Systematic Error Associated with Apparatus 2 of the USP Dissolution Test V: Interaction of Two Tableted Prednisone Formulations with Glass and Plastic Vessels

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Abstract □ Recently marketed glass vessels that are uniform and pass USP specifications were compared with uniform plastic vessels that also pass USP specifications. Two lots of prednisone tablets, Tablet 1 and Tablet 2, were tested in both types of vessels. Tablet 1 gave higher results (+12.7% of label claim) in glass vessels at 50 rpm but gave equivalent results in either vessel at 75 rpm. Tablet 2 gave equivalent results in either vessel at 50 rpm but gave higher results (+22% of label claim) in glass vessels at 75 rpm. The type of vessel used to obtain dissolution results for tablets should be specified.

Keyphrases □ USP Dissolution Apparatus 2—error associated with use of glass and plastic vessels □ Dissolution—systematic error associated with USP dissolution Apparatus 2, use of glass and plastic vessels

In a previous report (1), it has been shown that glass and plastic vessels may give different results when dissolution of prednisone tablets is measured with USP Apparatus 2. In the earlier work, the glass vessels[1] used had nonuniform inside bottom curvatures and did not conform to the USP specification (2) of spherical curvature; the inside bottom curvatures of the plastic vessels[2] were more uniform and approximated spherical curvature. It was thus concluded (1) that use of the plastic vessels would reduce systematic error in the USP Apparatus 2.

Glass vessels[3] advertised to meet USP specifications were recently introduced, and five were purchased for evaluation. To permit direct comparisons, the previously used techniques and tablet lots were employed to evaluate the suitability of the new glass vessels in the USP dissolution test for prednisone tablets (3), and the results are reported here.

EXPERIMENTAL SECTION

Tablets—In this laboratory, two commercial lots of prednisone tablets that originally gave wide ranges in dissolution results with Apparatus 2 have been used extensively. The dissolution rates of Tablet 1 (5-mg prednisone tablets) and Tablet 2 (10-mg prednisone tablets) are affected to an unusual degree by minor variations in the test. In this respect, they are not typical of prednisone tablets currently available to the public but are very useful for measurement of apparatus variations. The dissolution rate of Tablet 1 responds to variations in the physical alignment of the equipment (4) and vessel curvature (1). The dissolution rate of Tablet 2 is less affected by these variations but is increased considerably if gas concentrations in the dissolution medium exceed a critical value (5, 6). Tablet 2 has been collaboratively studied in 11 laboratories (7). Both lots exhibit similar physical dissolution behavior; disintegration takes place within 2 min, and the disintegrated tablet material stays on the bottom of the vessel, where it gathers into a dynamic conical mass. Undesirable changes in test conditions alter the fluid flow in the vicinity of the conical mass; the conical mass is displaced or dispersed, and higher dissolution results are obtained. In this laboratory, the dissolution results from Tablet 2 are currently used as an indicator to determine whether the dissolution equipment and medium are suitable for testing tablets by the procedure with the USP Apparatus 2.

Apparatus—A six-spindle dissolution drive[4] was used. The drive was mounted on an acrylic water bath equipped with levelers. A circulator-heater[5], mounted externally to the bath, maintained the bath temperature at 37.5 ± 0.1°C. The base of the drive was leveled[6], and the paddle shafts were aligned vertically[6]. A specially designed tool (8) was used to center the vessels around the paddle shafts[7]. Each vessel was held in place with three cam lugs. Each paddle was adjusted with a depth gauge[8] to provide 25 mm of clearance above the bottom of the vessel. Paddle rotation was maintained within ±1.7% of the nominal value.

Procedure—A 20-L carboy was filled with deionized water. To achieve the desired equilibrium of gases, air was drawn through the water for 15 min at 145 mm Hg (6). The water was siphoned into 500-mL volumetric flasks[9], which were placed in a water bath at 37.5°C until their contents had reached that temperature. The contents were then transferred to the dissolution vessels in a 37.5°C water bath. The tablets were dropped into the vessels with the paddles rotating. After 30 min, aliquots were taken and filtered. (The water temperatures were 37.0 and 36.5°C in the glass and plastic vessels, respectively.) The absorbance of each filtrate was measured at 242 nm in a 1-cm cell.

