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DETERMINATION OF THE REASONABLE OR PERMISSIBLE
 MARGIN OF ERROR IN DISPENSING. III. SUPPOSITORIES.*

BY MARVIN J. ANDREWS.¹

INTRODUCTION.

This, the third of a series of papers reporting the results of investigations made to determine what may be taken as the permissible margin of error in dispensing,² deals with suppositories.

Suppositories called for on prescriptions are usually prepared by mixing the active ingredients with the base in the solid state, then dividing and shaping

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¹ In collaboration with A. G. DuMez, Professor of Pharmacy, School of Pharmacy, University of Maryland. ² *JOUR. A. PH. A.*, 22 (1933), 755, 838; 23 (1934), 350, 421.

the resulting mass by hand; or by mixing the active ingredients with the melted base and pouring the mixture into molds to solidify. It is only in rare instances that suppositories are made by machine in the drug store. The vehicles commonly employed are cacao butter, glycerinated gelatin or sodium stearate.

For the purpose of this study, a typical suppository prescription was selected for compounding, and the suppositories were made by hand. Preparation of the suppositories by the other methods mentioned was not attempted as it appeared that these methods offered no additional possibilities for error, except the one due to a variation in the capacity of the individual molds. To discover if there was any appreciable variation in the capacities of the molds and to determine the effect of various methods of filling upon capacity, several series of experiments were carried out in which cacao butter alone was used.

EXPERIMENTAL PART.

The Pharmacopœia of the United States, Tenth Decennial Revision, page 366, gives the following information under suppositories:

"For suppositories made with Oil of Theobroma the following general processes may be employed:

Take of

The Medicinal Substance, the prescribed quantity.

Oil of Theobroma, grated, a sufficient quantity.

"Reduce the medicinal substance, if dry, to a very fine powder, or, if an extract, soften it with an appropriate liquid, then mix it thoroughly in a mortar with about an equal weight of grated oil of theobroma, and incorporate the remainder of the oil of theobroma until a homogeneous, plastic mass is obtained, adding if necessary, a small quantity of expressed oil of almond or wool fat. Roll the mass on a graduated tile until a cylinder of the proper length is formed, divide this into the required number of equal parts, and with a spatula, or other mechanical aid, form them into the desired shape.

"If the process of fusion is preferred, mix the medicinal substance with about an equal weight of grated oil of theobroma, as directed above, then thoroughly incorporate it with the remainder of the oil of theobroma, previously melted by a gentle heat on a water-bath, in a suitable vessel provided with a lip. Allow it to cool to about 38° C., and when the mixture begins to congeal, pour it immediately into suitable well-cooled molds. Keep the molds at a freezing temperature until the suppositories have hardened and are ready to be removed.

"Rectal suppositories should be cone shaped, and when made from oil of theobroma should weigh about 2 Gm."

Based on this information three series of tests were made. The first series of tests was carried out to determine the variation in weight and length of hand-made suppositories. The objective of the second series of tests was to determine the variation in capacities of the suppository molds used in the City of Baltimore in terms of cacao butter. The purpose of the third series of tests was to determine the effect, if any, of different methods of filling on the capacity of suppository molds.

With the first objective in view, the following prescription was filled, the suppositories being formed by hand.

℞ No. 1

Ext. Bellad.

Gm. 0.163

Pulv. Gall.

Gm. 1.300

Ol. Theobrom. *qs.*

Gm. 20.000

M. et ft. Supp. No. 10

In the actual performance of these tests, the suppository prescription was filled by 100 members of the senior class in dispensing pharmacy at the School of Pharmacy of the University of Maryland under working conditions described in the first paper. The completed suppositories were checked for accuracy with respect to weight by using a prescription balance, and for accuracy with respect to length by using a millimeter ruler. The standard deviation was computed from the results obtained.

In tests made to determine the variation in weight of suppositories prepared by hand, the students were instructed to follow the method outlined in the Pharmacopœia. In some instances a few drops of expressed oil of sweet almond, castor oil or a few grains of wool fat were added to the grated cacao butter. The suppository pipe was rolled and cut on a graduated tile. Some were prepared without the use of a dusting powder, while in others lycopodium or filter paper was used in the process of manufacture. The students were directed to make the suppositories cone shaped and to make them as near 25 mm. in length as possible.

The results of this series of tests are presented in Tables I and II.

