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A CRITICAL ASSESSMENT OF THE USP DISSOLUTION APPARATUS SUITABILITY TEST CRITERIA

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ABSTRACT

This report describes results of a survey conducted to assess the variability in drug release from the USP calibrators and its dependence on various deaeration methods. The calibrator data submitted by 33 laboratories, involved tests of 1659 sets (6 or 12 tablets/set) from four lots of prednisone and salicylic acid each, using apparatuses 1 & 2 run at 50 and 100 rpm. Overall variability-ranges for the individual sets, which met the USP dissolution apparatus *Suitability Criteria*, were 0.5-31.3% for prednisone/apparatus 1, 0-13.2% for salicylic acid/apparatus 1, 0.3-10.2% for prednisone/apparatus 2 and 0.7-20.2% for salicylic acid/apparatus 2. The results of this survey suggest that variability levels are dependent on apparatus/calibrator combination. Although deaeration of dissolution media tends to reduce the failures i.e. not meeting the *Suitability Criteria*, its effect on reducing the variability appears to be minimal. Among the various deaeration methods reported, de-gassing the media by a combination of heating with helium sparging or with filtering under vacuum tend to give the lowest failure rate. From our findings, a variability of up to 31% CV (co-efficient of variation) in percent drug release for the calibrator can occur with the samples still meeting the USP criteria. However, if the apparatus/calibrator combination is taken into consideration with appropriate deaeration method, the maximum expected variability can be reduced to 10% or less. The results of this survey show that rather than an eight point

dissolution calibration test criteria, a four point evaluation system i.e. testing non-disintegrating tablets with apparatus 1 and disintegrating tablets with apparatus 2 may provide sufficient information for system suitability. It is also recommended that a similar formulation/apparatus combination should be considered for drug products evaluation which might yield less variable results with an improved potentials of *in vitro/in vivo* correlations particularly for modified-drug release products.

INTRODUCTION

Drug dissolution testing is an integral part of pharmaceutical development and routine quality-control monitoring of drug release characteristics. Commonly, drug dissolution studies are conducted using basket (Apparatus 1) and paddle (Apparatus 2) methods as described in the compendia (e.g. USP) [1,2,3]. The USP require that before using the dissolution apparatuses for drug product analysis, they are to be calibrated with USP calibrators according to the system suitability tests. The calibrators used for such evaluation are of two types i.e. disintegrating (prednisone) and non-disintegrating (salicylic acid). The dissolution studies using these calibrators are conducted using water or phosphate buffer (pH 7.4) as medium, respectively. Percent drug released at 30 minutes is monitored. The instruments are considered suitable for drug dissolution experiments if the percent drug released falls within a pre-established range which is determined based on collaborative studies organised by USP. These prescribed ranges are specific for the particular calibrator lots and the type of apparatus running at a particular speed (50 or 100 rpm). Table 1 summarizes the given ranges for four recent lots of the calibrators. It is important to note that the values represent percent drug released from individual tablets rather than average values of a set of six or twelve tablets.

It is clear from the table that in some cases the ranges are quite wide. There is no distinction between variabilities arising from inter or intra-laboratory or instrument variability. In fact, establishing variability for single instrument or within laboratory may be more important, as the dissolution is commonly used for the evaluation of products from the same manufacturing site.

TABLE 1

USP Dissolution Apparatus Suitability Test Ranges As Described in the Sheets Accompanied 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.

Calibrator	Lot	Percent dissolved at 30 minutes			
		Apparatus 1 (Basket)		Apparatus 2 (Paddle)	
		50 (RPM)	100 (RPM)	50 (RPM)	100 (RPM)
Prednisone	**G**	2 - 26	29 - 58	33 - 51	48 - 67
	H	3 - 21	30 - 50	31 - 49	41 - 64
	I	7 - 23	28 - 62	34 - 53	50 - 66
	J	6 - 23	43 - 63	46 - 59	58 - 69
Salicylic Acid	**H**	11 - 20	20 - 30	13 - 23	18 - 31
	I	14 - 22	21 - 32	12 - 22	18 - 28
	J	14 - 20	22 - 30	12 - 22	17 - 27
	K	14 - 21	23 - 29	13 - 22	16 - 27

USP and other pharmacopeia (e.g. BP) publish very stringent requirements for the geometrical and operational limitation for dissolution apparatuses. However, unlike the BP and Ph. Eur. [2,3], the requirements for the use of dissolution media do not seem to be so strict, e.g. should the dissolution medium be deaerated. Recently, USP has recommended a deaeration procedure based on heating the medium to 45 °C followed by filtering under vacuum [4]. However, experimental results to establish suitability of this approach compared to other methods commonly used e.g. heating alone or helium sparging, appear to be lacking.