Reevaluation of Glass and Plastic Vessels—Dissolution data for Tablet 1 were obtained with the same six glass vessels[1] previously evaluated (1). A different set of six plastic vessels was used, however, because the plastic vessels used in the previous evaluation were not available for this study.

Evaluation of New Glass Vessels—The new glass vessels[3] have graduations from 500 to 1000 mL in 50-mL increments. Inside diameters were measured with inside calipers. The bottom curvatures were measured with a mechanic's depth gauge and plaster of Paris (1). The glass vessels were numbered 1 through 5 and placed in the dissolution drive with one plastic vessel. Two sets of six tablets each were subjected to the dissolution test. The vessels were then moved one position in a clockwise direction, and two more sets of six tablets each were subjected to the test. This procedure was continued until each vessel had been tested twice in each position of the dissolution drive for a total of 72 results. Twelve results were associated with each vessel, which were sequentially placed in all six positions. Likewise, 12 sets of results were associated with each position in which all six vessels had been sequentially placed. The experiment was conducted only with Tablet 1.

Plastic-Coated Glass Vessels—Ten grams of plastic from a broken plastic vessel was dissolved in 100 mL of chloroform. This solution was poured into a clean, dry, glass vessel[3]. The vessel was tilted and rotated until its inside surface was brought in contact with the solution. The solution was poured from the vessel, and the vessel was inverted and placed on a cork ring in a draft hood overnight. The inside of the glass vessel was coated with a thin layer of plastic. The vessels had to be recoated after each dissolution test because the plastic did not adhere to the glass. Tablet 1 and Tablet 2 were tested in these coated vessels.

Glass Vessels with Different Bottom Curvatures—Dissolution results for Tablet 1 were taken from a glass vessel[10], in which the bottom curvature came to a blunted point (1), and from a flat-bottom glass vessel[11] that was positioned in the dissolution apparatus in a manner similar to that for the other vessels.

Dissolution Results at Different Stirring Rates—Three plastic vessels and three glass vessels[3] were placed in alternating positions in the dissolution apparatus. The dissolution test was conducted at stirring rates from 25 to 100 rpm for Tablet 1 and Tablet 2.

Dissolution Results from One or More Tablets Per Vessel—Three plastic vessels and three glass vessels[3] were placed in alternating positions as before.

[1] Model No. 33730; Kimble, Div. of Owens-Illinois, Vineland, N.J. (currently available).
[2] Model No. EQ1900; Eli Lilly and Co., Indianapolis, Ind.
[3] Model No. V1000A; Applied Analytical Industries, Wilmington, N.C.
[4] Built by the Winchester Engineering and Analytical Center; Food and Drug Administration, Winchester, Mass.
[5] Haake, Model E52; Fisher Scientific Co., Pittsburgh, Pa.
[6] Nine-inch (22.86 cm) torpedo level; Stanley Tools, New Britain, Conn.
[7] Hanson Research Corp., Northridge, Calif.
[8] Van-Kel Industries, Chatham, N.J.
[9] Model No. 28045-500; Kimble, Div. of Owens-Illinois.
[10] Model No. 33730; Kimble, Div. of Owens-Illinois (discontinued in 1978).
[11] Model No. BSF-1000; Virtis Co., Gardiner, N.Y.

