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TECHNICAL ARTICLES

Variation in Dissolution Data Using an Apparatus Meeting USP–NF Requirements

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Abstract □ Variation in dissolution results between the two vessels recommended in USP XVIII and NF XIII prompted an investigation of vessel shape and its effect on dissolution. Further testing was carried out with a dissolution vessel whose concavity was obviously different from those recommended but still within compendial specifications. The dissolution results obtained in this modified apparatus were different from those obtained in the recommended vessels under the particular conditions of the test used. (The difference in results between the two recommended vessels was subsequently shown not to be statistically significant, although the modified vessel did cause changes.) A possible explanation for these observations is presented.

Keyphrases □ Dissolution tests—effect of vessel shape (concavity), compendial dissolution vessels, modified vessel □ Vessels for dissolution testing—effect of shape (concavity) on dissolution rates, compendial vessels, modified vessel □ Glass dissolution vessels—effect of shape (concavity) on dissolution rates, compendial vessels, modified vessel

Eight monographs carry a dissolution test requirement in USP XVIII (1) and six do so in NF XIII (2). Cooper and Hersey (3) presented a tabulation of these preparations and their specifications. Recently, Beyer and Smith (4) reported on an unexpected variable (vibration) in the USP–NF test. The purpose of this article is to report on an additional source of variation possible in the official test methods.

The compendia in their latest revisions include specifications for the rotating-basket method of dissolution testing. USP XVIII states that the vessel, which is one of four parts of this apparatus, must meet the following requirements: ". . . a covered, 1000 ml. vessel made of glass or other inert, transparent material; . . .. The vessel is cylindrical, with a slightly con-

Table I—Effect of Vessel Type on Hydrochlorothiazide Dissolution

Sample	Percent Hydrochlorothiazide —Dissolved in 30 min.[a]— Kimble	Pyrex
1	85	80
2	88	80
3	88	80
4	95	84
5	—[b]	81
6	—	79
Mean	89	81

[a] The USP XVIII monograph for hydrochlorothiazide tablets contains a specification of not less than 60% of labeled amount dissolved in 30 min. [b] Only four Kimble vessels were available for this initial study.

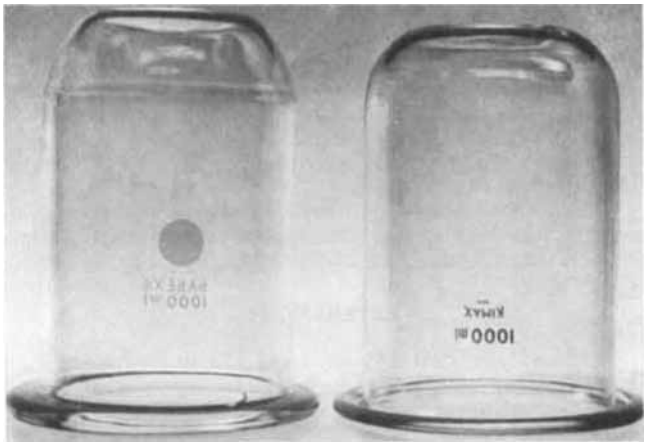

Figure 1—*Commercially available dissolution vessels with slight difference in concavity.*

cave bottom. It is 16 cm. high and is 10 cm. in inside diameter, and its nominal capacity is 1000 ml."

In addition, the USP states: "A suitable vessel is available commercially from laboratory supply houses as Pyrex No. 6947 or as Kimble Glass No. 33700."

Analysis of data from dissolution studies in these laboratories showed that slight differences were obtained when the two recommended reaction vessels were used. This finding prompted an investigation to show the effect of changes in reaction vessels on dissolution values.

EXPERIMENTAL

Materials—Hydrochlorothiazide tablets[1], 50 mg., were taken from two production lots.

Dissolution Studies—The test method for hydrochlorothiazide tablets specified in USP XVIII was followed. Only changes in the glass vessel were made, and those are described in the text. In some instances, the dissolution apparatus with multiple-testing stations, described by Castello *et al.* (5), was employed.