Concerns have also been expressed by pharmaceutical manufacturers regarding unexplained failures of the calibrators to meet the *Suitability Criteria*. Moreover, recently, during the development of Drugs Directorate Guidelines (Health Protection Branch, Health Canada) for acceptable methods for the conduct of dissolution studies, a proposed standard of low variability (i.e. 5%) was criticized by many manufacturers as being excessively strict.

To address these concerns and to suggest appropriate within laboratory variability levels, a survey was conducted with the cooperation of the Canadian pharmaceutical industry. This report describes results of this exercise.

SURVEY PROTOCOL AND DATA ANALYSIS

This survey was initiated at the suggestion of the Fields Operation Directorate, Health Protection Branch, Health Canada. A questionnaire (appendix) was sent to the pharmaceutical manufacturers, with a request that they should submit data from 5 dissolution runs for each apparatus, calibrator and rotation speed combination. The participants were requested to provide information regarding the type of deaeration methods employed, if any. Also, any noticeable abnormality in the quality of the USP calibrators was to be recorded.

The mean and co-efficient of variation (CV %) of percent drug released were calculated from the data reported. For evaluating the USP *Suitability Criteria*, values were rounded to the nearest integer. In this report, failure rates are described as percent of the sets which met the *Suitability Criteria*.

Considering the exploratory nature of the data, emphasis was directed at observing trends rather than formal comparisons of values for multiple groups using statistical procedures.

RESULTS

Thirty three laboratories responded to the survey by submitting data. Although, the request was for 40 sets per laboratory, many companies submitted results for a greater number of sets. The median number of sets per laboratory was 33 (5 to 652). All data received was included for the data analysis.

Most of the laboratories submitted data for both types of calibrators using the two apparatuses. However, there appears to be a trend for less use of apparatus 1, as several companies did not send results for this apparatus. A break-down of the sets with respect to apparatus and calibrator is given in Table 2. The reported data represent results from 4 lots of both calibrators i.e. lot G to J for prednisone and H to K for salicylic acid tablets. The data are quite representative of the various lots and experimental conditions for both calibrators. The only abnormal abberation reported for the tablets was chipped edges, and such cases were very few.

Of 1659 data sets reported, 244 (17.24%) were reported as failures, that is they did not meet the USP *Criteria*. Figure 1 shows the overall failure rate with respect to apparatuses and calibrator types. The figure shows that apparatus 1 tends to give higher percent failures than apparatus 2. Also, more failures were reported for disintegrating type (prednisone) calibrator than for non-disintegrating type (salicylic acid) calibrator.

A more representative and expanded break-down of the failure rate distribution is shown in figure 2. It is clear that using the basket method, particularly at 50 rpm, prednisone gives the highest percent failures. In this case the failure rate was as high as 66.7%. For the salicylic acid calibrator, there is no failure trend with respect to dissolution apparatus and generally failures were less than 20%

Table 3 shows variability values calculated as percent co-efficient variation (CV) for individual sets of dissolution-run which met the *Suitability*

TABLE 2

Distribution of Dissolution Calibrator Data Submitted by the Participants Categorized According to Tablet, Apparatus and Lot Types. Total Number of Participants=33, Number of Sets (N=6 Or 12) Submitted 1659 (Passed=1415 Failed=244).

