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Systematic Error Associated with Apparatus 2 of the USP Dissolution Test II: Effects of Deviations in Vessel Curvature from That of a Sphere

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Abstract □ Dissolution vessels made from glass or plastic are recognized by the USP as being suitable for dissolution testing. Glass vessels with a bottom inside curvature flatter than that of a sphere can cause a high bias in dissolution results; vessels with a steeper curvature can cause a low bias. The inside bottom curvature of plastic vessels adhered closely to the curvature of a sphere. The plastic vessels are preferable for use if the drug is not adsorbed and the vessel is not attacked by the dissolution medium. Bias in results between individual positions of a dissolution apparatus was traced to two shafts which were not vertical.

Keyphrases □ Dissolution—systematic error associated with USP dissolution Apparatus 2 □ USP—error associated with dissolution Apparatus 2 □ Apparatus—systematic error associated with USP dissolution Apparatus 2

Only one manufacturer[1] produces a glass, round-bottom vessel (1) suitable for the multiple-spindle drive equipment used for the USP dissolution test (2). The manufacturing process was changed in 1978 in an attempt to improve the vessel. The vessel was formed manually in the older process by using a mold to which the outside of the vessel could conform. These molded vessels vary considerably with respect to weight, inside cylindrical diameter, and inside bottom curvature. In the newer process the vessel is made from large-bore glass tubing, and the bottom of the vessel is shaped manually from the outside. The tubing-produced vessels examined compare closely with respect to weight and inside cylindrical diameter. However, the inside bottom curvature varies from one vessel to the next. Vessels made from the tubing process are in widespread use. Many vessels made from the older process do not pass the USP requirement that the inside diameter be 10.0–10.5 cm.

A plastic vessel[2] formed by injection molding has been available since 1979. The variation in physical dimensions (including bottom curvature) of individual plastic vessels is less than that of glass vessels because of the manner in which they are produced. Both types of vessels are currently recognized by the USP as being suitable for dissolution testing.

The effect of variations in physical dimensions of the vessels on dissolution results was studied. The study of the molded glass vessels was conducted under the test conditions described in the Fourth Supplement to USP XIX (3); *i.e.*, the stirring element consisted of a shaft with a detachable paddle blade positioned on the side of the shaft. The tubing-produced glass vessels and plastic vessels were studied with the currently official stirring element (4). The tubing-produced glass vessels and plastic vessels are compared for their suitability for use in the USP dissolution test for prednisone tablets.

EXPERIMENTAL

A commercial sample of 5-mg prednisone tablets was used to check the performance of dissolution equipment. Dissolution results from these tablets were reported recently (5). The tablets are reasonably uniform in total drug content. A randomly selected 60-tablet subsample gave an overall average result of 97.2% of label claim with a coefficient of variation (CV) of 2.88% in a content-uniformity assay (6). The average weight of the tablets was 143 mg. This tablet sample was referred to as Tablet 1 (7).

In 1979 a commercial sample of 10-mg prednisone tablets, referred to as Tablet 2, was characterized (the supply of Tablet 1 was running low). This second performance standard gave an average result of 100.0% of label claim with a CV of 1.5% when 20 tablets were subjected to content-uniformity assay. The average tablet weight was 225 mg. Both Tablet 1 and Tablet 2 disintegrate within 2 min into coarse, insoluble granules which stay on the bottom of the vessel throughout the test. The granules from three disintegrated units of Tablet 1 visually appear to occupy about the same volume in the bottom of the vessel as the granules from one disintegrated unit of Tablet 2.

Evaluation of Molded Glass Vessels—Three laboratories[3], each using a commercially available six-spindle dissolution apparatus[4], compared dissolution results from four sets of six molded glass vessels. Tablet 1 was used by all three laboratories. The data from this experiment were collected prior to the modification of the apparatus; *i.e.*, the apparatus described in the Fourth Supplement to USP XIX was used. All other experimental data reported in this paper were collected using the current apparatus.

