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NOTES

Systematic Error Associated with Apparatus 2 of the USP Dissolution Test I: Effects of Physical Alignment of the Dissolution Apparatus

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Abstract ☐ The physical alignment of the paddle and the vessel is critical in obtaining reproducible results from the USP dissolution test with Apparatus 2. Large variations in dissolution results were traced to minor variations in alignment of different apparatuses.

Keyphrases ☐ Dissolution—USP Apparatus 2, reproducibility of results ☐ USP—dissolution Apparatus 2, reproducibility of results ☐ Apparatus—USP dissolution Apparatus 2, reproducibility of results

This laboratory has been recently studying the systematic error associated with Apparatus 2 of the USP dissolution test (1). Collaborative studies conducted by the Academy of Pharmaceutical Sciences[1] and by the Food and Drug Administration (2) showed a wide variation in test results reported by different laboratories. The present report is the first of a series of papers describing sources of systematic error associated with the dissolution test.

The test method first appeared in the Fourth Supplement to USP XIX and NF XIV (3). The stirring element consisted of a shaft with a detachable paddle blade positioned on its side. In the Fifth Supplement of USP XIX and NF XIV, the stirring element was modified to its present configuration: the blade is now rigidly mounted through the diameter of the shaft. The data reported in this paper were collected prior to the modification of the apparatus.

EXPERIMENTAL

Two commercial samples of 5-mg prednisone tablets (referred to as Tablet 0 and Tablet 1) were used for the evaluation of six dissolution apparatuses. Dissolution data for the two samples from each apparatus were collected using a single set of six glass dissolution vessels[2] and uniform analytical technique. Two appartuses, designated A and B, were designed and built by the Food and Drug Administration. Four apparatuses, designated C, D, E, and F, were commercially available[3]. Each apparatus could test six tablets simultaneously.

The dissolution and analytical methodology is described in the Fourth Supplement to USP XIX and NF XIV (4).

RESULTS AND DISCUSSION

The data collected from the two samples with each apparatus are shown in Table I. The results for apparatuses E and F are considerably higher than those for the other four apparatuses. These discrepancies were traced to minor variations in the vertical alignment of the paddle shafts. The experiment pointed out two deficiencies in the dissolution methodology.

The first deficiency was that the equipment operator could not be certain that the USP alignment specifications were being met: the paddle shaft must be aligned so that its axis is not more than 0.2 cm from the vertical axis of the vessel at any point. Devices adequate to measure and adjust the equipment to meet this requirement were not available initially. Although the apparatus was adjusted to make the drive head parallel with the base, no conscientious effort was made to improve the precision with which a vessel was centered around its shaft.

The second deficiency lay in the design of the apparatus. The support

[1] Unpublished data, Dissolution Technology Committee, APhA Academy of Pharmaceutical Sciences.

[2] Kimble, Vineland, N.J.
[3] C: Model 72A, Hanson Research Corp., Northridge, Calif. D, E, and F: Three separate Hanson Model 72R apparatuses.

Table I—Comparison of Dissolution Data from Different Apparatuses for Two Samples of 5-mg Prednisone Tablets [a]

Apparatus	Tablet 0[b] $\bar{x}$	Tablet 0[b] $\pm SD$	Tablet 1[c] $\bar{x}$	Tablet 1[c] $\pm SD$
A	19.9	±6.4	52.6	±5.6
B	19.3	±7.8	53.7	±6.6
C	23.1	±11.5	56.1	±11.5
D	22.1	±9.5	54.5	±3.4
E	29.9	±13.1	63.2	±10.4
F	37.7	±17.0	80.7	±4.0

[a] Results in percent of label claim dissolved at 30 min. [b] $n = 12$. [c] $n = 6$.

Table II—Comparison of Dissolution Data from Two Samples of 5-mg Prednisone Tablets After Realignment of Apparatuses [a]

Apparatus	Tablet 0[b] $\bar{x}$	Tablet 0[b] $\pm SD$	Tablet 1[c] $\bar{x}$	Tablet 1[c] $\pm SD$
E	19.0	±6.3	48.8	±4.8
F	20.6	±6.8	46.3	±3.3

[a] Results in percent of label claim dissolved at 30 min. [b] $n = 12$. [c] $n = 6$.