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Table I—Dissolution Data [a] for Tablet 1 from Five Glass Vessels (Rearranged for Two-Way ANOVA)

Vessel	Percent of Label Claim at Position: 1	2	3	4	5	6	Mean ± SD[b]
1	54.2	49.5	55.7	52.0	55.7	54.0	
	53.1	51.6	54.4	52.5	53.1	53.8	53.3 ± 1.76
2	55.0	51.0	53.2	55.7	51.8	52.6	
	52.4	55.6	55.4	54.1	51.4	51.7	53.3 ± 1.76
3	52.3	53.0	54.6	50.9	51.3	49.9	
	51.8	52.5	52.2	51.6	52.0	52.0	52.0 ± 1.15
4	52.5	55.0	51.5	51.3	49.5	50.9	
	52.6	53.0	51.6	52.2	49.5	52.0	51.8 ± 1.50
5	57.2	49.9	53.1	50.4	52.7	53.0	
	52.1	53.6	54.3	50.3	53.8	54.8	52.9 ± 2.09
Position Mean	53.3	52.5	53.6	52.1	52.1	52.5	
Position *SD*	1.69	2.01	1.51	1.69	1.88	1.49	

[a] Percent of label claim dissolved at 30 min. [b] Mean ± *SD* of 12 individual tablets.

Table II—Dissolution Data [a] for Tablet 1 from One Plastic Vessel Carried Through ANOVA Experiment

Percent of Label Claim at Position: 1	2	3	4	5	6	Mean ± SD[b]
39.0	41.2	45.1	40.4	41.1	38.9	
40.8	38.5	43.3	41.1	40.2	41.1	40.9 ± 1.85

[a] Percent of label claim dissolved at 30 min. [b] Mean ± *SD* of 12 individual tablets.

One or several tablets were dropped into each vessel. The test was conducted at 50 and 75 rpm for Tablet 1 and Tablet 2, respectively.

RESULTS AND DISCUSSION

Physical Dimensions—The five glass vessels[3] had inside diameters that ranged from 103.0 to 103.5 mm. The bottom curvatures of the vessels corresponded to those of spheres of diameters from 102.4 to 105.2 mm. Plaster of Paris casts of the bottom curvatures revealed no irregularities. The depth of the vessels was 165 mm. The vessels thus met USP specifications.

The dimensions of the glass vessels[3] differ from those of the plastic vessels in two respects. For the glass and plastic vessels, the outside diameters of the flanges are ~122 and 135 mm, respectively. The outer edge of the flange is lopsided with respect to the outer wall of the glass vessel, but is symmetrical with the outer wall of the plastic vessel. This difference in flange dimension required larger cam lugs on the dissolution apparatus to hold each glass vessel centered around its paddle axis. The flanges were marked so that they could always be oriented in the same configuration before use.

The glass vessels[3] have parallel sides, but the plastic vessels are tapered toward the bottom. Both types of vessel have essentially the same inside diameter at the top (103 mm), but the plastic vessel has a diameter of 101 mm just above the start of its bottom curvature. This difference in internal dimension causes the glass vessel to have a slightly flatter bottom curvature and to hold a slightly larger volume of liquid at a specified depth.

Selection of Tablets for Evaluation—With Tablet 1, significant differences among glass and plastic vessels (1) were revealed when the amount of dissolved drug, expressed as a percentage of the amount purported to be in the tablet, was measured at 30 min. The difference between mean results from the two types of vessels was dramatic for Tablet 1 but slight for Tablet 2. Tablet 1 was therefore selected to be used to detect differences among the five new glass vessels[3].

Tablet 1 had not been tested for 3 years. New dissolution results were collected from the six glass vessels[1] evaluated previously (1) and from six plastic vessels. The mean results obtained for 12 tablets were 54.7 and 41.2% of label claim in glass and plastic vessels, respectively. The corresponding standard deviations were 1.68 and 2.23% of label claim. These results compare favorably with the results previously obtained from the four positions of the dissolution drive that had vertical shafts[12]. Thus, Tablet 1 had not deteriorated, and direct comparisons could be made between the results collected 3 years ago and those from the new glass vessels[3].

Analysis of Variance—The data collected in the test of five glass vessels[3] and one plastic vessel were rearranged for an analysis of variance (Tables I and II). The data in the rows are associated with the individual vessels, and the data in the columns are associated with the individual positions in the dissolution apparatus.