TABLE I.—STANDARD DEVIATION IN WEIGHT OF SUPPOSITORIES MADE BY HAND.

Batch Number.	Av. Wt. in Gm.	S. D. in Gm.	Batch Number.	Av. Wt. in Gm.	S. D. in Gm.
1	1.791	0.106	51	1.774	0.151
2	1.946	0.079	52	1.954	0.133
3	2.025	0.401	53	2.130	0.291
4	2.009	0.066	54	2.183	0.064
5	1.713	0.160	55	1.677	0.114
6	1.840	0.189	56	2.047	0.068
7	2.236	0.167	57	1.631	0.318
8	2.049	0.413	58	2.157	0.353
9	1.952	0.045	59	2.015	0.029
10	2.068	0.095	60	1.915	0.143
11	2.117	0.210	61	1.867	0.067
12	1.911	0.063	62	2.054	0.178
13	1.555	0.354	63	2.349	0.314
14	1.710	0.205	64	1.863	0.046
15	1.999	0.182	65	2.094	0.167
16	2.034	0.166	66	1.982	0.092
17	1.934	0.143	67	1.690	0.235
18	2.025	0.095	68	2.046	0.154
19	1.960	0.169	69	2.000	0.418
20	2.044	0.089	70	2.032	0.421
21	1.943	0.124	71	2.351	0.310
22	2.008	0.162	72	2.214	0.273
23	2.010	0.113	73	2.244	0.117
24	2.081	0.279	74	1.984	0.170
25	2.017	0.049	75	1.883	0.097
26	1.765	0.227	76	2.153	0.083
27	1.876	0.071	77	1.939	0.088
28	1.894	0.052	78	1.935	0.071
29	1.721	0.221	79	2.041	0.284
30	1.844	0.128	80	1.850	0.139
31	1.853	0.256	81	1.760	0.157
32	2.193	0.225	82	1.815	0.279
33	2.161	0.258	83	1.845	0.020
34	1.683	0.238	84	1.974	0.179

35	2.071	0.462	85	2.048	0.195	
36	1.683	0.252	86	2.036	0.229	
37	1.843	0.222	87	2.039	0.133	
38	1.959	0.090	88	1.979	0.183	
39	1.819	0.134	89	1.638	0.039	
40	2.256	0.235	90	1.863	0.067	
41	1.905	0.084	91	1.880	0.126	
42	2.051	0.085	92	1.860	0.155	
43	1.886	0.194	93	1.994	0.126	
44	1.962	0.210	94	1.877	0.269	
45	1.942	0.189	95	2.008	0.192	
46	1.919	0.122	96	1.940	0.214	
47	2.064	0.049	97	2.185	0.451	
48	1.913	0.065	98	1.926	0.061	
49	1.830	0.188	99	1.873	0.093	
50	2.176	0.121	100	2.121	0.119	
				Average	1.959	0.172

In Table I it will be observed that in the case of the weight of the individual suppositories, the average standard deviation is 0.172 Gm., or 8.81 per cent based on the average weight. Fifty-eight of the batches compounded fall within the average standard deviation of 0.172 Gm., thirty-four fall within twice the average standard deviation, or 0.344 Gm., while eight fall within three times the average standard deviation or 0.516 Gm.

TABLE II.—AVERAGE LENGTH AND AVERAGE STANDARD DEVIATION IN LENGTH OF SUPPOSITORIES MADE BY HAND.

Number of Batches of Suppositories Prepared.	Average Length of Suppositories Prepared.	Average S. D. in Millimeters.
100	25.76 mm.	0.831

In Table II, it will be observed that in the case of the length of the individual suppositories the average standard deviation is 0.831 millimeters, or 3.30 per cent when based on the average length. On studying the original results it was noted that fifty-one of the batches compounded fell within the average standard deviation of 0.831 mm., forty-two fell within twice the average standard deviation, or 1.662 mm., while the remaining seven fell within three times the average standard deviation, or 2.493 mm.

For the purpose of making it possible to compare the results presented in Tables I and II with similar data that may have been published, but which have not been expressed in terms of the standard deviation, the per cent of deviation from the theoretical has been calculated and is given in Tables III and IV.

TABLE III.—PERCENTAGE DEVIATION OF HAND-MADE SUPPOSITORIES FROM THE THEORETICAL WEIGHT OF 2 GRAMS.

