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AN IMPROVED, MULTIPLE STIRRER FOR THE ROUND-BOTTOM FLASK DISSOLUTION METHOD

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ABSTRACT

A multiple stirrer round-bottom flask dissolution apparatus was constructed which improved the reproducibility of dissolution test results when compared to single stirrer apparatus results. A statistical analysis comparing the single stirrer method and the new multiple stirrer dissolution apparatus showed that a significant reduction in variance resulted when the multiple stirrer apparatus was employed.

INTRODUCTION

Levy and Hayes (1) introduced a slow agitation dissolution method which was modified by Poole (2) to obtain reliable and reproducible results. Poole accomplished this by maintaining constant geometry (a standard Teflon® stirring paddle located in a standard position relative to the bottom of the flask) of the system and a constant agitation rate. However, since the introduction of Poole's method, few improvements in

the system have been reported, and many laboratories use Poole's original method.

The experimental apparatus described in this report has been shown to reduce the variation in the flask to flask measurements of dissolution as compared to a single stirrer method.

EXPERIMENTAL

A schematic diagram of the dissolution apparatus is shown in Figure 1. Figure 2 is a photograph of the apparatus. It consists of one stirring motor and a control unit (Model 12, Stedi-Speed Stirrer, Fisher Scientific, Pittsburgh, Pa.) with a pulley and belt system to drive four stirrers at a constant speed. The rest of the dissolution apparatus is similar to that of Poole. Four 1-liter, 3 neck, round-bottom flasks are employed as the dissolution vessels. Teflon® paddles, each with a 7.8 cm diameter blade, are positioned two inches from the bottom of the flasks to maintain constant geometry. Simulated gastric fluid USP (3) with-