Evaluation of Glass Tubing-Produced Vessels—An apparatus described previously (7) was selected for this experiment. The apparatus

[1] Kimble, Division of Owens-Illinois, Inc., Vineland, NJ 08360.
[2] Eli Lilly and Co., Indianapolis, IN 46206.
[3] Food and Drug Administration laboratories located in Los Angeles, Calif., St. Louis, Mo., and Winchester, Mass.
[4] Hanson Research Corp., Northridge, CA 91324.

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Table I—Dissolution Results (Percent of Label Claim) for Tablet 1 from Three Laboratories Using Four Sets [a] of Molded Glass Vessels

	Vessel Set											
	1			2			3			4		
Laboratory	n	$\bar{x}$	$\pm SD$	n	$\bar{x}$	$\pm SD$	n	$\bar{x}$	$\pm SD$	n	$\bar{x}$	$\pm SD$
A	—	—	—	—	—	—	12	52.4	1.82	24	37.5	3.48
B	24	43.2	3.18	—	—	—	24	49.3	1.66	12	42.7	5.90
C	6	40.0	3.94	24	52.0	3.15	—	—	—	—	—	—

[a] Vessel sets 1 and 3 originated from laboratory B. Vessel set 2 originated from laboratory C. Vessel set 4 originated from laboratory A.

Table II—Dissolution Data [a] for Tablet 1 from Glass Tubing-Produced Vessels Rearranged for Two-Way ANOVA

	Position						Vessel	
Vessel	1	2	3	4	5	6	$\bar{x}^b$	$\pm SD^b$
1	51.4	53.7	54.6	60.0	58.6	63.5		
	52.0	52.9	54.8	58.9	60.7	63.4	57.0	4.33
2	53.3	54.9	57.3	57.7	53.2	63.5		
	54.3	55.3	56.9	59.1	54.0	61.0	56.7	3.22
3	56.1	51.5	53.9	62.3	59.5	58.7		
	52.3	52.9	53.1	60.9	59.1	58.7	56.6	3.72
4	54.5	49.8	51.8	61.0	53.8	57.5		
	52.1	51.5	50.5	60.1	55.8	58.1	54.7	3.78
5	53.6	56.2	57.3	62.2	56.1	62.5		
	54.3	55.0	56.2	60.7	58.1	62.4	57.9	3.26
6	56.2	56.1	55.9	60.9	64.4	59.4		
	57.8	57.6	56.5	60.7	59.6	60.7	58.8	2.60
Position $\bar{x}$	54.0	54.0	54.9	60.4	57.7	60.8		
Position SD	1.96	2.30	2.22	1.33	3.29	2.25		

[a] Percent of label claim dissolved at 30 min. [b] Mean and standard deviation of 12 individual tablets.

Table III—Dissolution Data [a] for Tablet 1 from Plastic Vessels Rearranged for Two-Way ANOVA

	Position						Vessel	
Vessel	1	2	3	4	5	6	$\bar{x}^b$	$\pm SD^b$
1	38.4	36.9	38.0	49.0	42.3	48.9		
	38.5	38.4	38.6	46.8	40.3	47.6	42.0	4.73
2	42.3	38.6	39.2	47.8	40.5	51.2		
	37.8	37.8	39.1	49.3	44.0	49.8	43.1	5.11
3	37.1	38.8	38.4	46.0	42.4	45.5		
	38.2	38.5	36.3	51.5	39.9	47.2	41.7	4.82
4	38.8	42.0	42.0	44.3	45.2	49.4		
	39.9	41.3	39.4	51.2	44.5	49.2	43.9	4.16
5	40.5	38.0	40.7	50.7	42.2	46.9		
	39.5	36.7	46.8	51.8	41.0	50.5	43.8	5.30
6	40.8	40.5	47.2	56.3	45.5	54.7		
	44.1	41.6	42.6	52.0	42.7	51.2	46.6	5.60
Position $\bar{x}$	39.7	39.1	40.7	49.7	42.5	49.3		
Position SD	2.01	1.81	3.41	3.24	1.92	2.44		

[a] Percent of label claim dissolved at 30 min. [b] Mean and standard deviation of 12 individual tablets.

can be aligned to conform to USP specifications, but shafts 4 and 6 are not parallel with the other four shafts. Six glass tubing-produced vessels, purchased specifically for this experiment, were numbered one through six and placed in the apparatus. Two sets of six tablets each were subjected to the dissolution test (one tablet per vessel for each set of tablets). 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 apparatus. A total of 72 tablets was subjected to the test. Twelve dissolution results were associated with each vessel, which had been sequentially placed in all six positions. Likewise, 12 results were associated with each position in which all six vessels had been sequentially placed. The experiment was conducted with Tablet 1 and then with Tablet 2.

