Drug Information Journal, Vol. 30, pp. 1055–1061, 1996
Printed in the USA.
0092-8615/96

CALIBRATION—THE USP DISSOLUTION APPARATUS SUITABILITY TEST

SAEED A. QURESHI, DSC

Research Scientist, Bureau of Drug Research, Drugs Directorate, Health Protection Branch, Ottawa, Ontario, Canada

This report summarizes some trends observed in drug dissolution testing, based upon the United States Pharmacopeia (USP) dissolution Apparatus Suitability Test results and the preliminary data obtained from an international collaborative study to assess the pharmaceutical quality of furosemide products in different countries. Based on the USP calibrator data submitted by the participants, representing four lots each of nondisintegrating (Salicylic Acid) and disintegrating (Prednisone) tablets, overall variability can be high and failures to meet the specification in a dissolution run can be frequent. This high level of variability and failure seems to be dependent on the combination of calibrator and apparatus type. Although deaeration of dissolution media tends to reduce the frequency of failure, its effect on reducing the variability appears to be minimal. It appears that calibrator-apparatus combinations of Prednisone tablets/Basket Method and Salicylic Acid tablets/Paddle Method show some sort of interaction, therefore, use of these combinations to test suitability of dissolution apparatus needs to be evaluated. Prednisone Tablets with the Paddle Method and Salicylic Acid Tablets with the Basket Method, however, appear to provide sufficient information for dissolution apparatus calibration and their use should be continued.

Key Words: Drug dissolution; United States Pharmacopeia; Apparatus

DRUG DISSOLUTION STUDIES are commonly conducted using basket (Apparatus 1) and paddle (Apparatus 2) methods as described in the official compendia (eg, USP, Eur. Ph.). The USP requires that, before using the dissolution apparatuses for drug product analysis, they are to be calibrated with the USP calibrators according to the *Apparatus Suitability Test* described in the pharmacopeial general dissolution testing monograph (1). The calibrators used for the evaluation are of two types, that is, disintegrating (Prednisone tablets) and nondisintegrating (Salicylic Acid tablets). The instruments are considered suitable for dissolution experiments with drug products if the percent of drug released at 30 minutes from the calibrators using water (Prednisone tablets) or phosphate buffer pH 7.40 (Salicylic Acid tablets) falls within a preestablished range. These ranges for each combination of apparatus at 50 or 100 rpm and calibrators are established by the USP based on the data obtained from collaborative studies (eg, 2). The established ranges are usually different for each lot of calibrators.

As an example, the acceptance ranges of a recent lot for Prednisone and Salicylic Acid tablets are given in the Table 1. It is important to note that these values represent the percent

Presented at the DIA Workshop "*In Vitro* Dissolution of Immediate-Release (IR) Dosage Forms: Development, *In Vivo* Relevance and Quality Control Issues," June 6–7, 1995, Toronto, Ontario, Canada.

Reprint address: Saeed A. Qureshi, Bureau of Drug Research (PL # 2202C1), Drugs Directorate, Health Protection Branch, Tunney's Pasture, Ottawa, Ontario, K1A 0L2, Canada.

TABLE 1
USP Dissolution *Apparatus Suitability Test* Ranges as Described in the Sheets Accompanying the Calibrator Tablets. The Instruments are Considered Suitable for Dissolution Testing if the Percent Drug Release Values for Individual Tablets are Within the Specified Range

	PERCENT DISSOLVED AT 30 MINUTES			
	Apparatus 1 (Basket)		Apparatus 2 (Paddle)	
CALIBRATOR	50 (RPM)	100 (RPM)	50 (RPM)	100 (RPM)
Prednisone (Lot J)	6–23	43–63	46–59	58–69
Salicylic Acid (Lot K)	14–21	23–29	13–22	16–27

of drug release for individual vessels and not the averages, even though the dissolution devices are often equipped with six or 12 vessels and run simultaneously. For a vessel to be used for product dissolution testing it must, individually, provide acceptable drug release from the calibrator.

Although these calibrators have been in use for a number of years, there seems to be lack of a follow-up assessment of their efficiency, reproducibility, or perhaps justification of their continued use. There has been scattered discussion or communication, however, suggesting some concerns with the use of the calibrators (3,4,5).