Lots Tested (Sets)		BASKET METHOD	PADDLE METHOD
Prednisone (865)	G	10	10
	H	69	58
	I	121	120
	J	212	265
Salicylic Acid (794)	H	6	6
	I	49	38
	J	126	153
	K	176	240

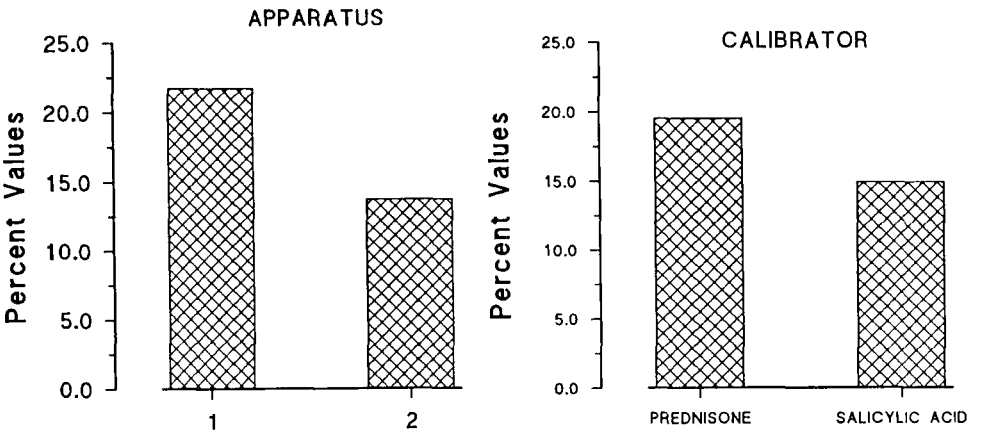

FIGURE 1

Percentages of sets (6 or 12 tablets/set) which did not meet the USP Apparatus Suitability Criteria according to the apparatus and calibrators types.

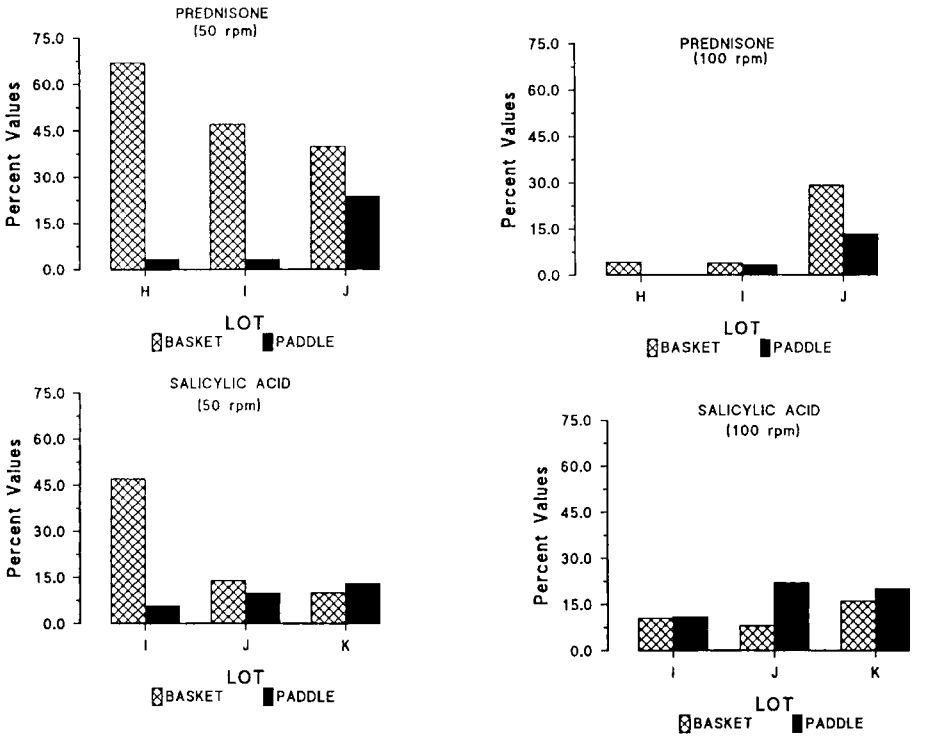

FIGURE 2

Distribution of failure rate of calibrator data according to the USP apparatus 1 and 2 among various lots of calibrators.

Criteria. It is apparent that the variability range is quite wide. The CV % ranges are 0.5-31.3, 0.0-13.3, 0.3-10.2 and 0.7-20.2% for combination (calibrator/apparatus) of apparatus 1 and 2 with prednisone and salicylic acid, respectively. A similar distribution of variation from a USP collaborative study has also been reported in the literature [5].

