Evaluation of Basket and Paddle Dissolution Methods Using Different Performance Standards

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Abstract □ Dissolution studies using both basket and paddle methods were carried out to evaluate two prednisone standards. Results of the experiments showed that the USP prednisone calibrator is sensitive to perturbations by the basket method but not to perturbations by the paddle method. However, the National Center for Drug Analysis (NCDA) prednisone performance standard is sensitive to perturbations by the paddle method but not to perturbations by the basket method. These results suggest that no single standard can predict the suitability of the dissolution equipment by the basket and paddle methods.

Keyphrases □ Dissolution—evaluation of basket and paddle methods using different performance standards, prednisone □ Prednisone—evaluation of basket and paddle dissolution methods using different performance standards □ Basket dissolution method—prednisone, evaluation using different performance standards □ Paddle dissolution method—prednisone evaluation using different performance standards

Dissolution analysis of pharmaceutical solid dosage forms has emerged as the single most important test that will ensure the quality of the product when carried out appropriately. In several instances, the dissolution results have been correlated with the bioavailability of the product, in which case the dissolution test can also ensure the bioavailability of the product between batches that meet the dissolution criteria. The dissolution test is generally carried out by either the basket or paddle method, both of which are official in USP XX, and are referred to as USP methods I and II (1). Important variables that play a major role in the dissolution methodology include dissolution medium and intensity of agitation. In addition, before the methodology can be used, it is imperative that the instrument be properly aligned and tuned to achieve reproducible and reliable dissolution results. A system suitability test is carried out using USP prednisone and salicylic acid calibrators to check alignment and fine tuning of the dissolution unit. Deficiencies in the equipment, such as the looseness of the chain, tilt of the stirring motor (tilt), misalignment of the flasks with respect to the stirring rod (off-centering), *etc.*, have been shown (2) to be easily detectable from the dissolution results of the basket method using the USP prednisone calibrator. The results obtained using the paddle method under the same conditions did not show significant differences in the dissolution results, although the equipment was judged as being not in good operating condition. These observations led to the conclusion that the basket method was superior to the paddle method. These are worthy conclusions, yet they do not lend support to the superiority of the basket method because of the lack of reproducibility (3, 4) and problems identified with mixing (5–8).

The National Center for Drug Analysis[1] (NCDA) has identified a prednisone tablet (NCDA prednisone performance standard II) that is highly sensitive to the aberrations of the equipment when the dissolution studies are carried out by the paddle method (9). However, no systematic study has been carried out to evaluate these two standards (USP prednisone calibrator and NCDA prednisone performance standard II) using the basket as well as paddle methods.

The purpose of this report is to evaluate the basket and paddle methods using both the USP calibrator and NCDA performance standard II, and to study the influence of various perturbations of the apparatus on the results.

EXPERIMENTAL

Method—The studies were carried out using commercially available dissolution equipment[2] and employing the basket method at 100 rpm and the paddle method at 50 rpm as previously described (1). The experimental directions provided with the official calibrator were followed in performing the study.

Instrument Operating Conditions—*Normal*—The instrument was aligned properly, finely tuned, and standardized according to a previous procedure (10).

Perturbed—The following perturbations were made to the dissolution apparatus, and the dissolution test was carried out under these conditions:

1. Tilt: The dissolution head (stirring motor) was tilted by raising the back rest of the unit. This produced deviations in shaft perpendicularity. The tilt produced was accurately measured by a universal protractor[3] at 1.5°.
2. Off-center: The dissolution head was moved to one side to displace the paddle or the basket from the exact center in the vessel by 3 mm.
3. Tilt with off-centering: A 1.5° tilt was produced with 3 mm off-centering.

Standards—Two prednisone standards, USP[4] 50-mg prednisone calibrator and NCDA 10-mg prednisone performance standard II, were used in this study.

Dissolution tests were carried out in deaerated water. Six tablets were used for each dissolution run. For the USP prednisone calibrator, 900 ml of the dissolution medium was used, and for the NCDA performance standard, 500 ml of the dissolution medium was used. The amount of the drug dissolved in 30 min was determined by comparing the absorbance of the sample with the USP prednisone reference standard at 242 nm in a spectrophotometer[5].

RESULTS AND DISCUSSION

The dissolution study results obtained by the basket and paddle methods, using a USP prednisone calibrator and an NCDA prednisone performance standard under normal standardized conditions and different perturbations, are summarized in Tables I–IV.

In the dissolution studies using the basket method, an agitation of 100 rpm was used. This agitation speed was used previously in different collaborative studies (4, 11). It was also used in a study where the influence of different perturbations on the dissolution characteristics of the

[1] National Center for Drug Analysis, Food and Drug Administration, Market Street, St. Louis, MO 63101.

[2] Easilift Dissolution Test Station Model 63-734-100, Hanson Research Corp., Northridge, Calif.

[3] Sears Roebuck & Co., Chicago, Ill.

[4] Batch F.

[5] Beckman Model 25/7 spectrophotometer, Beckman Instruments, Fullerton, Calif., or Variscan spectrophotometer, Varian Associates, Palo Alto, Calif.