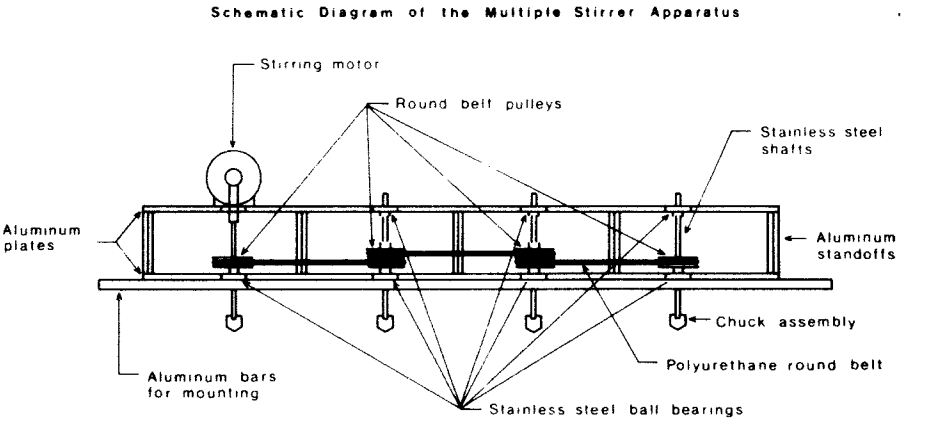

Figure 1

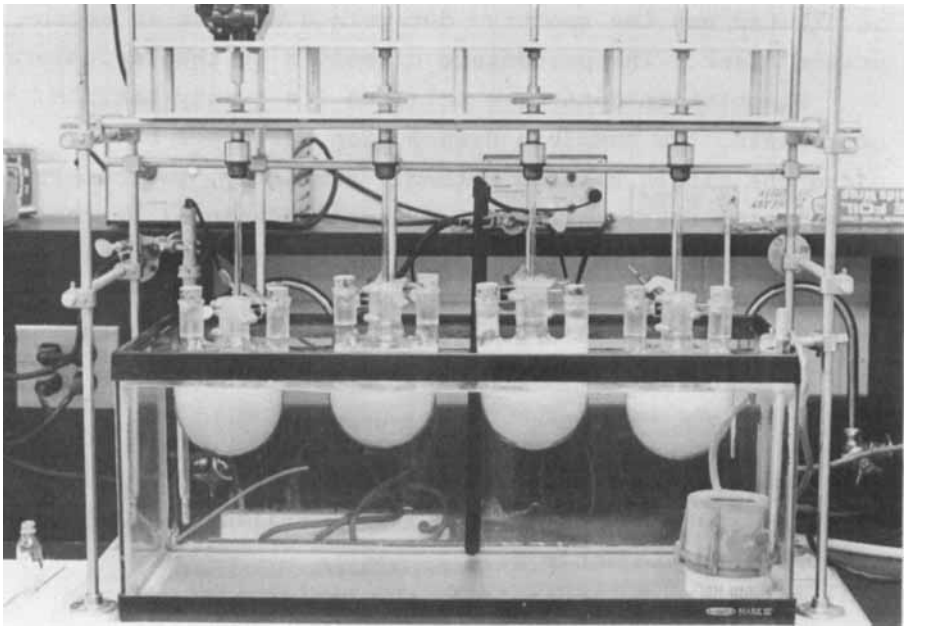

Figure 2

Photograph of the Multiple Stirrer Dissolution Apparatus

out pepsin, 750 ml, is employed as the dissolution medium. The dissolution flasks containing dissolution medium are immersed in a constant temperature water bath maintained at 37.5°C ± 0.5°C and allowed to equilibrate. The stirring rate is then adjusted and maintained at a constant 50 ± 2.5 RPM by the electronically controlled stirrer. At time zero, tablets are added to each dissolution vessel. At 5, 15 and 30 minutes, four ml samples are removed from each flask with a glass syringe fitted with a long blunt needle. The samples are filtered through a 0.45 μ MF Millipore® filter fitted with a Swinnex® adaptor. An aliquot of the sample

is diluted and the spectrum determined against an appropriate blank. The percentage dissolved is then calculated.

Dissolution data were obtained for twenty batches of tablets, two complete dissolution tests per batch, using the single stirrer method. Similarly, two complete dissolution tests on each of sixteen additional batches of tablets were performed employing the multiple stirrer method. Following completion of the dissolution tests, a statistical analysis (F test) was performed and the reproducibility of the two methods was compared.

RESULTS AND DISCUSSION

Table I summarizes the data obtained employing the single stirrer method. The multiple stirrer method data are presented in Table II.

Using the 5 minute data, the variance of the two tests from each batch was calculated, giving 20 variances for the single stirrer method and 16 variances for the multiple stirrer method. This information is presented graphically in Figure 3. It is notable that of the ten largest flask to flask differences in this study, only one was from the multiple stirrer method.

The 5 minute mean of the 20 variances for the single stirrer method is 15.1, while the corresponding mean for the multiple stirrer method is 4.4. The F ratio of these two pooled variances is (15.1/4.4)=3.43. Since the 1% value for an F with 20 and 16 df is 3.26, the variance of the multiple stirrer method was significantly less than that of the single flask method. In other words the multiple flask method provides better reproducibility at the 5 minute evaluation.

The 15 and 30 minute data were similarly analyzed. The pooled variance, F ratio, and P-value at 5, 15 and 30 minutes are summarized in Table III. The multiple

Table I - Dissolution Data Using the Single Stirrer Method.

Batch	Flask	% Dissolved 5 min.	15 min.	30 min.
1	A	71.1	91.1	98.1
	B	69.8	89.9	98.9
2	A	71.8	89.9	98.9
	B	68.2	87.8	97.1
3	A	74.9	89.8	97.0
	B	74.4	89.8	96.7
4	A	76.9	93.4	100.0
	B	75.4	90.0	98.9
5	A	75.5	92.2	100.7
	B	73.7	89.7	100.7
6	A	86.3	94.3	101.2
	B	71.0	87.9	100.0
7	A	84.3	94.8	100.0
	B	80.6	91.4	100.0
8	A	72.8	89.3	97.4
	B	77.5	94.6	100.4
9	A	65.8	86.7	97.5
	B	54.5	86.8	92.6
10	A	72.3	86.9	94.7
	B	67.9	86.8	94.6
11	A	73.9	84.1	93.3
	B	67.5	83.3	93.6
12	A	69.2	86.2	95.8
	B	74.1	89.5	96.8
13	A	68.1	86.3	96.8
	B	75.4	88.5	96.1
14	A	71.8	87.6	98.5
	B	69.2	86.0	95.9
15	A	70.9	86.2	96.2
	B	66.9	83.7	95.0
16	A	70.6	87.2	96.3
	B	70.1	86.7	96.2
17	A	67.0	84.0	93.8
	B	71.3	86.5	94.5
18	A	73.0	87.8	94.6
	B	71.6	86.5	96.2
19	A	64.9	85.3	96.2
	B	66.6	85.1	94.2
20	A	64.6	84.2	95.1
	B	64.6	82.9	93.7