Almost half of the sets (818) reported were tested without the use of any deaeration method. However, for the others, various degassing approaches were described. The types of degassing methods (# of sets) used were as follows: heating (147), helium sparging (138), heating with helium sparging (49), heating with sonication (25), heating and filtering

TABLE 3

Within-a-Set Variations calculated as co-efficient of variation (CV %) in Percent Drug Released Using USP Calibrator Tablets for Sets which Met the Suitability Requirements

	CALIBRATOR	LOT	50 (RPM)	100 (RPM)
Basket Method	PREDNISONE	G	7.9 - 22.5	3.4 - 8.2
		H	1.8 - 25.5	0.9 - 17.3
		I	0.5 - 29.6	0.9 - 21.7
		J	1.2 - 31.3	0.6 - 13.1
	SALICYLIC ACID	H	1.8 - 4.7	2.6 - 3.6
		I	1.3 - 4.9	0.7 - 5.5
		J	0 - 10.3	0 - 6.2
		K	1.2 - 13.2	0 - 4.9
Paddle Method	PREDNISONE	G	3.2 - 10.0	1.4 - 4.3
		H	1.6 - 10.2	0.7 - 6.0
		I	0.7 - 9.6	0.5 - 4.2
		J	0.4 - 7.4	0.3 - 4.6
	SALICYLIC ACID	H	3.7 - 10.4	4.1 - 4.9
		I	4.0 - 13.9	3.4 - 9.7
		J	0.7 - 14.1	1.4 - 12.1
		K	1.2 - 20.2	1.0 - 17.8

under vacuum (158), vacuum alone (264) and sonication (44). The data using the sonication method, were not representative over various combinations of tablets and apparatuses and therefore were excluded from further consideration.

The figure 3 shows failure rates with respect to the degassing methods. It appears that deaeration tends to decrease the failure rate. Failure rates for experiments which used heating and helium or vacuum, appear to give the lowest failure rate. However, considering, the smaller percentages of failure with helium alone than with vacuum alone, suggests that heating together with helium sparging may be more appropriate. Overall, reported cases of failures were less than 10.7% using heating with helium sparging or under vacuum.

The figure 4 shows variability (CV) values for the individual degassing method. There appears to be no noticeable trend in reduction in the variability depending on the deaeration method. For overall variability, the prednisone with basket method and salicylic acid with paddle method showed greater variability than those of prednisone with paddle method and salicylic acid with basket method, and the spread appears to be independent of deaeration method.

DISCUSSION

Deaeration Method: Dissolution experiments are to be conducted at 37 °C. The solubility of gases in the dissolution medium is dependent upon the temperature. Therefore, it is expected that if dissolved gases are not adequately removed from the medium, they can potentially contribute to high variability. Thus, it is expected that a degassed medium should give less erratic results (possible fewer failures) than a dissolution medium which was not deaerated adequately. This seems to be also reflected by the data. In this regard, degassing the medium by heating together with vacuum or helium sparging produced lower failure rates (Figure 3). As vacuum alone result in higher failure rates than filtering under vacuum along with heating, it may be because that with vacuum, the medium might have negative pressure and cause disturbances by dissolving air during temperature