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Table I—USP Prednisone Calibrator (Basket Method) Dissolution in 900 ml of Water at 100 rpm

Unit Operating Condition[a]	Mean ($N = 6$)	$\pm SD$	Range
Normal	68.3	0.9	67.2–69.3
	68.5	7.6	57.1–76.4
	68.9	3.2	63.2–73.7
Tilt	39.9	3.3	34.6–44.6
	40.6	0.6	39.5–41.2
Off-center	46.1	5.9	41.2–57.8
	48.9	1.0	47.7–49.9
Tilt with Off-center	36.3	1.1	34.2–37.1
	37.8	1.6	36.0–40.2

[a] ANOVA for conditions: $p = 0.0034$. Duncan's multiple range test ($\alpha = 0.05$): N O T T/O.

USP prednisone calibrator were examined (2). For normal conditions, the instrument was aligned, and all precautions were taken as described previously (10).

The basket method using the USP prednisone calibrator under normal conditions gave mean dissolution results of 68% (Table I). It is important to note that this value is very nearly identical to the normal mean value for the USP prednisone calibrator using the paddle method (4). However, when the equipment is perturbed, such as tilting the gear plate by 1.5°, the results are decreased to 40%. This is a substantial decrease. The off-centering of the basket (*i.e.*, from the center of the dissolution vessel) also produced a reduction in the mean dissolution value to 47%, which was similar to tilting. Both tilt and off-centering decreased the dissolution to ~37%, which although lower, did not suggest that these effects were additive.

This dramatic influence (*i.e.*, drop in the dissolution value, from 68 to 37% between normal and perturbed conditions) on the results of the basket method substantiates the findings reported earlier (2). The reason for the substantial decrease may partly be attributed to the decrease in the effective stirring of the dissolution medium under these perturbed conditions. The particles of the disintegrated tablet (USP prednisone calibrator) were observed to drop and collect at the center of the flask. Under tilt and off-center conditions, the particles are not sufficiently agitated because the rotating basket is not directly above the particles. These perturbed conditions, therefore, effectively lower the intensity of agitation resulting in lower dissolution value.

The intensity of agitation should not be confused with mixing, *i.e.*, uniform mixing. It was clearly established (12) that the basket method produces uniform mixing of the dissolution medium. This conclusion was based on the observation that samples drawn from different positions in the flask gave very similar results. In the cement investigation under tilt condition, the basket is positioned such that one side of the basket is close to the wall of the dissolution flask, whereas the other side is at the most distant position. Dissolution samples drawn from either side of the basket, at the same time using two probes, resulted in identical dissolution values, further indicating that there is no problem with mixing in the basket method.

The dissolution results using the USP prednisone calibrator and paddle method under normal and perturbed conditions are nearly the same (~70%, Table II). These results indicate that the paddle method cannot differentiate between the normal and perturbed conditions when the USP prednisone calibrator is used. A plausible explanation for the insensitivity of the USP prednisone calibrator to the perturbations in the paddle method is that the intensity of agitation (effective stirring) is adequate to disperse the tablet fragments throughout the medium under normal,

Table II—USP Prednisone Calibrator (Paddle Method) Dissolution in 900 ml of Water at 50 rpm

Unit Operating Condition[a]	Mean ($N = 6$)	$\pm SD$	Range
Normal	68.6	4.3	62.0–73.1
Tilt	71.7	0.8	70.7–72.8
	71.6	1.6	68.7–73.1
Off-center	64.1	2.7	60.1–67.7
	69.4	2.6	67.2–74.3

[a] ANOVA for conditions: $p = 0.72$. Duncan's multiple range test ($\alpha = 0.05$): T N O.

Table III—NCDA Prednisone Performance Standard (Paddle Method) Dissolution in 500 ml of Water at 50 rpm

Unit Operating Condition[a]	Mean ($N = 6$)	$\pm SD$	Range
Normal	41.0	2.5	36.2–43.2
	40.5	3.1	38.1–45.0
	39.2	3.8	35.4–44.5
Tilt	50.9	3.0	45.4–54.3
	53.8	4.4	49.0–59.5
Off-center	49.4	4.4	44.4–55.3
	48.9	6.0	39.6–56.8

[a] ANOVA for conditions: $p = 0.00005$. Duncan's multiple range test ($\alpha = 0.05$): T O N.

tilt, and off-center conditions, thus overcoming the inadequacies noticed in the basket method.

The results from several collaborative studies (3, 4, 11) indicate that the basket method always results in a wide range of dissolution values, where the paddle method has a narrow range of dissolution values. To establish the ruggedness and sensitivity of the paddle method, NCDA has identified a prednisone product (NCDA prednisone performance standard II) that can detect perturbations in the paddle method and that can be used for system suitability tests (9).

The dissolution results using the NCDA performance standard by the paddle method under normal and perturbed conditions are summarized in Table III. Under normal conditions, the dissolution results are ~40%, whereas under perturbed conditions they are ~ 50%. These values are significantly different when compared to normal conditions. The results thus indicate that the paddle method is sensitive to minor perturbations in the system and can differentiate between equipment that has been properly set up (normal) as opposed to a system that is improperly aligned, tilted, *etc.*, (perturbed) when NCDA performance standard II is used. The results of the NCDA performance standard using the paddle method were influenced by perturbations, and the reason might have been that after rapid disintegration, the particles are not very well dispersed, but form a mount (or cone) in the bottom of the flask. Because the particles are dense and settle down, the drug diffuses from the mound and not by dispersion throughout the medium.