Evaluation of Plastic Vessels—The plastic vessels were evaluated in the same manner as the glass tubing-produced vessels; the same apparatus was used. The experiment was conducted with Tablet 1 and then Tablet 2.

Evaluation of Inside Bottom Curvature of Vessels—The water was removed from the bath used with the dissolution apparatus. The empty vessels were placed in position in the base of the apparatus. A slurry of 60 g of plaster of Paris and 50 ml of water was poured into each vessel and allowed to set for 1–2 hr. The vessels were removed from the apparatus, and the plaster casts were removed. The casts retained the exact shape of the bottom inside curvature of the vessels.

RESULTS AND DISCUSSION

The data obtained from different sets of molded glass vessels are given in Table I. With different sets of vessels, a mean difference of 8.8% of label claim was obtained between laboratories B and C for Tablet 1. When the same vessels were used to analyze Tablet 1 in both laboratories, the mean difference between laboratories dropped to 3.2%. When two sets of vessels were exchanged between laboratories A and B, mean results of 52.4 and 49.3% of label claim, respectively, were obtained using one set, and 37.5 and 42.7% of label claim were obtained for laboratories A and B, respectively, using the other set of vessels.

The data indicate that there are significant differences between laboratories, even when the same vessels are used. The bias in results between the laboratories was reduced considerably when the same sets of vessels were available to each laboratory. These vessels vary considerably with respect to flange thickness, inside diameter, and inside bottom curvature. A correlation between the physical dimensions of the vessels and the dissolution data is difficult to make because of this lack of uniformity in all three critical areas. However, when plaster casts were made of the bottom of the vessels originally used by laboratory A, the impressed curvatures came to a distinct blunted point at what would be the bottom of the vessel. These curvatures were steeper than that of a sphere with a diameter equal to the width of the vessel. These vessels also gave the lowest results for Tablet 1.

The data collected in the evaluation of the plastic and glass tubing-

Table IV—Dissolution Data [a] for Tablet 2 from Glass Tubing-Produced Vessels Rearranged for Two-Way ANOVA

Vessel	Position 1	2	3	4	5	6	Vessel $\bar{x}^b$	$\pm SD^b$
1	37.5	36.7	34.9	58.7	45.8	46.5		
	34.9	35.2	33.9	55.1	51.1	48.5	43.2	8.81
2	35.5	35.7	39.3	52.0	37.3	57.0		
	34.8	35.1	33.0	44.6	53.0	51.5	42.4	8.70
3	33.9	35.6	34.5	57.7	36.7	55.0		
	36.2	34.7	33.3	46.6	38.1	53.0	41.3	9.15
4	32.6	38.1	33.7	40.6	42.0	54.0		
	32.3	34.0	38.9	49.0	37.7	47.1	40.0	6.95
5	36.0	39.3	49.8	65.2	39.9	61.0		
	37.1	35.6	52.8	72.0	53.2	58.8	50.1	12.50
6	56.8	49.6	39.6	69.5	57.5	58.2		
	34.0	38.2	51.4	61.5	40.6	64.5	51.8	11.47
Position $\bar{x}$	36.8	37.3	39.6	56.0	44.4	54.6		
Position SD	6.50	4.18	7.49	9.93	7.41	5.62		

[a] Percent of label claim dissolved at 30 min. [b] Mean and standard deviation of 12 individual tablets.

