SCIENTIFIC SECTION

DETERMINATION OF THE REASONABLE OR PERMISSIBLE MARGIN OF ERROR IN DISPENSING. VI. ELASTIC FILLED CAPSULES.[*,1]

BY MARVIN J. ANDREWS.[2]

In the first five papers of this series, a study was made of the different types of prescriptions which the pharmacist usually compounds in his own laboratory. The five papers presented to date deal with (1) powders and capsules, (2) ointments, (3) suppositories, (4) pills and (5) liquids. This, the sixth paper, deals with elastic filled capsules.

Prescriptions calling for liquids or suspensions in capsules usually fall within one of three classes, that is, (1) liquids in hard gelatin capsules, (2) liquids to be placed in empty soluble elastic capsules, and (3) soluble elastic filled capsules prepared by manufacturing concerns. As the first two classes are seldom prescribed, the study in this paper is limited to the variation in weight of soluble elastic filled capsules prepared by different manufacturing concerns and dispensed by the retail pharmacist.

Elastic filled gelatin capsules are usually prepared commercially by one of the following methods: (1) the plate mold and press method or (2) rotary die process. Briefly, the first method consists of placing a warmed sheet or leaf of gelatin over the bottom mold, adding the correct weight or volume of medicament, covering this with a second sheet of gelatin followed by the top plate of the mold. The set of molds is then placed under a press and pressure applied. When the pressure on the press is released, and the top plate of the mold removed, the finished capsules are removed by stretching the net. The second, or the rotary die machine (see Remington's Practice of Pharmacy, 8th Edition, page 1687) is a self-contained unit which produces filled capsules continuously and automatically. Two continuous gelatin ribbons are brought between a pair of revolving dies and an injection wedge which adds the medicament, and as the die revolves, it seals and severs the filled capsule.

EXPERIMENTAL PART.

For the purpose of this study the different types of elastic filled capsules which the pharmacist is most frequently called upon to dispense, were divided into two general classes, namely: (1) liquids in transparent capsules and (2) suspensions in non-transparent capsules.

To discover if there was any appreciable variation in the weight of individual elastic machine filled gelatin capsules, three series of tests were carried out. The first series of tests was conducted to determine the variation in weight, if any, of transparent capsules prepared in the same capacity molds and filled with different liquids by the same manufacturer. The second series was limited to liquids in transparent capsules containing fish liver oils, made by the same and different manufacturers. The principal object of the third series was to determine the variation in weight of suspensions in non-transparent capsules. The capsules in each instance were weighed directly, capsule with contents, as it was impossible to completely remove the contents from the capsules.

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A definite letter was assigned to each manufacturer whose products were used in these series of tests.

SERIES I.

In the first series of tests 10 capsules were selected at random from boxes of the same lot, made by manufacturer A. The samples selected bore the following labels: (1) santal oil, 5㎎, (2) benzyl benzoate, 5㎎, (3) creosote carbonate, 5㎎, (4 and 5) a speciality product and (6) castor oil, 20㎎.

The results of the first series of tests are presented in Table I on page 376.

The tabulated data given in Table I shows there is a variation in weight of individual filled liquid capsules taken from the same batch made by the same manufacturer. Likewise, there is a variation in the different varieties of capsules made in the same mold as indicated by comparison. In number one to three, 5 minim mold, the standard deviation is lowest for No. 2, S. D. equals 0.019 Gm. corresponding to 3.93%, while the highest is No. 3 with a S. D. of 0.036 Gm. corresponding to 7.05%.

As the size of the capsule increases (No. 6) the S. D. increases with a decrease in the percentage deviation. Numbers 4 and 5 indicate there is also a variation in the weight of two different lots of the same proprietary product.

SERIES II.

In the second series of tests a selection was made of frequently used 3 minimum transparent elastic capsules containing fish liver oils made by the same and different manufacturers. Each sample of ten represents capsules of a definite lot. The contents and manufacturer of each sample are as follows: Numbers 7 and 8—Haliver Oil with Viosterol made by manufacturer B; numbers 9, 10, 11 and 12—Haliver Oil with Viosterol made by manufacturer C; numbers 13 and 14—fish liver oil made by manufacturer D and sold under a trade name, and lastly numbers 15 and 16 which contain standardized cod liver oil made and sold under a trade name by manufacturer E.

The results of the second series of tests are presented in Table II on page 376.