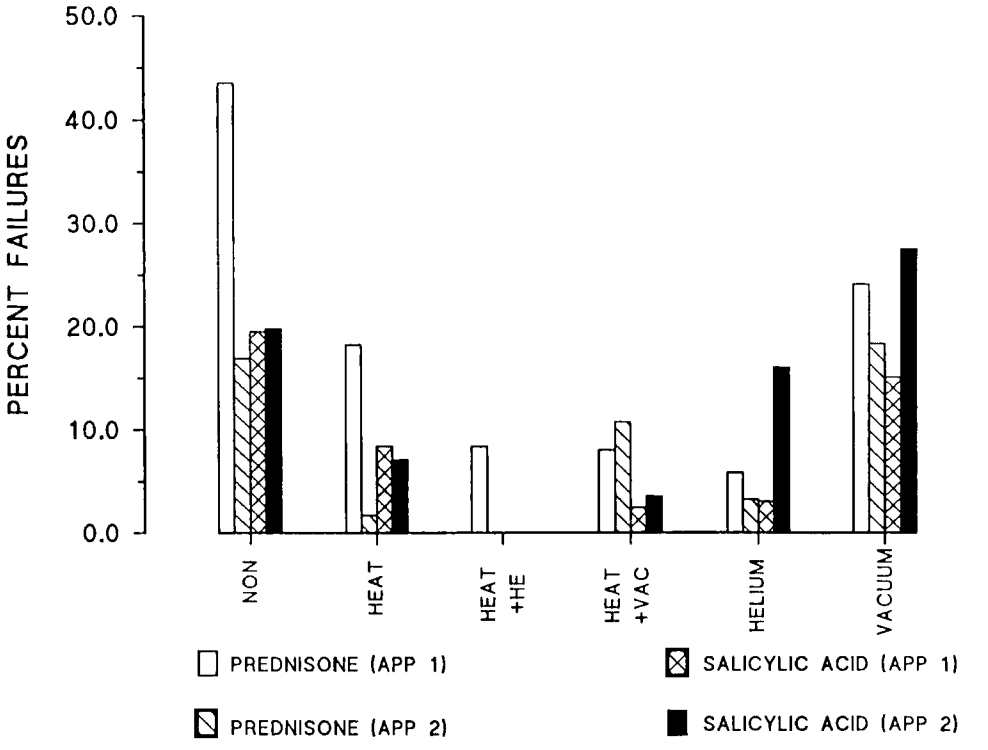

FIGURE 3

Percentages of dissolution-runs which did not meet the USP criteria for *System Suitability Criteria* according to the deaeration methods reported.

equilibration to 37 °C or during the dissolution experiment. Therefore, even after degassing, the medium needs to be sufficiently equilibrated to attain the appropriate saturation with the atmospheric gases. Equilibration time would become a critical factor for such a deaeration method. However, it seems that with helium sparging, attaining such an equilibrium is either not critical or achieved faster. As times for degassing were not reported in the survey, it is difficult to suggest an appropriate duration for degassing.

It is generally regarded that vibration related to the instrument could be one of the main determinants of failures. Intuitively, and as reported in the literature [6] if the problems (failures) were due to excessive vibration,