Batch Number.	Average Weight in Gm.	Number of Suppositories in Each Batch That Deviate from the Theoretical by—				
		5% or Less.	From 5% Plus to 10%.	From 10% Plus to 15%.	From 15% Plus to 20%.	Over 20%.
1	1.791	2	5	2	1	..
2	1.946	10
3	2.025	4	...	2	3	1
4	2.009	9	1

5	1.713	...	1	5	2	2
6	1.840	2	3	1	1	3
7	2.236	4	3	1	1	1
8	2.049	2	4	3	...	1
9	1.952	5	3	1	1	..
10	2.068	4	1	...	4	1
11	2.117	4	1	3	2	..
12	1.911	8	1	1
13	1.555	1	...	3	2	4
14	1.710	5	3	1	1	..
15	1.999	4	2	4
16	2.034	4	4	1	1	..
17	1.934	7	1	1	1	..
18	2.025	8	1	1
19	1.960	2	6	1	1	..
20	2.044	8	2
21	1.943	6	3	1
22	2.008	6	1	2	1	..
23	2.010	5	4	1
24	2.081	1	8	1
25	2.017	8	2
26	1.765	2	3	3	2	..
27	1.876	9	1
28	1.894	4	4	1	1	..
29	1.721	3	1	1	1	4
30	1.844	6	...	2	2	..
31	1.853	2	2	3	2	1
32	2.193	4	4	2
33	2.161	1	...	5	4	..
34	1.683	...	1	2	1	6
35	2.071	4	...	3	1	2
36	1.683	1	3	...	2	4
37	1.843	5	2	1	2	..
38	1.959	5	4	1
39	1.819	3	3	2	1	1
40	2.256	1	3	...	5	1
41	1.905	...	6	4
42	2.051	7	3
43	1.886	4	3	1	1	1
44	1.962	4	1	3	2	..
45	1.942	3	1	4	1	1
46	1.919	3	4	2	...	1
47	2.064	9	1
48	1.913	7	3
49	1.830	2	6	2
50	2.176	6	2	1	...	1
51	1.774	2	2	2	3	1

Number of Suppositories in Each Batch That Deviate from the Theoretical by—

Batch Number.	Average Weight in Gm.	5% or Less.	From 5% Plus to 10%.	From 10% Plus to 15%.	From 15% Plus to 20%.	Over 20%.
52	1.954	4	3	1	2	..
53	2.130	6	2	...	1	1
54	2.183	1	4	2	3	..
55	1.677	...	1	1	6	2
56	2.047	6	3	1

57	1.631	2	2	6
58	2.157	3	3	2	2	..
59	2.015	1	3	5	1	..
60	1.915	6	2	1	1	..
61	1.867	5	3	2
62	2.054	5	4	1
63	2.349	2	2	2	...	4
64	1.863	3	4	...	1	2
65	2.094	4	3	2	...	1
66	1.982	6	4
67	1.690	...	1	3	4	2
68	2.046	4	3	3
69	2.000	1	5	...	2	2
70	2.032	5	4	1
71	2.351	1	2	3	...	4
72	2.214	3	1	1	3	2
73	2.244	3	5	2
74	1.984	4	1	4	1	..
75	1.883	6	3	1
76	2.153	3	5	2
77	1.939	5	4	...	1	..
78	1.935	9	...	1
79	2.041	...	6	4
80	1.850	4	4	...	1	1
81	1.760	2	2	2	2	2
82	1.815	5	1	1	2	1
83	1.845	...	10
84	1.974	3	3	4
85	2.048	3	3	1	3	..
86	2.036	7	2	1
87	2.039	6	2	2
88	1.979	3	5	1	1	..
89	1.638	2	7	1
90	1.863	2	5	3
91	1.880	6	3	1
92	1.860	7	2	1
93	1.994	5	4	1
94	1.877	4	3	2	1	..
95	2.008	3	4	3
96	1.940	6	3	1
97	2.185	4	1	1	...	4
98	1.926	6	3	1
99	1.873	4	4	2
100	2.121	3	3	2	2	..
Totals		395	271	155	102	77

The data presented in Table III show that for a total of 1000 hand-made suppositories prepared by 100 different operators, 66.6 per cent fall within a deviation of 10 per cent of the theoretical weight, 82.1 per cent fall within 15 per cent, while 92.3 per cent fall within 20 per cent.