During the process of developing guidelines for dissolution testing (6), an awareness was raised of relatively widespread concerns among pharmaceutical manufacturers in this regard. To address these concerns, or to learn about the probable problems associated with use of calibrators, a survey was conducted by obtaining file data on dissolution calibration from the industry and the Government Field Operation Laboratories. The results of this survey have been published separately (7,8).

The purpose of this report is to present some of the trends observed from the data and to suggest potential solutions for developing improved standards for calibration of dissolution apparatuses. Summarizing the data, along with discussions with the participants, three trends in dissolution can be observed with the USP *Apparatus Suitability Test*:

1. High variability,
2. Frequency of failures, and
3. An apparent lack of correlation with results obtained for drug products testing.

Table 2 shows the coefficient of variation (%CV) values for a dissolution run with different combinations of calibrators and apparatuses, mostly using six tablets per run. In some cases the variability is very high, in particular, for the Prednisone tablets/Basket Method combination. It is important to note that these are the values for sets which met the USP *Apparatus Suitability Test* criteria. The results are based on dissolution tests representing more than 1,600 sets of Prednisone (Lots G, H, I, and J) and Salicylic Acid (Lots H, I, J, and K) tablets. The variability does not appear to be lot-dependent, as the values were consistent across several lots of the calibrators.

There are no requirements with respect to the variability of the system within a set dissolution run. In fact, the *Apparatus Suitability Test* allows an extremely high variability for a dissolution test and this is a concern because it could impact on the development limits for a quality control (QC) test for a drug product.

In a recently conducted survey by the USP, based on the calibration results obtained for Lot J (Prednisone tablets) and Lot K (Salicylic Acid tablets) similar high variability in dissolution testing has also been reported (5). In fact, for the combination of

TABLE 2
Within-a-set Variation Calculated as Coefficient of Variation (CV%) in Percent Drug Released Using USP Calibrator Tablets *For Sets Which Met* the Suitability Requirements

			CV (%)	
APPARATUS	CALIBRATOR	RPM	NON-DEAERATED MEDIA	DEAERATED MEDIA
1 (Basket)	Prednisone	50	3.5–25.5	0.5–31.3
		100	0.9–21.7	0.6–21.7
	Salicylic Acid	50	0.0– 7.5	0.8–13.2
		100	0.0– 5.5	0.8– 6.2
2 (Paddle)	Prednisone	50	1.3–10.2	0.4–10.0
		100	0.6– 6.0	0.3– 4.6
	Salicylic Acid	50	3.7–14.2	0.7–17.0
		100	3.2–13.5	1.0–17.8

the Prednisone tablets/Basket Method, within-a-run variability was reported up to 37.6 (%CV).

The second trend is frequency of failures of the *Apparatus Suitability Test* which may significantly impact on the productivity of a laboratory. Consistently high percentages of failures are reported for Prednisone tablets with the Basket Method at 50 rpm (Table 3). Following an industry-wide survey to address the issues and difficulties with dissolution calibration, a similar observation is reported by McCormick (9) that: "A large majority of the respondents (94%) have had difficulty meeting the USP calibration tablet specifications . . . the largest problem reported (61%) was 'failing results' for no apparent reason."

To summarize, it can be said that the variability in percent drug release from calibrators appears to be dependent on the apparatus/calibrator combination which was observed as high as 31% in the case of the Prednisone tablets/Basket Method and up to

TABLE 3
Percentages of Dissolution-runs which did not Meet the USP Criteria for *Apparatus Suitability Test* Criteria According to Various Combinations of Apparatuses and Calibrators

			% FAILURES (OUT OF) REPORTED	
APPARATUS	CALIBRATOR	RPM	NON-DEAERATED MEDIA	DEAERATED MEDIA
1 (Basket)	Prednisone	50	44.4 (133)	9.5 (84)
		100	11.9 (101)	16.0 (94)
	Salicylic Acid	50	18.8 (96)	7.5 (80)
		100	13.8 (94)	6.9 (87)
2 (Paddle)	Prednisone	50	19.0 (105)	7.8 (128)
		100	9.4 (96)	6.5 (124)
	Salicylic Acid	50	12.5 (96)	9.0 (122)
		100	20.6 (97)	13.9 (122)

18% for the Salicylic Acid tablets/Paddle Method, in cases for which the dissolution apparatus would still comply with the USP criteria and thus be considered acceptable for evaluating marketed products. Similarly, failures to meet the *Apparatus Suitability Test* criteria also seem to be associated with calibrator/apparatus combinations. In particular, the Basket Method/Prednisone tablets combination was reported to result in the highest number of failures which were as frequent as 44.4% (Table 3).