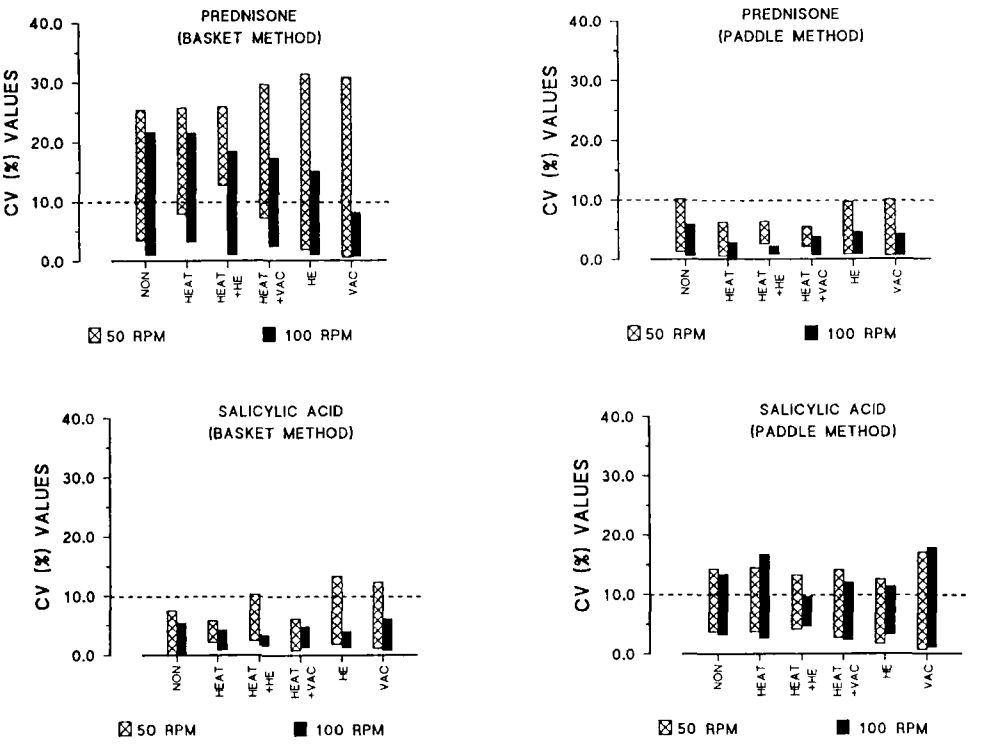

FIGURE 4

Distribution of variability calculated as co-efficient of variation for the sets which met the *System Suitability Test* according to the deaeration methods.

the failures would be expected to result from release of a higher percent of drug than expected. However, examination of the data shows that, except for prednisone at 50 rpm using apparatus 1, the majority of failed-sets of the calibrators gave lower than expected percent drug release (Table 4). It should be noted that, even with prednisone using apparatus 1, the majority of the failures owing to "higher than expected" results were in the no-degassing category. This suggests that higher percent drug release can be avoided by appropriate deaeration of the medium. Among the reported deaeration methods, vacuum appears to give large number of failures due to higher percent drug than expected being released, which suggests deaeration using vacuum may not be the best choice for degassing the dissolution media.

TABLE 4

Number of Tablets That Showed Lower Or Higher Percent Drug Release Values Than Expected to Meet the *Suitability Criteria*.

Deaeration Method		RPM	PREDNISONE		SALICYLIC ACID	
			Lower	Higher	Lower	Higher
Basket Method	Non	50	131	229	107	1
		100	75	9	80	10
	Heat	50	.	.	6	.
		100	12	.	.	.
	Heat + Helium	100	6	.	.	.
	Heat + Vacuum	100	12	.	5	.
	Helium	100	12	.	6	.
	Vacuum	50	4	44	24	.
		100	35	1	20	4
Paddle Method	Non	50	117	3	62	16
		100	54	.	93	33
	Heat	50	6	.	5	7
		100	.	.	5	7
	Heat + Vacuum	50	6	.	8	4
		100	12	.	.	.
	Helium	50	6	.	5	1
		100	.	.	15	9
	Vacuum	50	28	8	5	25
		100	24	6	7	41

Moreover, if this problem were due to excessive instrument vibration, then most of the tablets in a failed dissolution-run would be expected to fall outside (higher) the acceptable range. However, most sets failed because only one or two tablets per set did not meet the *Suitability Criteria*. On the other hand, for the majority of the failure cases with lower than expected percent drug release, 5 or 6 tablets/set did not meet the criteria (Table 5). These observations suggest that vibration is not the major cause of failures in this survey.

Variability: Considering the *Suitability Test* as described in the USP general monograph, one can expect a variability of up to 31.3% for a 6 tablet-run still meeting the *Suitability Criteria*. Acceptance of such a high variability level for an instrument calibrator should be a cause of concern.

The data suggest that there are two distributions of CV values. Relatively smaller values were observed for prednisone tablets using apparatus 2 and salicylic acid tablets using apparatus 1. On the other hand, higher percent variabilities were seen with prednisone calibrators using apparatus 1 and salicylic acid calibrator with apparatus 2.

It is quite difficult to explain the two sets of variabilities without considering probable interactions between calibrators and apparatuses. For example, if prednisone tablets are to show a variability level of 10% or less with apparatus 2, then why would the same calibrator give higher variability with apparatus 1? It can be argued that perhaps apparatus 1 would be more sensitive to the operation of the instrument. If so, then it is not clear why the same apparatus would give smaller variability values with the salicylic acid tablets.

Drug dissolution depends upon many factors which can be due to formulation and/or the dissolution apparatus itself. Considering the use of same source of calibrators (i.e. USP), the formulation effects can be considered constant. Therefore, the observed variability should be a characteristic of a dissolution experiment itself. Dissolution from a drug product depends upon at least two factors, (i) surface area and (ii) the transfer of drug from the surface/medium interface layer of the tablet into

TABLE 5

Distribution of Number of Sets Which Were Failed Because Percent of Drug Release From One or More Tablets Per Dissolution-run was Higher (A) Or Lower (B) Than Expected to Meet the *Suitability Criteria*.

