrated.

Stomach	60 pills	30.0 per cent
Small Intestine	77 pills	38.5 per cent
Ascending Colon	48 pills	24.0 per cent
Transverse Colon	3 pills	1.5 per cent
Total	188 pills	94.0 per cent

Pills of Undetermined Location at the Time of Disintegration.

Stomach	3 pills	1.5 per cent
Small Intestine	1 pill	.5 per cent
Ascending Colon	4 pills	2.0 per cent
Descending Colon	2 pills	1.0 per cent
Lost	2 pills	1.0 per cent
Total	12 pills	6.0 per cent

A comparison of these tables shows that the mastic-magnesium stearate coating was more efficient than the mastic-talc. This statement is based on the fact that a higher percentage of pills disintegrated in the small intestine and fewer in the transverse colon. There were fewer pills undetermined and of these only six were in the colon at the time of the last radiograph. It would seem that these advantages would more than compensate for the increased disintegration in the stomach.

SUMMARY.

1. That the efficiency of the mastic-talc coating was found to be 48.5 per cent as compared with 62.5 per cent for mastic-magnesium stearate.

2. That the efficiency of the mastic-talc coating was not sufficiently high to warrant its recommendation for use on enteric medicaments. However, it must be remembered that this material has a higher efficiency value than such material as shellac, shellac-salol, which are in common commercial use.

3. That the efficiency of mastic-magnesium stearate as an enteric coating material was sufficiently high to warrant its recommendation to the pharmaceutical manufacturers.

4. That both the mastic-talc and the mastic-magnesium stearate coating were applicable to factory methods in which the coating pan is used.

5. That a high-boiling solvent such as methyl propyl ketone (B. P. 102° C.) was a better solvent for the mastic than the more volatile solvents, such as acetone (B. P. 56.5° C.) since the higher boiling solvent did not produce blisters in the coating.

6. That it is possible to determine the entirety of an enteric coating from the weight of the enteric material adhering to the pill, capsule or tablet, assuming they were uniform in size. The determination was based on the average gain in weight for lots of twenty-five or more pills, capsules or tablets.

7. That for a better degree of enteric efficiency, it was found advisable to make this determination from the number of pills disintegrating in the small intestine and the ascending colon, since absorption from the transverse and descending colons would not be as complete.

SULFANILAMIDE ADDITION COMPOUNDS WITH CINCHONA-ALKALOIDS.*

BY E. H. STUART, H. M. POWELL, C. L. ROSE AND F. E. BIBBINS.*

In 1935 Domagk (1) announced that certain azo dye derivatives were specific remedies in the treatment of infections by beta hemolytic streptococcus. Out of this work came *p*-aminobenzenesulfonamide, officially named by the Council on Pharmacy and Chemistry of the American Medical Association, "Sulfanilamide" (2). This compound has proven to be one of the outstanding developments in the field of chemotherapy during recent years. There has been an increasing amount of evidence with regard to the extraordinary effectiveness of sulfanilamide against various infections with the result that it is now reported as having been tried in the treatment of a great variety of diseases, including malaria.

The chemotherapeutic action of the sulfanilamide compounds on malaria reported in the literature are both favorable and unfavorable although the total number of favorable case reports far exceed the unfavorable ones. Hill and Goodwin, Jr., (3) reported on the use of 2,4-di-aminoazobenzene-4′-sulfonamide (4) in one hundred cases of plasmodium vivax malaria with beneficial results. Read and Pino (5) used 2,4-diaminoazobenzene-4′-sulfonamide in three cases of plasmodium

* From the Control Laboratories, Eli Lilly and Company.