Relevant to the dissolution *Apparatus Suitability Test* would be its implication for drug product testing, that is, if an apparatus shows results outside the expected range, one might expect to observe corresponding higher or lower percent drug release from a product. This does not, however, seem to be the case.

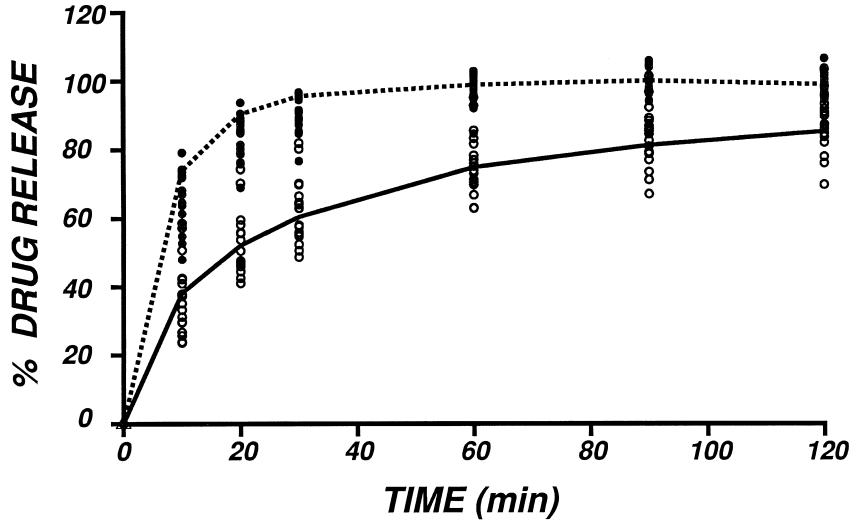
During a recently conducted international collaborative study to evaluate drug release characteristics of furosemide products available in different national markets, each participating laboratory was asked to calibrate its dissolution apparatus using the Prednisone calibrator, both at 50 and 100 rpm, using the Paddle Method. Also, each laboratory was sent a common sample, referred to as "standard sample" of 50 tablets of the same lot of innovator's furosemide (Lasix), to be analyzed using the Paddle Method at 50 rpm in addition to the marketed products from respective countries.

The release characteristics of the "standard sample" along with other furosemide products were analyzed in two media; one, as required in the USP monograph with phosphate buffer of pH 5.8 and the other using acetate buffer pH 4.6. The USP requirement, as the first stage criterion, is that percent drug release at 60 minutes in phosphate buffer is not less than 85%. The results for the "standard sample" from a particular laboratory are represented by lines, and data from other laboratories are shown as circles (Figure 1). The results for the "standard sample" from the particular laboratory show that it would meet the USP requirement and mean percent drug release profiles fall in the middle of the values reported by other laboratories. Similarly, in acetate buffer, drug release characteristics fall in the middle of data reported by other laboratories. This particular laboratory, however, reported that its dissolution apparatus would not meet the USP dissolution criteria. The *Apparatus Suitability Test* showed that drug release from Prednisone tablets is on the higher end and for one tablet, drug release is outside of the required range. More puzzling are the drug release characteristics from Prednisone at 100 rpm. The 50 rpm results show that the dissolution apparatus is producing higher percent drug release than expected or "average," however, at 100 rpm the results were in the low to medium range. In fact, drug release from one tablet at 100 rpm is about the level of others at the 50 rpm level.

The overall impression from preliminary evaluation of the data from the international collaborative study is that, with respect to the relationship between extent of drug release from calibrator and from a marketed drug product, there appears to be a poor correlation or association.

Analyzing the calibrator data in more detail suggests two possible causes of the trend of high variability, frequency of failure and, perhaps, low correlation of percent drug release from calibrators versus products. One is the deaeration of the media and the second is the combination of calibrator and apparatus types.

