WHY HAND-MOLDED HYPODERMIC TABLETS VARY.*

BY S. WALLEY BOWER.

In a previous paper, dealing with variations in Hand-Molded Hypodermic Tablets,[1] it was shown that the variations in the molding of Morphine Sulphate Tablets ranged from 3.63% over strength to 7.67% under strength.

It was thought desirable to consider the subject more in detail to determine what variations occurred in hypodermic tablets other than those of morphine sulphate. Inasmuch as the morphine sulphate mass to make these tablets consisted of from 50 to 90 per cent of sieved morphine sulphate, it was considered advisable to take for comparison, tablets, the mass of which consisted principally of milk sugar, with very small quantities of medicinal ingredients. This would make it possible to determine whether the densities of the powders entering into the various tablet masses made an appreciable difference with the errors in the final results.

The tablets selected for this study were Atropine Sulphate, $^1/_{100}$ grain, Strychnine Sulphate, $^1/_{60}$ grain, and Scopolamine Hydrobromide, $^1/_{100}$ grain. Thus, for comparison, different conditions were obtained as to the densities of the ingredients, the morphine sulphate being of a much lighter density than the sugar of milk in the tablets now to be considered.

These tablets were hand made, a steel plate with 200 perforations being used, thus turning out 200 tablets with each molding. The yields obtained in the pressing of these tablets, also the variations from the theoretical are shown in Table I.

The figures in the first column represent the number of finished tablets calculated to be made from the tablet mass, and called the theoretical. The second column shows the number of tablets obtained upon completion of the molding, while the third shows the count over or under theoretical. The last column represents the error in per cent of each lot, taken as a single unit. Considering the theoretical as one hundred per cent, those producing an over yield of tablets will be shown naturally as being under the theoretical, while those having an under yield will be shown as having a percentage over the theoretical.

TABLE I.—ERROR IN YIELD BASED ON THEORETICAL.

Atropine Sulphate.	Theoretical.	Yield.	Over or under Theoretical.	Per Cent.
Lot 1	56,000	53,602	2,398 under	104.47
2	56,000	56,315	315 over	99.44
3	28,000	27,583	417 under	101.51
Strychnine Sulphate.				
Lot 1	70,000	73,132	3,132 over	95.74
2	70,000	70,090	90 over	99.87
3	70,000	69,070	930 under	101.35
Scopolamine Hydrobromide.				
Lot 1	21,000	21,215	215 over	98.99
2	21,000	20,800	200 under	100.96
3	21,000	20,330	670 under	103.30

* Section on Practical Pharmacy and Dispensing, Washington meeting, 1934.

[1] JOUR. A. PH. A., 23 (1934), 36–40.

The tablets of each lot were counted into as many complete divisions of 500 tablets as possible. Each 500 was now weighed to obtain the highest and lowest 500 tablets in weight of the several lots. This high and low were then compared with the theoretical weight of 500 tablets of the corresponding lot, and the percentage error computed. This error is shown in Table II. Also the percentage variation of each entire lot is repeated in the last column to afford an easy comparison with reference to this high and low per cent.

TABLE II.—COMPARISON OF HIGH AND LOW OF 500 TABLETS.

Atropine Sulphate.	High Per Cent.	Low Per Cent.	Difference.	Per Cent Variation in Entire Lot.
Lot 1	105.23	101.22	4.01	104.47
2	102.95	100.07	2.88	99.44
3	100.22	97.69	2.53	101.51
Strychnine Sulphate.				
Lot 1	96.89	92.99	3.90	95.74
2	99.14	95.78	3.36	99.87
3	101.67	100.06	1.61	101.35
Scopolamine Hydrobromide.				
Lot 1	98.85	97.22	1.63	98.99
2	101.87	97.02	4.85	100.96
3	103.90	100.05	3.85	103.30

The 500 high tablets and the 500 low tablets of each lot were now subdivided into five parts of 100 tablets each and weighed. From the 500 high tablets, the weight of the 100 tablets highest was noted. The error in per cent of these was determined as based on the theoretical. Also from the low 500 tablets, the weight of the 100 lowest was obtained, and its percentage error determined in the same manner.

This percentage of the high 100 tablets may be used to represent the greatest deviation from the theoretical on the plus side, and the percentage of the low 100 tablets, the greatest deviation from the theoretical on the minus side. As these two figures are the extreme limits of variation from the theoretical, the difference between these two percentages represents the variation in per cent of each lot of tablets.

TABLE III.—EXTREMES OF VARIATION.

Atropine Sulphate.	High Per Cent.	Low Per Cent.	Difference Per Cent.	Variation in 500 Per Cent.
Lot 1	105.57	100.92	4.65	4.01
2	103.47	99.92	3.55	2.88
3	100.40	97.39	3.01	2.53
Strychnine Sulphate.				
Lot 1	97.66	92.77	4.89	3.90
2	99.67	95.39	4.28	3.36
3	102.00	99.59	2.41	1.61
Scopolamine Hydrobromide.				
Lot 1	98.98	97.10	1.88	1.63
2	102.17	96.48	5.69	4.85
3	104.40	99.80	4.60	3.85

These results are shown in Table III. The first column shows the greatest variation from the theoretical on the plus side, of 100 tablets; column two, the

greatest variation from the theoretical on the minus side. The third column shows the difference of these extremes. The last column contains the difference in variation of the extremes of 500 tablets from the preceding table.