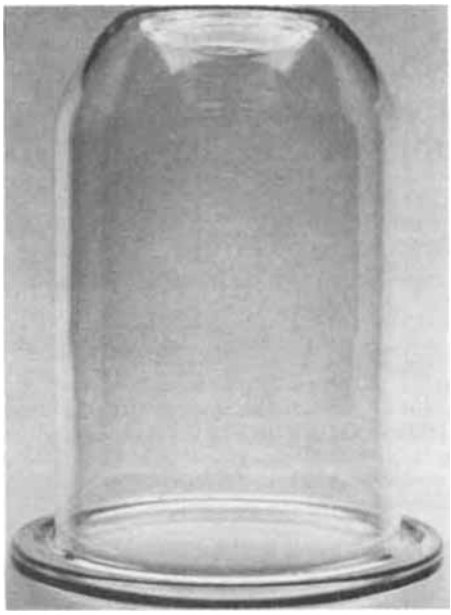

Figure 2—*Fabricated dissolution vessel.*

[1] HydroDiuril, Merck Sharp & Dohme, West Point, Pa.

Table II—Comparison of Dissolution Values between USP Recommended and Fabricated Vessels

	Percent Hydrochlorothiazide Dissolved in 30 min.			
	USP Recommended Vessels[a]		Fabricated Vessel	
	Pyrex	Kimble	Sample I Group	Sample II Group
Batch 1				
Mean	86[b]	86[c]	52[d]	59[d]
High	95	91	61	65
Low	80	79	45	52
Batch 2				
Mean	93[b]	93[c]	62[d]	63[d]
High	96	97	70	75
Low	90	86	53	55

[a] Although the differences between Pyrex and Kimble Glass vessels were not found to be statistically significant in this particular test, the matter is one of degree. Data in the text show dissolution differences caused by a change in curvature. Therefore, the slight changes between Pyrex and Kimble Glass could possibly show up in a more discriminating test. [b] Mean of five individual measurements. [c] Mean of 13 individual measurements. [d] Mean of 18 individual measurements.

RESULTS AND DISCUSSION

Slight differences (Table I) in the dissolution results for hydrochlorothiazide tablets, 50 mg., were observed when the test was simultaneously performed in Pyrex and Kimble Glass vessels, both of which are recommended by the USP. A Student t test performed on the mean values (6) indicated that they are statistically different ($p < 0.005$).

It was noted that the concavity at the bottom of the two flasks was different, being slightly greater in the Pyrex flask than in the Kimble Glass. A slight difference in shape at the bottom was also observed. These differences are illustrated in Fig. 1. It was hypothesized that both the concavity and the shape were changing the hydrodynamics within the dissolution medium enough to cause a significant change in the resulting dissolution patterns.

For comparative purposes, a third type of vessel was obtained (Fig. 2). The concavity of this vessel is more than *slight*, although the authors maintain that the vessel conforms to official specifications since such interpretation is left to the individual investigator. For example, the schematic illustration of the dissolution apparatus in NF XIII (p. 802) shows a generous concavity in the flask.

Subsequent and more comprehensive testing indicated that the observed differences between the two recommended dissolution vessels were statistically insignificant. The results obtained in the fabricated vessel, however, were significantly different from both of the other vessels (Table II).