[12] The Hanson dissolution drive used in the previous study (1) had two paddle shafts that were nonparallel with the other four shafts; results from the two nonparallel (nonvertical) positions were considered to be anomalous.

Table III shows the ANOVA. The *F* ratios indicate that at the 95% confidence level, there were no significant differences among the positions on the dissolution apparatus. However, the chance that Tablet 1 would give the same results in each of the glass[3] vessels is only ~1 in 40. The maximum range of the 12-tablet means associated with the glass vessels[3] is only 1.5% of label (Table I). The maximum ranges obtained previously (1) were 4.1% of label for six glass vessels[1] and 4.9% of label for six plastic vessels. Therefore, the dissolution data from Tablet 1 indicate that the new glass vessels[3] are more uniform than either type of vessel previously evaluated.

The overall mean of dissolution results for Tablet 1 in the new glass vessels[3] (52.7% of label claim; Table I) agrees well with the mean from the previously evaluated glass vessels[1] (54.7% of label claim). Neither of these means agree with the mean from plastic vessels (~41% of label claim; Table II), yet both the glass[3] and plastic vessels met USP specifications.

Results from Coated Vessels—It has been observed in this laboratory that at the beginning of the dissolution test, certain tablets seem to become more centered in glass vessels than in plastic vessels, which suggests that friction between a tablet and the wetted vessel surface may be greater for plastic than glass. Also, certain tablets become more centered in glass vessels cleaned with soap and water than in those rinsed with water and 95% ethanol, which suggests that a tablet may interact with residual films on the glass surface. Thus, certain tablets may interact differently with wetted plastic and glass surfaces.

The glass vessels[3] were coated with the material from which the plastic vessels were made. Five tablets of Tablet 1 were individually tested in plastic-coated vessels. A mean of 55.1% of label claim with an *SD* of 1.05% of label claim was obtained. These results indicate that the plastic coating had little or no effect.

Vessel Curvature—A correlation has been established between the dissolution data obtained for Tablet 1 and the shape of the bottom curvature of glass vessels (1). A glass vessel with an oblate deformation produces a higher dissolution result than one with a prolate deformation. Tablet 1 was used to estimate a maximum magnitude of this curvature effect; a single tablet was tested in a molded glass dissolution vessel[10] that possessed a bottom curvature that came to a blunted point, and a single tablet was tested in a flat-bottom glass vessel[11] similar to those used in the spinning-filter dissolution apparatus (9). Results were 38.9 and 70.3% of label claim, respectively. The extreme difference in vessel curvature gave a difference of ~31% of label claim which supports the idea that the difference in curvature between the glass[3] and the plastic vessels may have an effect. This supposition could not be further investigated because of the lack of glass vessels that have exactly the same dimensions as the plastic vessels.

Different Stirring Rates—Unlike Tablet 1, Tablet 2 does not give a large difference in dissolution results in glass and plastic vessels at 50 rpm. Results reported earlier (5) suggest that Tablet 2 would respond differently at 100 rpm. Tablet 1 and Tablet 2 were tested in glass and plastic vessels at stirring rates from 25 to 100 rpm (Table IV). For Tablet 1, the largest divergence in results between glass and plastic vessels occurred at 50 rpm, and the results converged at higher stirring rates. For Tablet 2 the dissolution results did not begin to diverge until stirring rates >50 rpm were attained.

Individual tablets from Tablet 2 were tested simultaneously at 75 rpm in three plastic-coated glass vessels[3] and three plastic vessels. The mean dissolution results (±*SD*) as percentage of label claim were 55.4 (4.68) and 60.7 (4.30) from plastic and plastic-coated glass vessels, respectively. Comparison of these results with those in Table IV (Tablet 2, 75 rpm) indicates that the plastic surface does interact with Tablet 2.