Table V—Dissolution Data [a] for Tablet 2 from Plastic Vessels Rearranged for Two-Way ANOVA

Vessel	Position 1	2	3	4	5	6	Vessel $\bar{x}^b$	$\pm SD^b$
1	35.4	38.3	39.7	42.1	40.8	47.6		
	38.8	37.5	37.2	46.4	45.7	47.5	41.4	4.35
2	36.6	40.9	33.7	42.2	42.6	41.7		
	38.0	34.9	37.5	44.7	35.1	41.9	39.2	3.62
3	40.3	31.8	32.8	44.9	37.1	48.8		
	33.2	40.0	34.4	45.3	41.1	46.9	39.7	5.90
4	39.9	35.3	39.3	45.5	35.5	47.1		
	35.7	33.5	41.9	43.2	39.8	41.1	39.8	4.25
5	38.4	33.0	33.5	44.1	39.7	42.7		
	33.8	33.9	39.2	46.4	37.4	41.4	38.6	4.49
6	34.4	38.4	38.4	47.7	34.5	44.0		
	37.6	32.1	40.1	45.6	36.3	44.7	39.5	4.99
Position $\bar{x}$	36.8	35.8	37.3	44.8	38.8	44.6		
Position SD	2.36	3.12	3.01	1.71	3.40	2.84		

[a] Percent of label claim dissolved at 30 min. [b] Mean and standard deviation of 12 individual tablets.

produced vessels were analyzed by a two-way analysis of variance (ANOVA) (8). The data collected from the test runs[5], rearranged for the ANOVA, are shown in Tables II–V. The data in the rows are for the individual vessels and the data in the columns are for the individual positions on the apparatus. (For example, the data in row one are the dissolution results from vessel one after it had been placed in all six positions; the data in column one are the dissolution results from position one after all six vessels had been rotated to position one.) Table VI shows the results of the ANOVA for each combination of tablet and vessel.

Table VI shows the difference between the mean dissolution results for 72 tablets of Tablet 1 with the glass tubing-produced vessels and with the plastic vessels. Ideally the results should compare closely if both types of vessels are equivalent for use with Apparatus 2. However, the glass vessels give results that are higher by 13.5% of label claim.

Tablet 2 responded in a similar manner, but the overall difference in results is smaller (5.1%). The difference between the mean squares of the data from these two sets of vessels is more pronounced. The total mean square for the Tablet 2 results collected from the glass vessels is over five times that of the plastic vessels.

Each of the mean squares listed in Table VI for Tablet 1 or 2 is an independent estimate of the variance of that particular tablet. These independent estimates differ widely from each other in most instances. The smallest variance is the within-groups mean square, which is the pooled variance of the tablets taken under the most repeatable conditions for each experiment, *i.e.*, the mean of the variances derived from the duplicate results. The square root of the within-groups mean square gives the best estimate of the inherent standard deviation of the tablets. The standard deviation of Tablet 1 is 1.1% of label claim in the glass vessels and 2.0% of label claim in the plastic vessels. The standard deviation of Tablet 2 is 5.5% of label claim in the glass vessels and 2.7% of label claim in the plastic vessels. The overall standard deviations, derived from taking the square root of the respective total mean squares, are 3.6, 5.1, 10.4, and 4.6% of label claim. Thus, Apparatus 2 is not measuring the variation of the tablets. Instead, the tablets are measuring the variations in Apparatus 2.

[5] The data, in the original order taken, are available from the authors upon request.

The within-groups mean square was divided into mean squares associated with the vessels, apparatus position, and the interaction between vessels and apparatus position to obtain the F ratios shown in Table VI. The magnitudes of the F ratios indicate that there are statistically significant differences in the mean dissolution results associated with the individual vessels and apparatus positions. Tablet 1 showed differences between the individual glass vessels and between the individual plastic vessels. Tablet 2 showed differences only between the individual glass vessels. Both tablets showed differences between the apparatus positions. Finally, Tablet 1 revealed a significant interaction between the glass vessels and the apparatus positions.

Tables II–V clearly show where the major sources of the variations are located. The mean results of 12 tablets associated with a position on the dissolution apparatus (the column means) show that positions 4 and 6 give higher results than positions 1, 2, 3, and 5 for each combination of tablet and vessel type. It was established previously (7) that the paddle shafts in positions 4 and 6 were not parallel with the other four shafts. If the other four shafts were made vertical, shafts 4 and 6 would each be misaligned in relation to the vertical axis of the respective vessel. Though misaligned, the shafts still meet the USP specification because each is within 0.2 cm of the vertical axis of its vessel at all points along the shaft. The manufacturers of dissolution equipment must take special care in the design and manufacture of their equipment if this source of variation is to be reduced.

