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Collaborative study on the development of a standard for evaluation of vibration levels for dissolution apparatus

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Abstract

This collaborative study in which seven laboratories participated was carried out in order to develop a dissolution standard for evaluating vibration levels for dissolution apparatus using enteric-coated granules of cefalexin (EG). Vibration levels for the dissolution apparatus were not dependent on whether the rotating basket (50 rpm) or paddle (50 rpm) methods were used. However, dissolution rates of cefalexin from EG were significantly increased by dissolution apparatus at high levels of vibration in the rotating basket method, while they were not affected by the variation in vibration levels in the paddle method. Dissolution apparatus could be divided into two groups according to their vibration levels and the dissolution test results by the rotating basket method at 50 rpm. The critical value of acceleration was about 0.05 m/s^2. The upper limit of normal dissolution rates of EG was calculated from the results of the rotating basket method at 50 rpm obtained from low vibration apparatus. All high vibration apparatus used in this study were distinguished by the confidence limit of the EG dissolution rate determined from low vibration apparatus. These results suggest that EG would be useful as a calibrator for detection of apparatus at high vibration levels.

Keywords: Calibrator; Dissolution apparatus; Enteric-coated granules; USP calibrator; Vibration level

1. Introduction

Dissolution testing is an important tool for checking batch-to-batch variation in quality and for preventing significant bioinequivalence of

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solid oral dosage forms. Thus, dissolution systems should provide accurate and reproducible results for both purposes. However, there are many sources of variation which can affect the dissolution test results; these include the eccentricity of the stirring drive (Hanson, 1991), the geometry of vessels, vibrations from a dissolution apparatus itself and external sources (Hanson, 1991), the dissolved gas (Hanson, 1991), components and temperature of the test medium (Hanson, 1991; Kaniwa et al., 1995). Some sources of variation such as temperature or the components of the test medium can be controlled using a well-calibrated thermometer or balance. In contrast, it is difficult to directly confirm whether other factors such as vibration of a dissolution system, the shape of vessels, and eccentricity of the stirring drives are in the normal condition. The current USP (U.S. Pharmacopeia) dissolution calibrators were introduced to control for unseen vibration of the dissolution apparatus (Grady, 1995). However, it is believed that abnormalities in other factors besides vibration in dissolution testing can be also detected by USP calibrators; these have often been used as standards for suitability testing of dissolution apparatus.

Fujiwara et al. (1997) recently reported that the dissolution rate of an active ingredient from enteric-coated granules determined by both the paddle and rotating basket methods was increased by extraordinary vibration of the dissolution apparatus, which could not be detected by USP calibrators. This fact suggests that current USP calibrators are not sensitive enough to evaluate the vibration levels of dissolution apparatus, and that the enteric-coated granules might be useful as a calibrator for evaluation of the vibration levels of dissolution apparatus. In this manuscript, we describe a collaborative study by seven laboratories performed to clarify dissolution characteristics of the enteric-coated granules and to establish a standard for checking the vibration levels of dissolution apparatus.

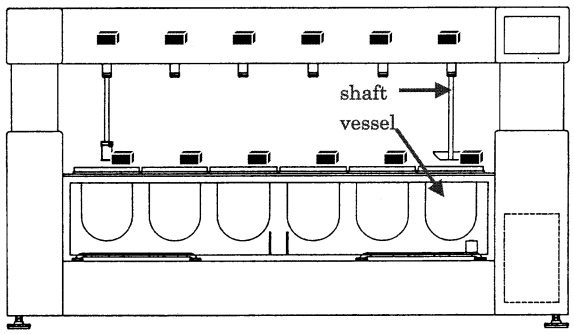

Fig. 1. Measurement points of vibration levels of dissolution apparatus. Black boxes indicate points where a pick up was placed for measurement of the vibration level.