Volume of Disintegrated Tablet Material—The higher dissolution results obtained for Tablet 1 and Tablet 2 in glass vessels suggest that these tablets are subjected to higher fluid flow rates in glass vessels. During the dissolution

Table III—ANOVA for Six Apparatus Positions and Five Glass Vessels

Source	Sum of Squares	df[a]	Mean Square	F ratio	F (0.95)	F (0.975)
Position means	20.40	5	4.08	2.15	2.53	—
Vessel means	25.08	4	6.27	3.30	2.69	3.25
Interaction	77.97	20	3.90	2.05	1.93	—
Within means	56.97	30	1.90	—	—	—
Total	180.42	59	3.06	—	—	—

[a] Degrees of freedom.

Table IV—Effect of Stirring Rate on Dissolution Data[a] for Tablet 1 and Tablet 2 from Glass and Plastic Vessels[b]

Stirring Rate, rpm	Percent of Label Claim for Tablet 1			Percent of Label Claim for Tablet 2		
	Glass	Plastic	Difference[c]	Glass	Plastic	Difference[c]
25	24.7 ± 1.15	30.3 ± 1.76	−5.6	14.6 ± 0.17	17.0 ± 2.57	−2.4
35	35.3 ± 1.66	31.4 ± 1.44	3.9	—	—	—
50	52.9 ± 1.47	40.2 ± 1.17	12.7	34.0 ± 1.65	35.7 ± 1.42	−1.7
60	—	—	—	46.1 ± 2.51	47.2 ± 4.43	−1.1
70	—	—	—	66.4 ± 6.70	54.2 ± 2.14	12.2
75	66.3 ± 1.76	65.0 ± 1.73	1.3	81.5 ± 4.76	59.5 ± 5.36	22.0
100	71.2 ± 2.20	70.0 ± 0.58	1.2	97.2 ± 1.17	73.6 ± 6.52	23.6

[a] Percent of label claim dissolved at 30 min. Three individual tablets were tested in each type of vessel. [b] Mean ± SD. [c] Difference of mean values obtained using glass and mean values obtained using plastic.

Table V—Dissolution Data[a] for Increasing Loads of Tablet 1 and Tablet 2 in Glass and Plastic Vessels

Tablets/Vessel	Percent of Label Claim for Tablet 1[b]		Percent of Label Claim for Tablet 2[c]	
	Glass	Plastic	Glass	Plastic
1	53.3	41.0	87.2	55.2
2	56.2	43.9	84.0	62.1
4	54.5	45.0	66.6	66.9
8	55.9	43.5	—	—

[a] Percent of label claim per tablet at 30 min. [b] At 50 rpm. [c] At 75 rpm.

test of a single tablet, the volume of the conical mass of disintegrated tablet material on the bottom of the vessel from Tablet 2 is about three times that from Tablet 1. It was speculated that this difference in volume could cause Tablet 1 to be more sensitive to slight differences among vessels because there might be less tendency for the tablet material to pack together at a specified stirring rate, *i.e.*, fewer particles would have greater freedom of movement in a given space.

The data in Table V show that this speculation is false for Tablet 1, but true for Tablet 2. For Tablet 1 at 50 rpm, the amount of drug dissolved per tablet remains relatively constant as the number of tablets per vessel is increased. For Tablet 2 at 75 rpm, the amount of drug dissolved per tablet decreases for the glass vessels[3] and increases for the plastic vessels until the amounts converge at about four tablets per vessel.

CONCLUSIONS

The glass vessels[3] are uniform and comply with USP specifications. At a given stirring rate, certain tablets may give higher dissolution rates in glass[3] than in plastic vessels. Although the results from Tablet 1 indicate that the vessel material is not important, the results from Tablet 2 indicate that tablets may significantly interact with the plastic or glass surface. Tablet 1 and Tablet 2 are affected to an unusual degree by minor changes in the test. However, if reproducible results are to be obtained for a wide range of products, it is important to specify which type of vessel was used in the dissolution test.

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