VARIATION IN CAPACITY OF SUPPOSITORY MOLDS IN TERMS OF CACAO BUTTER.

A second series of tests was carried out to determine to what extent suppository molds used in retail pharmacies in the City of Baltimore varied in capacity.

TABLE IV.—PERCENTAGE DEVIATION OF HAND-MADE SUPPOSITORIES FROM THE THEORETICAL LENGTH OF 25 MILLIMETERS.

Number of Suppositories Prepared.	Number of Suppositories That Deviated from the Theoretical Length by—				
	5% or Less.	From 5% Plus to 10%.	From 10% Plus to 15%.	From 15% Plus to 20%.	20% or Over.
1000	624	214	124	37	1

The percentage deviation from the theoretical length of 25 millimeters show that 62.4 per cent fall within 5 per cent, 83.8 per cent fall within 10 per cent, 96.2 per cent fall within 15 per cent, while 99.9 per cent fall within 20 per cent.

For these tests, ten different sets of suppository molds were borrowed at random from retail drug stores and the capacities of the individual molds determined in terms of cacao butter.

To obtain the desired data, suppositories of cacao butter were prepared by fusion in each of the ten sets of molds borrowed. The melted cacao butter was cooled to the congealing point and then poured into the well-cooled molds. The excess was removed by running the edge of a spatula over the top of the molds immediately after the cacao butter had solidified. The individual suppositories were then weighed and the weights recorded.

A summary of the results of the second series of tests is given in Table V.

TABLE V.—CAPACITY OF SUPPOSITORY MOLDS IN TERMS OF CACAO BUTTER.

No. of Sets of Molds.	Av. Capacity in Gm.	S. D. in Gm.	No. of Sets of Molds.	Av. Capacity in Gm.	S. D. in Gm.
1	1.493	0.008	6	2.032	0.022
2	2.095	0.009	7	1.390	0.027
3	1.915	0.026	8	1.975	0.023
4	1.887	0.014	9	1.481	0.051
5	2.400	0.023	10	1.318	0.037
			Average	1.798	0.024

The data obtained in this series of tests show that the weight of individual suppositories made with the ten sets of borrowed molds range from a low of 1.255 Gm. (in mold No. 10) to a high of 2.440 Gm. (in mold No. 5), or a difference of 1.185 Gm.

The average capacity in grams in terms of cacao butter of all of the ten sets of suppository molds as shown in the table is 1.798 Gm., while the average standard deviation is 0.024 Gm. On further study of the table it will be observed that the deviations for six of the sets of molds fall within the average standard deviation of 0.024 Gm., three fall within twice the average standard deviation or 0.048 Gm., while only one falls within three times the average standard deviation or 0.072 Gm.

To make it possible to compare the results presented in Table V with similar data that may have been published but which have not been expressed in terms of the standard deviation, the per cent of deviation has been calculated.

The weights of the individual suppositories showed the variation from the average to be less than 5 per cent in every instance, except for the suppositories prepared with mold No. 9. In the latter case the weight of 90 per cent of the suppositories fell within 5 per cent of the average weight, while in the remaining 10 per cent there was a variation of 9.8 per cent from the average weight. On ex-

amination, it was discovered that some of the individual molds of this set were bored deeper than others.

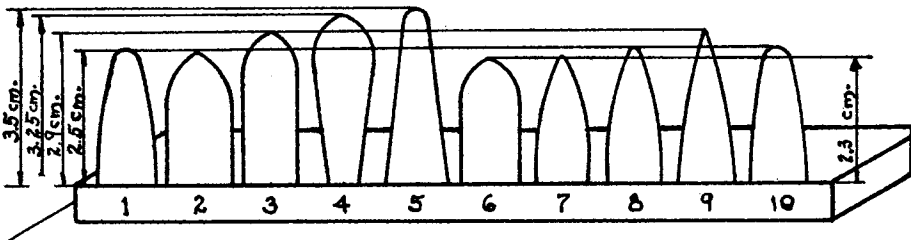
The per cent deviation from the theoretical weight of 2 Gm. of cacao butter has also been calculated, the results are given in Table VI.

TABLE VI.—PERCENTAGE DEVIATION BASED ON THE THEORETICAL WEIGHT OF 2 GM. OF CACAO BUTTER.