	Calibrator	Apparatus	Number of tablets failed / set							
			1	2	3	4	5	6	7	12
A	Prednisone	1	10	12	7	8	8	24	.	1
		2	3	1	.	.	.	2	.	.
	Salicylic Acid	1	6	.	.	.	2	.	.	.
		2	25	5	4	1	4	12	.	.
B	Prednisone	1	8	8	7	14	8	20	.	2
		2	.	.	.	2	4	37	.	.
	Salicylic Acid	1	2	.	.	.	6	32	.	2
		2	3	1	4	5	25	6	1	.

the dissolution medium. A disintegrating tablet would offer larger surface area and therefore would have a higher dissolution rate, perhaps with less variability. However, a non-disintegrating tablet (salicylic acid) provides less surface area, and changes which would further reduce the surface area would produced marked effects on the dissolution rate of such tablets. As reported in the literature [7] if air bubbles adhere on to the tablet surface, the dissolution can be drastically reduced. Perhaps that could serve to explain the higher variability of salicylic acid with paddle method.

On the other hand, if the same non-disintegrating tablets are to be used in the basket apparatus, constant rotation of the basket would help to reduce the air bubble formation on the surface and also may assist in eroding (peeling) the surface of the tablet. Moreover, once released from the surface, drug would have sufficient time to dissolve before reaching the bottom of the container, therefore better and reproducible dissolution levels can be expected.

For disintegrating (prednisone) tablets using apparatus 1, once the tablet disintegrates, which is relatively a fast process, the deaggregates may either clog the basket thus reducing sink conditions, or quickly pass through the basket to settle on the bottom of the container. All these factors can contribute, individually or collectively, to produce high variability. The problems of the basket method, in this regard, are well documented in the literature [8]. This high level of variability is also reflected by the allowed (Table 1) wide ranges (63-2=61%) of dissolution expected for multiple lots from this combination as compared to others: (69-31=37%) prednisone (apparatus 2), (32-11=22%) salicylic acid (apparatus 1) and (31-12=19%) salicylic acid (apparatus 2).

Therefore, based on the variability levels and the dependence of dissolution characteristics on instrumentation the calibration test can be divided into two groups i.e. group A, salicylic acid/apparatus 1 and prednisone/apparatus 2, while group B consists of salicylic acid/apparatus 2 and prednisone/apparatus 1. Briefly, it would appear that tablets which are non-disintegrating in nature should be analyzed using basket method and the tablets which are of disintegrating type should be evaluated using

paddle method. Such an evaluation criterion (Group A) may furnish more reproducible results with low variability.

Let us re-evaluate the data for variability and effect of degassing based on this classification. First, the failure rate is 12.5% in group A as compared to the group which had 22.15%. Secondly, variability levels were consistently higher in group B and in group A (Figure 5). It is important to note that both groups represent both apparatuses and calibrators. As mentioned earlier, deaeration does not have significant effect in reducing the variability. Overall variability levels are the same. However, deaeration tends to decrease failure in both groups (Figure 6).

There has to be concern about what extra information is obtained by running both sets (groups) of experiments. It seems that one set is producing exaggerated variability levels and may not be representative of actual variability of the system. Therefore, it might represent an extra burden on the laboratory. Moreover, if a variability of 30% is acceptable for a calibrator, then for a drug product of disintegrating nature using the basket method, a variability of up to 30% could be expected within a six-tablet run as well. In this situation, how can lot to lot variability be differentiated from the variability due to dissolution itself.

When comparing drug release characteristics of drug products from different laboratories (different manufacturing sites) or using different instruments, one would attempt to normalize the data using calibrator drug-release data from the two sources. However, if high variability is permissable (and occurs) for calibrators then the majority of the data will fall in the acceptable range, which would diminish the credibility of the test as a calibrator. Moreover, with the development of modified release products for which more precise control on the release characteristics are desired, a proper selection of a dissolution apparatus will become more critical.