The mean results of 12 tablets associated with the glass vessels in Tables II and IV show that vessel 4 gives the lowest mean and vessels 5 and 6 the highest means for both Tablet 1 and Tablet 2. The rank correlation from the vessel giving the lowest results to the vessel giving the highest results is the same for both samples (vessels 4, 3, 2, 1, 5, 6). The mean results for the plastic vessels from Tablet 1 (Table III) showed statistically significant differences; however, the mean results from Tablet 2 (Table V) were not significantly different. These findings indicate that Tablet 1 is being affected by a characteristic of the plastic vessels to which Tablet 2 does not respond.

Plaster casts were made of the lower bottom curvatures of both sets of vessels. Visual inspection of the casts showed that all six of the glass vessels had a flattened area on the bottom. The flattened area was not uniform from one glass vessel to the next. Vessels 1, 2, and 3, although

Table VI—Results of Two-Way ANOVA from Data Presented in Tables II—V

	Tablet 1				Tablet 2				
	Glass		Plastic		Glass		Plastic		
	Mean Square	*F* Ratio	Mean Square	*F* Ratio	Mean Square	*F* Ratio	Mean Square	*F* Ratio	*F*.95
Vessels (rows)	23.0	18.2	37.8	9.8	288.2	9.5	10.7	1.4	2.5
Apparatus position (columns)	117.6	93.2	278.1	71.6	886.9	29.4	193.3	26.2	2.5
Interaction	7.5	6.0	4.0	1.0	31.3	1.0	7.9	1.1	1.8
Subtotal	25.5		48.0		190.2		34.8		
Within-groups	1.3		3.9		30.2		7.4		
Total	13.2		25.6		109.1		20.9		
Mean for 72 tablets	57.0		43.5		44.8		39.7		

exhibiting a flattened area, possessed some curvature over this area. Vessels 5 and 6 had areas of ~1 cm in diameter that were almost completely flat. Vessel 4 exhibited a curvature similar to vessels 5 and 6, except that there was a small indentation in the middle of the flattened area.

Plaster casts revealed that all six plastic vessels had uniform bottom curvatures which were considerably greater than the curvatures of the glass vessels. The bottom curvatures of the plastic vessels did not vary from one vessel to the next as determined by visual comparison of the plaster casts.

It is known that dissolution rate depends on the surface area of the dissolving substance in contact with the dissolution medium and the velocity of the liquid passing over the substance (9). A tablet which disintegrates fairly rapidly into granules of sufficient specific gravity will appear as a rotating cone-shaped mass of particles on the bottom of the dissolution vessel shortly after being introduced to Apparatus 2 (Fig. 1). If the inner surface of the vessel is symmetrical around the center axis of the paddle, liquid flow in a vessel with a small indentation in the bottom or with a steeper curvature will gather the particles into a more compact mass than in a vessel with a flatter curvature. If the inner surface of the vessel is not symmetrical around the center axis of the paddle, the liquid flow in the vessel will not be symmetrical; the tablet particles will be more agitated, and the conical shape of the mass of particles may be disrupted as the asymmetrical flow of liquid buffets the particles. Asymmetrical liquid flow can be generated by a misaligned paddle, *i.e.*, a paddle whose center axis does not coincide with the cylindrical axis of the vessel, as well as by a vessel that is not symmetrical.

These hypotheses may explain the differences between the tablet results associated with the glass vessels and with apparatus positions. They may also explain the fact that significant interactions exist between the glass vessels and the apparatus positions for Tablet 1. If the individual vessel curvature and paddle misalignment are unique, the liquid flow pattern, and thus the tablet results, will be unique for that combination.

Tablet 1 revealed significant differences which were associated with the plastic vessels. Table III shows that vessel 6 gave higher results than the other five vessels. No physical difference was observed which would account for the higher results in vessel 6. Vessel 6 was obtained at a later time to replace one of the original vessels that was broken before any testing was conducted. As the manufacturing history of none of the vessels is known, this observation may be meaningless; on the other hand, it may point to a subtle difference in manufacture of the plastic vessels.