Commenting on this table, it will be seen that the difference in variation of each lot of tablets seems to remain quite constant; the percentage error depending upon the number of tablets produced from the several lots, as varying from the actual number of tablets to be made; and upon which each formula is based. While the extremes of variations of these tablets, which consist principally of milk sugar, seem to be less than those found in morphine sulphate tablets,[1] the difference is not so great, that a statement of fact can be made, as so many factors enter into human workmanship. A slight change in pressure of the operator in molding may change the entire calculation. However, these figures may be taken as a general average, covering a considerable period of time, and for control work are very satisfactory.

WHY TABLETS VARY.

Referring to Table I, this relationship can be noted more clearly. Those lots of tablets having an over yield in the number of tablets, show a percentage weight under the theoretical, which runs consistently throughout the entire lot. The same is true of those lots producing an under yield, as shown by the percentages over the theoretical.

As an example, let us consider the three lots of scopolamine hydrobromide. The mass of each was made from the same formula, namely, Scopolamine Hydrobromide, U. S. P., 210 grains; milk sugar, 10,500 grains. This mixture weighed 10,710 grains; to yield theoretically 21,000 tablets, each 100 to weigh 51 grains. The material entering into each mass was obtained from the same source of supply, and in the preparation passed through the same process. The tablets were molded by the same person, but at varying times. These facts being considered, similar yields of tablets should be expected. But instead of this, one mass produced 21,215 tablets; another 20,800 tablets and the third 20,330 tablets. The data covering scopolamine hydrobromide are collected in Table IV.

TABLE IV.—SCOPOLAMINE HYDROBROMIDE TABLETS.

Lot.	Yield.	Per Cent.	Extremes of 500 Tablets in Per Cent.	Extremes of 100 Tablets in Per Cent.
1	21,215	98.99	98.85 — 97.22	98.98 — 97.10
			Difference 1.63	Difference 1.88
2	20,800	100.96	101.87 — 97.02	102.17 — 96.48
			Difference 4.85	Difference 5.69
3	20,330	103.30	103.90 — 100.05	104.40 — 99.80
			Difference 3.85	Difference 4.60

A study of this table shows the difference in pressure exerted in molding, not only in the result of the entire lot, but in the component subdivisions as well. While the three lots, taken as single units, have variations in per cent of 1.01 under, 0.96 over and 3.30 over, respectively; the subdivisions show extremes in percentages of 1.88, 5.69 and 4.60, respectively.

This variation, both in yield and of the tablets in various lots, shows why a tolerance from the declared strength is necessary in the manufacture of tablets of

[1] JOUR. A. PH. A., 23 (1934), 40.

this nature. This tolerance should be sufficiently large to cover uncontrollable factors that enter into the molding, but not too large as to impair the accuracy of dosage.

This paper is not intended to offer any suggestions in the manufacture of hand-molded hypodermic tablets. It merely shows what variations take place in the molding of tablets by the comparison of various yields, and what problems confront the manufacturer, endeavoring to turn out a uniform product.

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DETERMINATION OF THE REASONABLE OR PERMISSIBLE MARGIN OF ERROR IN DISPENSING. IV. PILLS.

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(*Continued from page 1122, November Journal.*)

For the purpose of making it possible to compare the results presented in Tables Nos. I to III 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 average has been calculated and is given in Tables IV, V and VI.

TABLE IV.—PERCENTAGE DEVIATION FROM THE AVERAGE WEIGHT OF PILLS PREPARED IN FILLING PRESCRIPTION NO. 1.

Batch Number.	Av. Wt. of Batch in Gm.	Number of Pills in Each Batch That Deviate from the Average Weight by— 5% or Less.	From 5% Plus to 10%.	From 10% Plus to 15%.	From 15% Plus to 20%.	Over 20%.
1	3.969	8	2			
2	3.873	10				
3	4.110	3	3	4		
4	3.532	6	3	1		
5	4.300	5	1	2	2	
6	3.725	10				
7	3.870	8	1	1		
8	3.594	2	7	1		
9	3.875	10				
10	3.650	3	2	3	2	
11	3.600	9	1			
12	3.540	7	2			1
13	3.475	6	1	2	1	
14	3.700	1	7	2		
15	3.577	4	3	3		
16	3.685	6	3	1		
17	3.680	3	5	2		
18	3.750	7	3			
19	3.770	4	2	2	2	
20	3.538	4	6			
21	3.402	4	4	2		
22	3.620	10				
23	4.483	7	2	1		
24	3.932	9			1	
25	3.573	10				
26	3.570	8	1		1	