In summary, it can be said that the variability in the dissolution test is dependent on calibrators and dissolution method. An eight-point dissolution apparatus calibration approach may be considered excessive. A four-point calibration based on disintegrating tablets/paddle method and

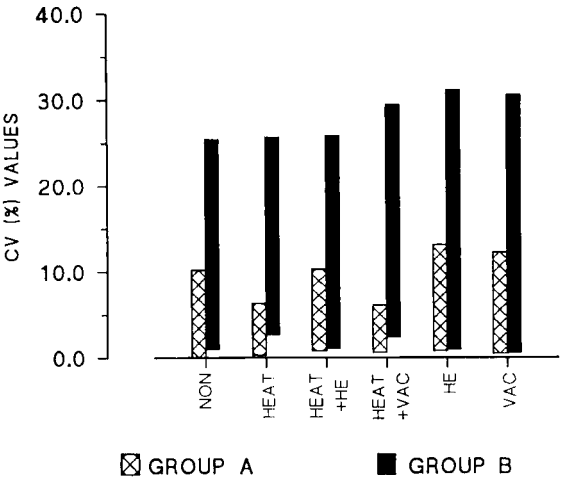

FIGURE 5

Distribution of variability calculated as co-efficient of variation for the sets which met the *System Suitability Test* for the two groups. Group A, represent ranges of data for prednisone and salicylic acid using apparatus 2 and 1, respectively. Group B, represents ranges of data for prednisone and salicylic acid using apparatus 1 and 2, respectively.

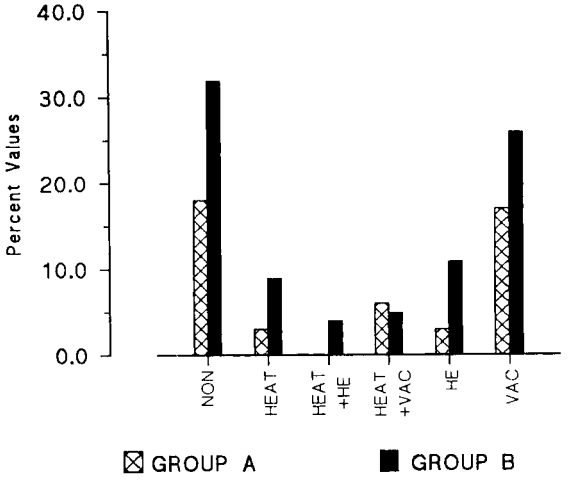

FIGURE 6

Distribution of percent failures for the *System Suitability Test* for the two groups according to the deaeration method. Group A, represent ranges of data for prednisone and salicylic acid using apparatus 2 and 1, respectively. Group B, represents ranges of data for prednisone and salicylic acid using apparatus 1 and 2, respectively.

non-disintegration tablets using basket method may provide sufficient information for calibrating the instrument. Deaeration of a dissolution medium appears to reduce the instances of failing the USP criteria. Of the many approaches reported for degassing, heating along with helium sparging or with filtering under vacuum tends to produce the lowest number of failures. Considering the formulation type with an appropriate dissolution apparatus combination and suitable degassing method, one can expect a more stable calibration test with a variability of less than 10%.

An important implication of this study is that the choice of dissolution apparatus for drug product evaluation should also be dependent on the dosage form type i.e. if drug product is a non-disintegrating type then it should be analyzed using apparatus 1, on the other hand the disintegrating type should generally be analyzed by paddle method. Such an approach may lead to improved characterization of drug dissolution and may provide improved *in vitro-in vivo* correlation.

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Appendix

USP Dissolution Calibrators (Tablets) Performance Record

Company:			
Calibrator Tablet:	☐ Prednisone ☐ Salicylic Acid		Lot:
	Any Noticeable Abberation (e.g. rough edges, cracks.)		
Dissolution Apparatus:	☐ 1 (Basket Method)	☐ 2 (Paddle Method)	
Rotation Speed (RPM):	☐ 50	☐ 100	
Medium Deaeration Method:	Heat	Vacuum	Helium Sparge
	Others (Brief description):		
Date Analyzed (Year/Month/Day):			

Percent Drug Released Data

Time ►* / Vessel ▼	___ (min)	___ (min)	___ (min)	**30** (min)	___ (min)
1					
2					
3					
4					
5					
6					

* Please list the data for 30 minutes (the USP requirement). If available, data for the earlier and later times would be useful.

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