NCDA prednisone performance standard II using the basket method resulted in a mean dissolution of 74% under normal conditions (Table IV). The dissolution results under perturbed conditions are also shown in Table IV. Different perturbations do not influence the results of NCDA performance standard II when the basket method is used. The tablet components of this standard, after disintegration, remained inside the basket longer, whereas the USP prednisone calibrator rapidly disintegrated and settled to the bottom of the flask. These observations partly explain the anomaly observed in the results of these two prednisone tablets when tested by the basket method. If one notices the USP calibrator results by the basket procedure, the differences between the normal and perturbed conditions are dramatic. Thus, one can reasonably conclude that the USP prednisone calibrator is sensitive to perturbations in the basket procedure, whereas the NCDA prednisone performance standard II is insensitive to any unanticipated aberrations in the equipment. The differences in the physical state of the deaggregated tablet matrix as well as the differences in the density of the particles (as observed in the flask) can, at the present time, explain these differences in the results.

The dissolution data on both standards using both methods are summarized in Fig. 1. It is interesting to note that identical perturbations

Table IV—NCDA Prednisone Performance Standard (Basket Method) Dissolution in 500 ml of Water at 100 rpm

Unit Operating Condition[a]	Mean ($N = 6$)	$\pm SD$	Range
Normal	77.4	2.6	74.7–80.5
	72.1	6.1	65.4–78.2
Tilt	81.5	3.1	77.6–85.9
	80.3	2.6	77.0–84.7
Off-center	77.9	2.1	77.0–80.6
	81.9	1.4	80.0–83.5

[a] ANOVA for conditions: $p = 0.20$. Duncan's multiple range test ($\alpha = 0.05$). T O N.

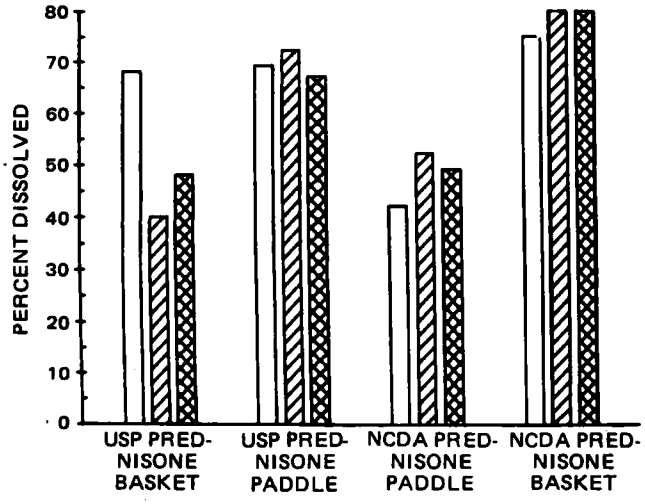

Figure 1—*Evaluation of the basket and paddle method using the USP prednisone calibrator and the NCDA prednisone performance standard. Key = (□) Normal; (▨) Tilt; (▩) Off-center.*

result in increased dissolution of the NCDA performance standard by the paddle method but decreased dissolution of USP prednisone calibrator by the basket method. The conclusion that one method (basket or paddle) is better than the other is, therefore, largely dependent on the standard product used in the system suitability test. At the present time neither the USP prednisone calibrator nor NCDA prednisone performance standard II alone can predict the suitability of a dissolution system when both the basket and paddle methods as described in the USP, are to be used.

All the dissolution results were statistically analyzed using ANOVA and Duncan's Multiple Range Test. The statistical results indicate that the dissolution results of the basket method using the USP prednisone calibrator and the dissolution results by paddle method using NCDA performance standard II under normal conditions were significantly different from the results obtained under perturbed conditions. It is therefore concluded that the USP prednisone calibrator is sensitive to perturbations by the basket method, and can be used as a calibrator in the system suitability test by the basket method only. Similarly, NCDA prednisone performance standard II is sensitive to perturbations by the paddle method and can be used as a calibrator for the system suitability test of the paddle method only. From the ANOVA it is also concluded that the USP prednisone calibrator is insensitive to perturbations by the paddle method, and NCDA performance standard II is insensitive to perturbations by the basket method. These results are summrized in Table V and indicate the necessity of an official calibrator similar to NCDA prednisone performance standard II to perform the system suitability test when the paddle method is used.

Table V—Statistical Analysis of Dissolution Data between Methods, Conditions, and Calibrators

Method	Calibrator	ANOVA[a]
Basket	USP Prednisone	$p = 0.0008$
	NCDA Prednisone	Not Significant
Paddle	USP Prednisone	Not Significant
	NCDA Prednisone	$p = 0.0001$

[a] Comparison of the dissolution data between the normal and perturbed (tilt, off-center, and tilt with off-center) conditions.

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