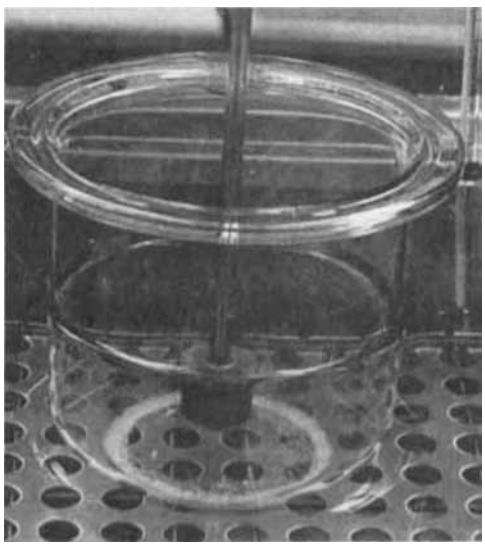

Figure 3—*Granules at bottom of fabricated dissolution vessel.*

Table III—Rotational Effect on Dissolution in the Various Vessels

Vessel	Percent Hydrochlorothiazide Dissolved in 30 min.—Rotational Speed of Basket			
	50	100	150	200
Pyrex	21	69	91	96
	22	74	92	98
Kimble	36	78	87	94
	18	70	80	96
Fabricated	22	69	55	63
	24	68	68	70

[a] Values are for individual samples.

During the test, one could observe particles of the disintegrated tablet forming a ring at the bottom of the fabricated flask (Fig. 3).

It is not likely that one would use the type of dissolution vessel shown in Fig. 2 when the other two types are commercially available. There are, however, other commercially available resin pots or dissolution vessels and possible differences of the type illustrated could occur with these vessels. These could be important to a formulator or a quality control investigator working with other products and under varying conditions. Finally, the testing discussed here was done at 150 r.p.m., as called for in the USP XVIII monograph for hydrochlorothiazide tablets. The data presented in Table III appear to indicate that the magnitude of the difference between the various flasks is a function of the basket's rotational speed. This phenomenon will be dependent not only on the hydrodynamics in the bulk of the solution but, more importantly, in the concavity at the base of the flask where the granules tend to accumulate and lie relatively undisturbed.

Each product having a dissolution test in its USP XVIII or NF XIII monograph should be investigated in this manner. Such studies are underway in these laboratories.

CONCLUSIONS

These observations led to the following conclusions:

1. The shape of the dissolution flask, which is not clearly defined in USP XVIII and NF XIII, can significantly affect dissolution patterns (ostensibly by affecting hydrodynamics).
2. The magnitude of these differences is a function of the rotational speed of the USP basket.
3. Formulators should be aware that these differences exist, and it is recommended that there be more definitive specifications for the dissolution vessel in the compendia.

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NOTES

Muscarinic Receptors: 2-Trimethylammonium-7-oxabicyclo[2.2.1]heptane Iodide Epoxides and 2-Trimethylammoniumbicyclo[2.2.1]heptane Iodides

WENDEL L. NELSON▲, DAVID R. ALLEN, and FRANK F. VINCENZI

Abstract □ The syntheses of *endo-* and *exo*-2-trimethylammonium-*exo*-5,6-epoxy-7-oxabicyclo[2.2.1]heptane iodides are reported. Muscarinic assay results are reported and compared with *endo-* and *exo*-2-trimethylammoniumbicyclo[2.2.1]heptane iodides. Of the compounds tested, only *exo*-2-trimethylammoniumbicyclo-[2.2.1]heptane iodide demonstrated muscarinic activity, but it was only marginally active.

Keyphrases □ 2-Trimethylammonium-7-oxabicyclo[2.2.1]heptane iodide epoxides—synthesized and screened for muscarinic activity □ 2-Trimethylammoniumbicyclo[2.2.1]heptane iodides—synthesized and screened for muscarinic activity □ Muscarinic activity—2-trimethylammonium-7-oxabicyclo[2.2.1]heptane iodide epoxides and 2-trimethylammoniumbicyclo[2.2.1]heptane iodides

In a previous study (1), conformationally rigid analogs of the cholinergic agonist muscarine (I) in the 7-oxabicyclo[2.2.1]heptane system were reported. In that report, *endo-* and *exo*-2-trimethylammonium-7-oxabicyclo[2.2.1]heptane iodides (II and III) showed only marginal muscarinic activity. This report describes an effort to prepare additional compounds in the series, namely the 5,6-epoxides and 6-oxygenated species, which are more closely related to muscarine. To compare II and III with their carbon analogs, *endo-* and *exo*-2-tri-