Since the plastic vessels are physically more uniform than the glass vessels, the plastic vessels are preferable for dissolution testing. The chance for bias in dissolution results between laboratories is less if the plastic vessels are used. The USP specifies that the inside bottom curvature for the dissolution vessels be spherical. Thus, a quantitative determination of vessel curvature for comparison to that of a sphere is required before a conclusion can be reached about the suitability of the vessels for use in the USP dissolution test.

The following relationship exists between the diameter of a circle and a chord parallel to the diameter:

$$D = (L^2/4h) + h \qquad \text{(Eq. 1)}$$

where D is the diameter, L is the chord length, and h is the perpendicular distance from the center of the chord to the circumference of the circle.

A diameter was calculated from the equation for each vessel by determining the values of h and L. A mechanic's depth gauge[6] was used for

Table VII—Physical Measurements [a] Relating to Vessel Curvature

Vessel		h [b]	Diameter	
			Calculated	Measured
Glass	1	11.5	107.9	103.2
	2	11.9	105.1	102.1
	3	11.5	107.9	100.7
	4	10.7	114.3	102.7
	5	9.9	121.9	102.3
	6	10.7	114.3	101.7
Plastic	1	12.3	102.5	101.5
	2	12.7	100.0	101.2
	3	12.3	102.5	101.4
	4	12.7	100.0	101.3
	5	12.7	100.0	101.2
	6	12.7	100.0	101.4

[a] All measurements in mm. Chord length (L) was 66.6 mm in all vessels. [b] Perpendicular distance from center of chord to circumference of circle.

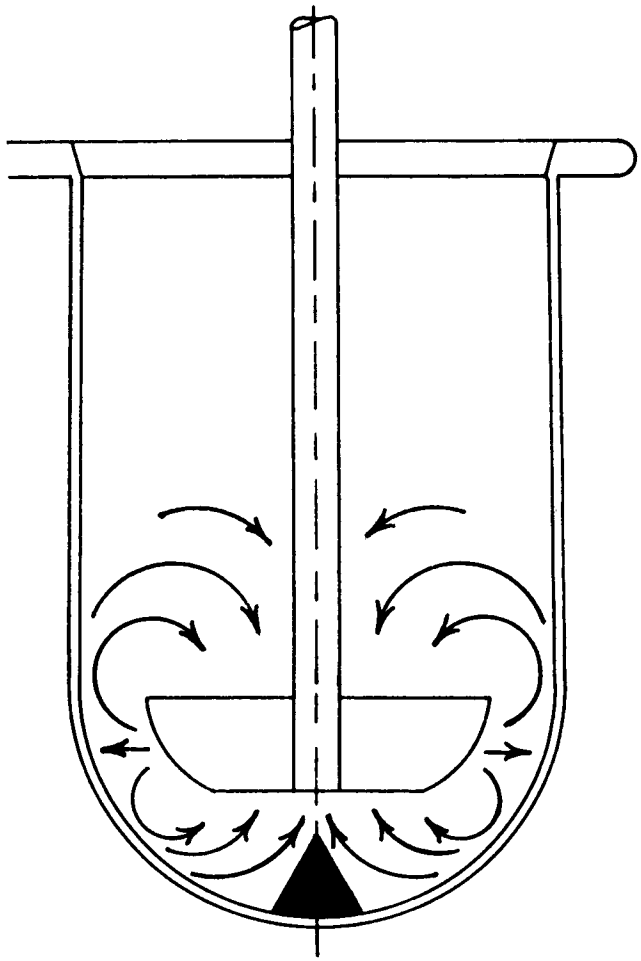

Figure 1—*Vertical cross-sectional view of USP Apparatus 2 illustrating formation of cone-shaped mass of particles due to a symmetrical liquid flow.*

[6] Combination depth and angle gauge, No. 236, L. S. Starrett Co., Athol, MA 01331.

this purpose. The base of the gauge was measured for the chord length (L). The gauge was then set inside the vessel with the ends of the gauge base resting on the curved surface of the vessel. The distance (h) between the base and the bottom of the vessel was taken from the gauge rule. The cylindrical diameter of the vessel was then taken 2 to 3 cm above opposite points where a tangent to the curved bottom of the vessel coincides with the vessel wall. Inside calipers were used for this purpose.