The greatest variation in the Haliver Oil with Viosterol elastic filled capsules was noted in sample number 10 with a standard deviation of 0.029 Gm. corresponding to 8.92%, while the smallest variation was number 7 with a standard deviation of 0.015 Gm. corresponding to 3.49%. The capsules containing fish liver oils and sold under a trade name, although slightly smaller, with the exception of number 13, proved to be more uniform than any of the others in this series. The minimum variation for the entire series was sample number 15 with a standard deviation of 0.004 Gm. corresponding to 1.37% while the highest variation was found to be sample number 10 with a standard deviation of 0.029 Gm. corresponding to 8.92%.

SERIES III.

The third series of tests was performed to determine the variation in weight, if any, of non-transparent capsules filled with a suspension in oil. For this series the popular brands of capsules containing combinations of vitamins A, B, D and G were selected.

The consistency of the contents of these samples varied from a relatively limpid liquid containing a suspension to a thin paste. To date we have not had sufficient replies from the manufacturers to make a definite statement as to what type machine these products were made in, neither do we know whether the medicaments were weighed or measured, with two exceptions—manufacturer A capsules are made on the plate mold and press machine, the medicament being measured, while those of manufacturer F were made on the Rotary Die machine. However, from general information, one would expect the variation to be slightly higher than in the case of transparent capsules filled with a clear liquid. The manufacturers of the products used are as follows: numbers 17, 18, 19 and 20, manufacturer B; numbers 21, 22 and 23, manufacturer C; number 24, manufacturer D; and numbers 25 and 26, manufacturer F.

The results of the third series of tests are presented in Table III on page 377.

The standard deviation for the individual lots of capsules made by the same manufacturer in the third series of tests is slightly higher than those in the second series. Different lots made by the same manufacturer are quite uniform, yet there is quite a variation between different manufacturers. The lowest variation in weight is found in number 25 with a standard deviation of

TABLE I.—VARIATION IN WEIGHT OF ELASTIC FILLED CAPSULES PREPARED BY MANUFACTURER A.

| Batch No. | Weight of Each Capsule in Gm. | | | | | | | | | | Av. Wt. in Gm. | S. D. in Gm. | % D.* | Number Falling within | |
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.				1 × S. D.	2 × S. D.
1	0.515	0.451	0.443	0.473	0.484	0.485	0.432	0.495	0.501	0.523	0.480	0.028	5.83	6	4
2	0.485	0.475	0.508	0.484	0.465	0.499	0.501	0.505	0.472	0.445	0.483	0.019	3.93	7	3
3	0.454	0.495	0.497	0.531	0.529	0.530	0.445	0.531	0.519	0.571	0.510	0.036	7.05	7	3
4	0.971	1.081	1.042	1.102	0.932	0.986	0.926	1.041	1.018	1.061	1.016	0.057	5.61	6	4
5	1.036	1.174	1.015	0.994	1.017	1.177	1.095	1.011	1.022	0.925	1.046	0.075	7.17	6	4
6	1.956	1.962	1.891	1.912	1.958	1.746	1.873	1.832	1.787	2.013	1.893	0.066	3.49	6	4

* Percentage deviation based on average weight.

TABLE II.—VARIATION IN WEIGHT OF 3 MINIMUM ELASTIC FILLED CAPSULES PREPARED BY THE SAME AND DIFFERENT MANUFACTURERS.

| Batch No. | Mfg. | Weight of Each Capsule in Gm. | | | | | | | | | | Av. Wt. in Gm. | S. D. in Gm. | % D.* | Number Falling within | | |
		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.				1 × S.D.	2 × S.D.	3 × S.D.
7	B	0.421	0.415	0.432	0.450	0.423	0.453	0.432	0.419	0.405	0.446	0.429	0.015	3.49	6	4	:
8	B	0.536	0.545	0.516	0.466	0.463	0.485	0.511	0.509	0.497	0.543	0.507	0.028	5.52	5	5	:
9	C	0.269	0.276	0.306	0.279	0.270	0.279	0.302	0.291	0.284	0.236	0.279	0.019	6.81	7	2	1
10	C	0.333	0.307	0.334	0.382	0.295	0.330	0.333	0.315	0.271	0.346	0.325	0.029	8.92	6	4	:
11	C	0.291	0.293	0.263	0.296	0.243	0.300	0.315	0.301	0.293	0.282	0.288	0.020	6.94	7	2	1
12	C	0.321	0.283	0.353	0.367	0.335	0.296	0.340	0.331	0.339	0.347	0.331	0.024	7.25	7	3	:
13	D	0.261	0.263	0.254	0.272	0.255	0.243	0.263	0.232	0.240	0.234	0.252	0.013	5.15	7	3	:
14	D	0.262	0.276	0.282	0.262	0.271	0.265	0.267	0.262	0.275	0.267	0.269	0.007	2.60	9	1	:
15	E	0.291	0.293	0.281	0.286	0.291	0.292	0.293	0.292	0.292	0.295	0.291	0.004	1.37	8	1	1
16	E	0.305	0.307	0.307	0.290	0.286	0.284	0.290	0.284	0.285	0.287	0.293	0.009	3.07	7	3	:

* Percentage deviation based on average weight.

TABLE III.—VARIATION IN WEIGHT OF NON-TRANSPARENT CAPSULES FILLED WITH A SUSPENSION IN OIL.

Batch No.	Mfg.	Weight of Each Capsule in Gm.										Av. Wt. in Gm.	S. D. in Gm.	% D.*	Number Falling within		
		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.				1 × S.D.	2 × S.D.	3 × S.D.
17	B	0.465	0.474	0.510	0.524	0.543	0.541	0.571	0.540	0.602	0.525	0.530	0.039	7.36	6	4	..
18	B	0.563	0.549	0.479	0.502	0.610	0.553	0.511	0.547	0.515	0.486	0.532	0.038	7.14	7	2	1
19	B	0.505	0.543	0.551	0.548	0.553	0.497	0.546	0.590	0.527	0.522	0.538	0.025	4.64	8	1	1
20	B	0.537	0.522	0.546	0.533	0.580	0.547	0.526	p.571	0.518	0.533	0.541	0.019	3.51	7	2	1
21	C	0.523	0.593	0.437	0.513	0.591	0.503	0.490	0.491	0.468	0.446	0.505	0.051	10.09	7	3	..
22	C	0.506	0.538	0.559	0.611	0.446	0.568	0.664	0.578	0.524	0.480	0.547	0.060	10.96	6	4	..
23	C	0.584	0.597	0.500	0.606	0.561	0.564	0.491	0.601	0.591	0.520	0.562	0.041	7.29	6	4	..
24	D	0.631	0.645	0.599	0.637	0.641	0.643	0.621	0.640	0.622	0.633	0.631	0.013	2.06	8	1	1
25	F	0.512	0.511	0.506	0.501	0.497	0.524	0.513	0.503	0.508	0.499	0.507	0.008	1.58	8	1	1
26	F	0.519	0.526	0.531	0.516	0.514	0.547	0.534	0.537	0.517	0.531	0.527	0.010	1.90	7	3	..

* Percentage deviation based on average weight.

0.008 Gm. corresponding to 1.58%, while the highest is number 22 with a standard deviation of 0.060 Gm. corresponding to 10.96%. This wide variation in products made by different manufacturers is no doubt due to the thickness and uniformity of the coating; the consistency of the suspension in oil; the accuracy with which this suspension is measured or weighed; the uniformity with which it is distributed in preparing the capsules; and the type machine used in making the products.

For the purpose of making it possible to more readily compare the results of these three series with similar data that have been published, but which have not been expressed in terms of the standard deviation, the per cent of deviation from the average weight has been calculated and is presented in Table IV.

TABLE IV.—PERCENTAGE OF ERROR COMPUTED FROM DATA IN TABLES I, II AND III.