No. of Sets of Molds.	5% or Less.	Percentage of Individual Suppositories Deviating from 2 Gm. by—				
		From 5% Plus to 10%.	From 10% Plus to 15%.	From 15% Plus to 20%.	From 20% Plus to 25%.	25% or More.
1	60%	40%
2	87.5%	12.5%
3	75.0%	25.0%
4	50.0%	50.0%
5	62.5%	37.5%
6	100%
7	40.0%	60%
8	100%
9	40.0%	60%
10	100%

The variation in length and the difference in shape of the suppositories prepared with the ten sets of suppository molds used are shown in Table VII.

TABLE VII.—VARIATION IN LENGTH AND SHAPE OF SUPPOSITORIES PREPARED IN THE 10 SETS OF MOLDS.



EFFECT OF DIFFERENT METHODS OF FILLING ON THE CAPACITIES OF SUPPOSITORY MOLDS.

A third series of tests was carried out to determine to what extent, if any, the capacity of suppository molds is affected by the method of filling. With this objective in view suppositories of cacao butter were prepared in the same mold by each of the following methods:

1. Melting and pouring cacao butter into well-chilled molds.
2. Preparing rough suppositories by hand, then forcing them into the mold to obtain a uniform shape.
3. Preparing suppositories by compression in a suppository machine.

The results of this series of tests are presented in Table VIII.

TABLE VIII.—EFFECT OF THE METHOD OF FILLING ON THE CAPACITIES OF SUPPOSITORY MOLDS.

Method of Preparation.	Capacity in Gm. of Cacao Butter.				Average Capacity in Gm.	S. D. in Gm.	Per Cent Deviation.
	1.	2.	3.	4.			
Melting and pouring into mold	2.300	2.305	2.305	2.285	2.298	0.008	0.34%
Massed and forced into mold	2.200	2.220	2.300	2.225	2.236	0.037	1.70%
Made by compression in machine	2.395	2.390	2.380	2.345	2.377	0.019	0.79%

An examination of the results in Table VIII shows that the method of filling has a definite influence upon the capacities of suppository molds. Based on the results obtained it may be stated that the capacity in grams of cacao butter, beginning with the smallest and ending with the largest, varies in accordance with the following order of arrangement: (1) Suppositories prepared by hand and then forced into the molds to shape; (2) suppositories prepared by melting the ingredients, then pouring into well-chilled molds and allowing to solidify and (3) those made by compression in a suppository machine. Likewise, it will be found that the greatest variation in weight occurs in the suppositories prepared by hand and forced into the molds to shape, while the most uniform are those prepared by fusion.

The variation in capacity due to a difference in the method of filling the molds as observed in the above tests was surprisingly small being less than 2 per cent for all suppositories except in the case of those prepared by hand and then forced into the molds when it was less than 3.5 per cent. All of the suppositories in this series fall within twice the standard deviation.

CONCLUSIONS.

1. The weight of suppositories prepared by hand varies with the working temperature, the technique of the individual operator and the size and shape of the suppository to be prepared.

2. The results of the first series of experiments show that 92 per cent of a total of 1000 different suppositories prepared by 100 different operators fall within twice the average standard deviation for weight of 0.344 Gm. This corresponds to a variation of 17.2 per cent when based upon the theoretical weight of 2 Gm.

3. The results of our experiments showed that there is no greater variation in length than in weight of suppositories made by hand if a definite length is decided upon. In ordinary practice, however, this is not true as there are no official standards for length, and each pharmacist makes his own standards.

4. Individual suppositories in a set of molds do not vary in capacity beyond reasonable limits. There was observed, however, a great variation in the capacity of the sets of suppository molds as used in different retail drug stores. The latter variation is believed to be due to the fact that the manufacturers of suppository molds do not have any definite specifications to follow.

5. A difference in the method of filling was observed to have an appreciable effect upon the capacities of suppository molds.

(To be continued.)

THE OPENING SESSION.

Time has once more brought us round to the renewal of those medical studies of which pharmacy is a branch. Year by year it assumes a more definite character; and the period is not far distant when both in teaching and in practice it will occupy an independent place. At Bloomsbury Square, where official pharmacy is enshrined, history was seen to repeat itself; there was the same crowd of visitors and friends to welcome successful candidates; the same band of young aspirants who had gained distinction; the same professional congratulations; and a lecturer to give the accustomed introduction address. Retrospect of Fifty Years Ago.—*The Chemist and Druggist*, October 15, 1884.