Table VII shows the measurements taken from the vessels and the comparison of the theoretical diameters calculated from these measurements with the actual diameters. The glass vessels possess a flatter curvature than a sphere of the same diameter. The curvature of the plastic vessels closely approximates a sphere of the same diameter. When the results from plastic vessels differ from those obtained from glass vessels, the results from the plastic vessels are more correct, because the plastic vessels conform more closely to the USP specifications.

CONCLUSIONS

Differences in the bottom curvature of dissolution vessels can cause bias in the dissolution results obtained from prednisone tablets. Vessels with a curvature which is less (flatter) than that of a sphere cause a high bias. Vessels with a curvature that is greater (steeper) than that of a sphere cause a low bias. The plastic vessels are more uniform than glass vessels and possess a curvature that more closely approximates the curvature specified in the USP. As such, they are preferable to the glass vessels for use in the dissolution test when the drug is not adsorbed and the vessel is not attacked by the dissolution medium.

The dissolution rate is controlled by the velocity of the liquid passing over the tablet. The liquid velocity at any point in a stirred vessel is controlled by the stirring rate and the geometry of the system. An idealized geometry is defined in the USP. Minor variations from this idealized geometry, such as those discussed in this paper and previously (7), change the liquid velocity in the vicinity of the tablet and, thus, the dissolution results. If the reproducibility of the test is to be improved, equipment must be made available which allows the analyst to adhere to this idealized geometry as closely as possible.

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HPLC Determination of D and L Moxalactam in Human Serum and Urine

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ABSTRACT □ A high-pressure liquid chromatographic procedure was developed to determine the D and L isomers of moxalactam in human plasma and urine. After protein precipitation with hydrochloric acid the sample was extracted with ethyl acetate. It was then back extracted into tromethamine buffer (pH 8.0) and washed with octanol. Extraction recovery from plasma ranged from 73–81%. An aliquot of the tromethamine buffer was then injected onto a C_{18}-μBondapak column. The mobile phase was 3% acetonitrile in 0.05 *M* ammonium acetate pH 6.5 buffer. Samples were quantitated by UV detection at 275 nm and 0.01 aufs. The lower limit of detection was 0.5 μg/ml for each isomer. Preliminary stability studies were performed to assess proper sample handling and storage conditions. The procedure was evaluated in a clinical setting to demonstrate its applicability to the study of moxalactam pharmacokinetics in critically ill patients.

Keyphrases □ Moxalactam—determination in human plasma and urine by high-pressure liquid chromatography, D and L isomers □ High-pressure liquid chromatography—determination of moxalactam in human plasma and urine, D and L isomers □ Anti-infectives—moxalactam, high-pressure liquid chromatographic determination, D and L isomers

Moxalactam is a new oxycephalosporin derivative undergoing clinical trials in the United States and Europe. *In vitro* experiments have demonstrated that moxalactam is active against a broad spectrum of microorganisms, including resistant Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Bacteroides fragilis*, some indole-positive *Proteus* species (1), β-lactamase-producing strains of *Enterobacteriaceae* (2), and clinical isolates shown to be cephalosporin resistant (3). Its expanded spectrum of activity compared to conventional β-lactam antibiotics is attributed to replacement of the thio group at the 1 position of the dihydrothiazine nucleus with an oxygen moiety (4).

The pharmacokinetics of moxalactam elimination usually have been evaluated employing standard microbiological techniques (5, 6). However, a more specific analytical procedure was required for pharmacokinetic studies of this compound in critically ill patients. A high-pressure liquid chromatographic (HPLC) assay developed recently, although more specific than microbiological techniques, had limited applicability in the critical care setting[1]. A more specific HPLC analysis was required for studies in seriously ill patients. The present report describes a suitable HPLC procedure for the quantitation of both moxalactam isomers in patient plasma and urine.

[1] D. J. Miner, D. L. Coleman, A. M. Shephend, and T. Hardyn, Antimicrob. Agents Chemother., in press.

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