Table III—Effect of Verticality of Paddle Shafts on Dissolution Results Obtained from Tablet 1

Condition	Dissolution Results[a] $\bar{x}$	$\pm SD$	$\bar{x}$	$\pm SD$
Shafts in vertical position	50.1	±5.2	48.6	±2.7
Shafts 0.5 degree from vertical position	53.8	±4.6	54.6	±4.2
Shafts realigned to vertical position	50.6	±3.6	—	

[a] Duplicate runs. Results in percent of label claim dissolved at 30 min. $n = 6$.

for the dissolution drive for apparatuses D, E, and F consisted of a keyed center post. The drive could be moved vertically on the post and pivoted up and out of the way to facilitate the changing of vessels between tests. Because of this design the dissolution drives of apparatuses D, E, and F were held less rigidly and precisely over the holes in the base of the apparatus than the dissolution drive of apparatus C.

Alignment procedures were developed for the apparatus. A centering tool, a paddle depth gauge, and a means of holding the vessel in a position centered around the paddle shaft were developed. These procedures and tools (5) were used to realign apparatuses E and F. The dissolution test was repeated on Tablet 0 and Tablet 1. Realignment improved the test results for apparatuses E and F (Table II), which were in closer agreement with the Table I results for the other four apparatuses than before realignment.

Data collected from Tablet 1 after alignment of a commercial apparatus[4] are shown in Table III. The shafts were then tilted ~0.5 degree by raising one side of the drive base by 3 mm. Additional data were collected. The shafts were readjusted to a vertical position, and the test was repeated a third time. The data (Table III) show that the effect of tilting the shafts from a vertical position by only 0.5 degree is substantial and reproducible.

The shafts in a six-spindle apparatus can all be made vertical only if the chucks hold the shafts parallel to each other. The shafts of one of the commercial apparatuses showed small deviations from parallelism. Vernier calipers, capable of measurement to the nearest 0.02 mm, were used to measure the distances between shafts. Measurements were taken in a horizontal plane near the chucks and in a horizontal plane 17 cm below the chucks. The differences in the measurements (Fig. 1) are small but significant. If shafts 1, 2, 3, and 5 are made vertical, shafts 4 and 6 will not be vertical. Shaft 4 in particular will be displaced about 0.5 degree

[4] Model 72RL, Hanson Research Corp.

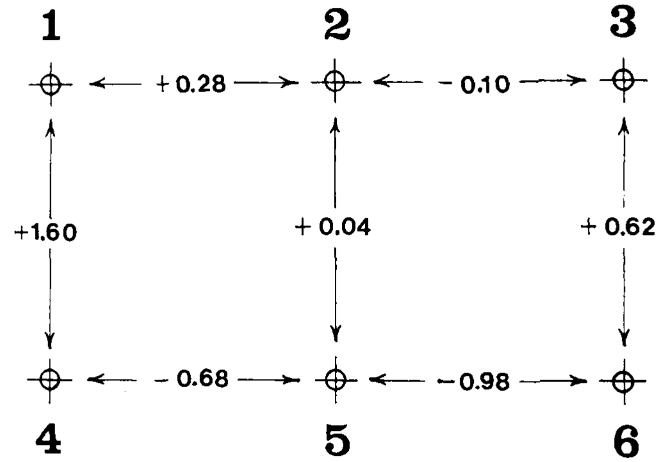

Figure 1—*Deviations (in millimeters) from parallelism of shafts of one commercial apparatus. Measurements were taken where the shafts come out of the chucks and compared to measurements taken 17 cm below the chucks. A positive sign indicates the two shafts are divergent. A negative sign indicates the two shafts are convergent.*

from a vertical position. When Tablet 1 was examined with this apparatus, the data from shafts 4 and 6 were markedly different from those from shafts 1, 2, 3, and 5, and the differences were of the same magnitude as the differences in averages reported in Table III.

Experience has since indicated that an analyst who is new to the dissolution test may interpret the USP requirement for paddle shaft alignment as a requirement to center the tops of the vessels around the shafts to within 0.2 cm. It is equally important that the shafts are precisely vertical. Despite the fact that the top of each vessel was centered around its shaft, minor vertical deviations of shafts caused large changes in the test results from Table 1.

CONCLUSIONS

The liquid flow rates generated in different sections of the vessel are controlled by the location of the paddle in the vessel as well as the rotational rate of the paddle. Dissolution results obtained prior to modification of the paddle blade can differ from results obtained after modification. The system geometry of both paddle designs must be precisely controlled if results from either are to be reproducible. To minimize error resulting from minor variations in the system geometry of Apparatus 2, the base of the apparatus must be horizontal, the shafts must be vertical, each shaft must be positioned along the vertical axis of each vessel, and the paddles must be set at a standarized depth in the vessels. These alignments must be made as precisely as current technology will allow.

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