Table II - Dissolution Data Using the Multiple Stirrer Meth

Batch	Flask	% Dissolved 5 min.	15 min.	30 min.
21	A	75.5	92.6	96.0
	B	69.8	91.6	95.3
22	A	73.4	92.3	96.7
	B	75.7	92.6	95.2
23	A	68.9	89.1	96.7
	B	71.5	92.2	95.8
24	A	68.9	90.3	97.3
	B	69.1	92.2	96.3
25	A	68.2	92.0	95.9
	B	68.4	90.3	96.8
26	A	68.4	91.0	92.2
	B	66.7	87.9	96.3
27	A	74.0	93.2	98.9
	B	70.5	91.2	96.9
28	A	71.9	91.7	95.5
	B	69.3	93.1	98.1
29	A	69.4	91.4	95.2
	B	68.0	92.1	98.4
30	A	68.2	91.4	96.7
	B	71.9	93.1	97.8
31	A	71.5	93.1	97.5
	B	74.1	93.9	96.9
32	A	70.5	91.9	96.7
	B	67.0	91.7	95.9
33	A	67.1	89.6	95.0
	B	70.4	91.0	96.3
34	A	75.1	92.3	96.2
	B	71.6	91.0	95.0
35	A	69.8	89.9	95.6
	B	73.7	89.8	94.6
36	A	74.9	91.3	95.8
	B	76.0	93.6	96.3

stirrer method has increased the reproducibility at the 5 and 15 minute measurements. However, the two methods are equivalent at the 30 minute evaluation, at which time the dissolution is essentially complete.

In conclusion it can be said that the multiple stirrer method reduces flask to flask dissolution var-

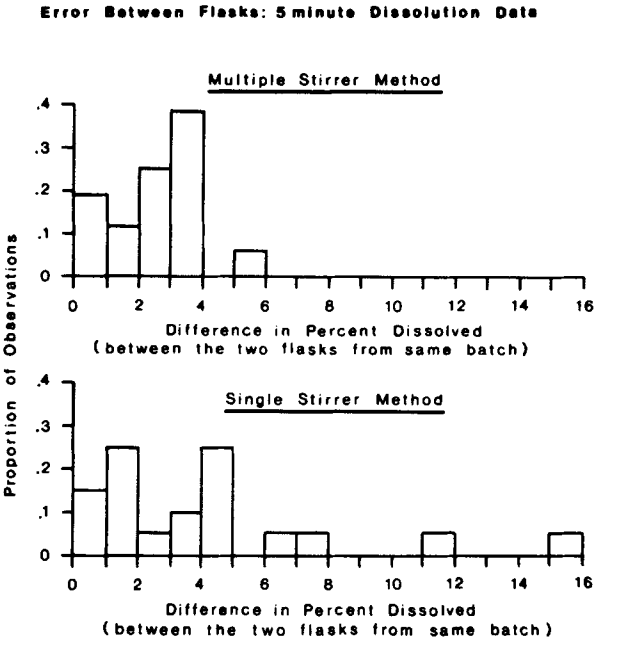

Figure 3

iability. Therefore, by optimizing the mechanical stirrer mechanism one can significantly increase data reproducibility at times when the dissolution undergoes maximum rates of change. Thus, more confidence can be

Table III - Pooled Variances of Multiple and Single Stirrer Methods.

Dissolution Time, min.	Single Stirrer Method	Multiple Stirrer Method	F-Ratio	P-Value
5	15.1	4.40	3.43	0.008
15	3.45	1.43	2.44	0.038
30	1.46	1.41	1.03	0.40

assigned to the results. Although data have been presented for only one product, similar results have been obtained of others. Since the flask and stirrer are comparable in design to those in the proposed USP paddle dissolution method, the benefits of the multiple stirrer assembly should be applicable to it as well.

ACKNOWLEDGEMENT

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