It has been suggested in the literature that, due to lower solubility of dissolved gases in the media at the higher temperature of 37°C (at which a dissolution test is run) compared to room temperature, the dissolved gases in the form of bubbles will be released and may cause erratic results. Therefore, it has been proposed, and also recently recommended by the USP, that the dissolution medium should be deaerated. From this survey, in which the participating laboratories were also asked to include deaeration methods employed in obtaining the calibration results, it became evident that there were a variety of methods commonly employed for deaeration of dissolution media. Overall, the trend is that deaeration in general reduces the number of failures. Considering the various deaeration



RPM	1	2	3	4	5	6	USP RANGE
50	59.6	58.6	57.4	58.6	58.9	58.0	46 - 59
100	59.0	61.2	59.9	64.6	63.6	64.6	58 - 69

FIGURE 1. Mean (n = 6) percent furosemide release values at times from a "standard sample" in different dissolution media (● = Phosphate buffer, pH 5.8; ○ = Acetate buffer, pH 4.6) reported by the participating laboratories. Dotted and solid lines represent mean (n = 6) percent furosemide release values for the "standard sample" in the phosphate and acetate buffer, respectively, from a laboratory which reported noncompliance with the USP dissolution *Apparatus Suitability Test*. The table below the figure shows values of percent drug release from the USP Calibrator (Prednisone tablets, Lot = J) for individual vessels from the "noncompliance" laboratory.

techniques reported, methods based on heating alone, heating with helium sparging, heating with filtering under vacuum or helium alone appear to be appropriate as degassing procedures as they result in a smaller number of failures than other methods employed.

Therefore, it can be said that deaerating is necessary, however, there is a need to establish an approach for monitoring the reproducibility of deaeration of a medium from run to run. Perhaps equilibrating the medium at 37°C, with or without the deaeration techniques mentioned above, may be more appropriate in providing deaeration in a reproducible manner.

What may be causing the high variability or failures which may be interrelated will be discussed. It is generally accepted that dissolution depends on at least two factors, that is, surface area of a product and removal of drug content from the solid-liquid interface which, in turn, is reflected by the agitation in the case of a dissolution test. The dissolution characteristics of calibrators in terms of these two aspects will be examined.

When Prednisone tablets, that is, a disintegrating calibrator, are analyzed with the Paddle Method, it is expected that tablets will disintegrate, thus increasing the surface area. Then, with sufficient agitation from the paddles running at 50 or 100 rpm, one would expect a high or adequate environment for dissolution. Similarly, on examining the Sali-

cylic Acid calibrators which are nondisintegrating, with the Basket Method, there appears to be sufficient agitation because there should be constant hitting or eroding of the tablet. Thus, once material is eroded from the tablet, it should have sufficient time for dissolution before it would settle to the bottom of the dissolution vessel, and should result in appropriate dissolution. Figure 2 is a schematic representation of this process.

If the other combination (Figure 3), that is, Prednisone tablets with the Basket Method, is considered, however, there should be an inherent high variability depending on the transfer of drug particles from the basket. If particles are sieved through fast, they will not have time to dissolve and would tend to form a cone. Then the basket will behave only like a thick rotating rod, causing very low agitation and resulting in low dissolution. If the degassing is not done appropriately or sufficiently, however, then the dissolved gases will emanate and, therefore, might be expected to cause significantly higher agitation, even, perhaps, more than the rotating basket itself. If that is the case, then dissolution would be a reflection of agitation due to the dissolved gases rather than the dissolution apparatus. Perhaps that is why this combination is more sensitive to deaeration. Similarly, if one considers the other combination of Paddle Method and Salicylic Acid tablets which are nondisintegrating in nature and provide very little surface area for dissolution, when air bubbles adhere to the surface, the area will be reduced further and that would cause high variability or failures.

In short, considering the high variability and frequency of failure with the combinations of the Salicylic Acid tablets/Paddle Method and the Prednisone tablets/Basket Method, it can be said that these combinations may not be reflecting the true characteristics of the apparatuses or the calibrators. The variability and failures observed in these combinations may be attributable to the interaction of calibrators and apparatuses, because both calibrators and apparatuses ap-