Batch Number	Mfg.	Average Weight in Gm.	Number of Capsules Falling within												
			1%.	2%.	3%.	4%.	5%.	6%.	7%.	8%.	9%.	10%.	11%.	12%.	13% or Over.
1	A	0.480	2	1	..	1	1	1	..	2	1	1	..	..	..
2	A	0.483	2	1	1	3	1	1	..	1	..	..	..	..	..
3	A	0.510	..	1	2	2	2	..	..	..	..	..	1	1	1
4	A	1.016	1	..	3	..	2	..	1	..	3	..	..	..	..
5	A	1.046	1	..	3	1	2	..	..	..	..	..	..	1	2
6	A	1.893	2	1	..	4	..	2	..	1	..	..	..	..	..
7	B	0.429	2	2	1	2	1	2	..	..	..	..	..	..	..
8	B	0.507	2	2	..	..	1	1	..	2	2	..	..	..	..
9	C	0.279	3	1	1	2	..	..	..	1	1	..	..	..	1
10	C	0.325	..	1	3	1	..	1	1	..	..	1	..	..	2
11	C	0.288	1	2	2	1	1	..	..	..	2	..	..	..	1
12	C	0.331	1	1	2	1	..	1	..	1	..	..	..	2	1
13	D	0.252	2	..	..	2	3	..	1	1	1	..	..	..	..
14	D	0.269	3	2	4	..	1	..	..	..	..	..	..	..	..
15	E	0.291	2	6	1	1	..	..	..	..	..	..	..	..	..
16	E	0.293	2	1	4	1	2	..	..	..	..	..	..	..	..
17	B	0.530	1	2	2	1	..	..	..	1	..	..	..	1	2
18	B	0.532	..	..	1	2	2	1	1	..	..	1	1	..	1
19	B	0.538	1	2	3	1	..	..	1	..	1	..	1	..	..
20	B	0.541	2	3	1	1	1	1	..	1	..	..	..	..	..
21	C	0.505	1	1	2	1	..	..	..	1	..	..	..	1	3
22	C	0.547	..	1	1	..	2	..	1	..	1	..	..	..	4
23	C	0.562	2	..	..	1	1	1	2	1	..	..	1	1	..
24	D	0.631	4	4	1	..	1	..	..	..	..	..	..	..	..
25	F	0.507	5	4	..	1	..	..	..	..	..	..	..	..	..
26	F	0.527	3	4	2	1	..	..	..	..	..	..	..	..	..

NOTE: All percentages are calculated from the average weight. 1% equals 1% or less; 2% equals from 1% plus to 2%; etc.

The results of Tables I, II and III are summarized in Table V which follows.

TABLE V.

Series No.	1 × S. D.	Number of Capsules Falling within 2 × S. D.	3 × S. D.
I	38	22	
II	69	28	3
III	70	25	5
Totals	177	75	8

An examination of the tables shows that 96.92% (68.08% and 28.84%) of a total of the 260 capsules weighed fall within twice the standard deviation. So far as the capsules used in these tests are concerned, therefore, the deviation might well be taken as defining the limit for reasonable or permissible error.

CONCLUSIONS.

1.   The factors largely responsible for the variation in weight of machine made elastic filled gelatin capsules are (1) the uniformity in thickness and elasticity of the gelatin sheet used as the shell, (2) the accuracy with which the medicament is measured or weighed, (3) the uniformity of the molds, (4) the uniformity with which the medicament is distributed throughout the capsules of one batch, and (5) the uniformity of pressure applied by the machine in sealing.

2.   From the data obtained in the tests made it would seem that twice the standard deviation is a reasonable margin of error for machine made elastic filled gelatin capsules.   This would include 96.92% of the capsules weighed.

REFERENCES.

(1)   Andrews, Marvin J., JOUR. A. PH. A., 22, 755 and 838 (1933).
(2)   Andrews, Marvin J., *Ibid.*, 23, 350 and 421 (1934).
(3)   Andrews, Marvin J., *Ibid.*, 23, 1003 (1934).
(4)   Andrews, Marvin J., *Ibid.*, 23, 1117 and 1210 (1934).
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A STUDY OF ENTERIC COATINGS.[1]

BY J. T. GOORLEY[2] AND C. O. LEE.[3]

INTRODUCTION.

For many years pharmacists have tried to prepare medicines so that they would not be liberated for absorption until they had reached the intestine.   Therefore, studies have been made from time to time to determine the value of enteric coatings by various test-tube methods.   More recently attempts have been made to trace the disintegration of enteric coatings in the body by means of the X-ray.

The purposes of this investigation were: *First*, to study the physiological processes to which enteric coatings are subjected; *second*, to study the relative merits of the materials now used for enteric coatings; and *third*, to provide a more reliable enteric coating.   The study of the passage of coated pills and capsules through the body was made possible by the installation of a General Electric X-ray machine in the Purdue University School of Pharmacy.

It was pointed out as early as 1889 by Bourquelot (1) that there are at least four classes of medicines which should be enterically coated.   They are as follows:

(1)   Medicines that by prolonged contact cause irritation to the stomach.

(2)   Medicine that can injure the digestion by giving insoluble precipitates with pepsin and peptones.

(3)   Medicines that are rendered inactive or decomposed by the gastric juice.

(4)   Medicines which should arrive in the intestine as concentrated as possible.

In addition to the types of medicines mentioned above, the logic of enteric medication is evidenced by the fact that the intestine is the normal site for absorption.   Former investigators have not taken the physiological factors influencing

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