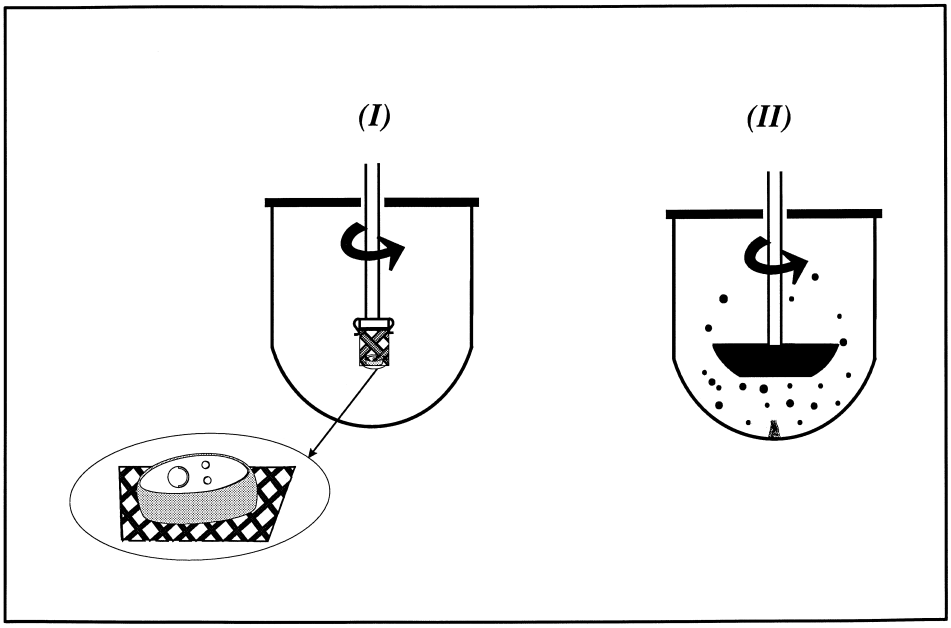


FIGURE 2. Schematic representation of drug release process from nondisintegrating (Salicylic Acid) tablets using the Basket Method (I) and disintegrating (Prednisone) tablets using the Paddle Method (II).

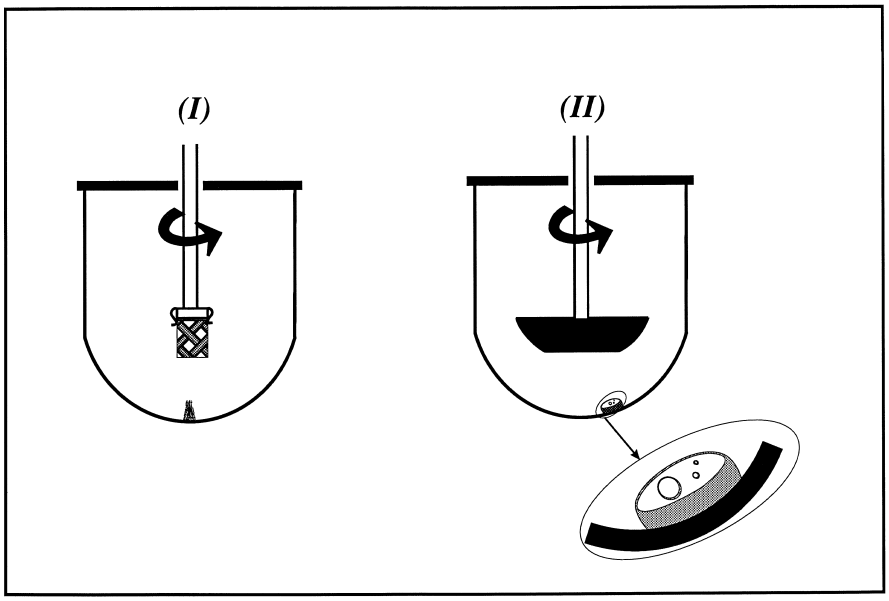


FIGURE 3. Schematic representation of drug release process from disintegrating (Prednisone) tablets using the Basket Method (I) and nondisintegrating (Salicylic Acid) tablets using the Paddle Method (II).

pear to give significantly lower variability and frequency of failure with the other combinations, that is, the Prednisone tablets/Paddle Method and Salicylic Acid tablets/Basket Method.

It is evident that dissolution apparatuses should be tested with a calibrator which should not have calibrator-apparatus interactions. It seems that the Prednisone tablets/Basket and Salicylic Acid tablets/Paddle Method may well have interactions and, therefore, use of these combinations to test suitability of a dissolution apparatus needs to be reconsidered. Prednisone tablets with the Paddle Method and Salicylic Acid tablets with the Basket Method, however, could well provide sufficient information for dissolution apparatus calibration and its use should be continued.

Acknowledgments—The help and support of Dr. I. J. McGilveray, R. Brien, A. Butterfield, and J. Lee of the Drugs Directorate, Dr. Siewert of Hoechst Germany, and all collaborators from national and international laboratories is gratefully acknowledged for participating in discussions and/or for providing the data.

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