2. Materials and methods

2.1. Materials

Cores of enteric-coated granules of cefalexin (EG) were prepared by mixing cefalexin, D-mannitol, starch, methyl cellulose and hydroxypropyl cellulose, granulation of the mixture and drying. The cores were coated with a mixture of hydroxypropyl methyl cellulose acetate succinate, talc, triethyl citrate, wax and silicon dioxide. EG contained 50% of cefalexin and had a cylindrical shape with a diameter of 0.5 mm and an average height of 1.5 mm. USP disintegrating type calibrator tablets (prednisone tablets, Lot L) and USP non-disintegrating type calibrator tablets (salicylic acid tablets, Lot M) were used. Cefalexin (Shionogi, Osaka), salicylic acid (JP13) and prednisone (Wako Pure Chemical Industries, Osaka) were used as obtained. Other chemicals were of reagent grade.

2.2. Measurement of vibration levels of dissolution apparatus

As shown in Fig. 1, vibration levels of the dissolution apparatus were measured at six points on the front panel of the stirring device (shaft) and at the upper edge of each vessel by VM-7000 using a Piezo resistive acceleration pickup (IMV Corporation, Osaka). Vibration levels in horizontal and vertical directions were assessed on acceleration, velocity and disposition. Vibration levels at shaft and vessel for each dissolution apparatus were expressed as the average values of six measurements, unless otherwise described.

Table 1
Dissolution apparatus used in this study and their vibration levels

Laboratory	Apparatus ID	Acceleration (m/s^2)[a]
A	A	0.029
	a	0.568
B	B	0.015
	b	0.117
C	C	0.014
	c	0.173
D	D	0.020
E	E	0.035
	e	0.170
F	F	0.014
	f	0.095
G	G1	0.007
	G2	0.030

[a] Average vibration levels in a horizontal direction measured at the edge of vessels.

2.3. Dissolution apparatus

Dissolution apparatus used in this study and their vibration levels assessed on acceleration are shown in Table 1. The dissolution apparatus at high levels of vibration in laboratories C and E were installed on desks on which instruments generating vibration were set, while magnetic stirrers and touch mixers were set on dissolution apparatus in laboratories A and F in order to generate high levels of vibration. Magnetic stirrers for the water bath were considered to be the main source of vibration of the dissolution apparatus at high levels of vibration in laboratory B.

2.4. Dissolution test

2.4.1. Standard procedures of dissolution testing of EG

A large amount of concentrated test medium containing 1695 g of citric acid monohydrate and 939 g of sodium hydroxide in 10 l of water was prepared and divided into seven portions. Each portion was distributed to each collaborator. The collaborators diluted the distributed buffer 15 times with deionized water and used it without pH adjustment. The diluted solution was 0.05 mol/l citrate buffer of pH 6.5. The solution was deaerated by being kept at 45°C for 2 h before use. Dissolution tests for 700 mg of EG were performed by the rotating basket and paddle methods at 37°C using 900 ml of the test medium at 50 rpm. Three millilitres of the dissolution medium was sampled using a whole pipette with a filter for injection syringes (Fine filter F216, Ishikawa Seisakusho) at 30 min. The sampled dissolution medium was appropriately diluted with 0.01 mol/l HCl and the dissolved cefalexin was determined by UV spectrophotometric method ($\lambda_1 = 260$ nm; a maximum absorption wavelength and $\lambda_2 = 320$ nm; used to avoid the possible effect of turbidity caused by excipients).

2.4.2. USP calibrators

Dissolution rates of USP calibrators were measured by the rotating basket and paddle methods at 37°C using 900 ml of test medium at 50 rpm.

2.5. Experimental design

The one-way layout in which the source of variation was the vibration levels was employed in order to investigate the effect of vibration levels of the dissolution apparatus on the dissolution rate of cefalexin from EG in the paddle method, and the dissolution rates of USP calibrators. The result from each dissolution apparatus was the mean of results obtained from six vessels.

An experimental design shown in Fig. 2 was employed to investigate the effect of vibration levels of the dissolution apparatus on the dissolution rate of cefalexin from EG in the rotating basket method. That is, each participant repeated dissolution testing twice using one of the dissolution apparatus they had, with the exception of laboratory D that repeated it three times. The precision of dissolution rates measured using the low vibration apparatus was estimated according to an unbalanced nested design (Ojima, 1984).

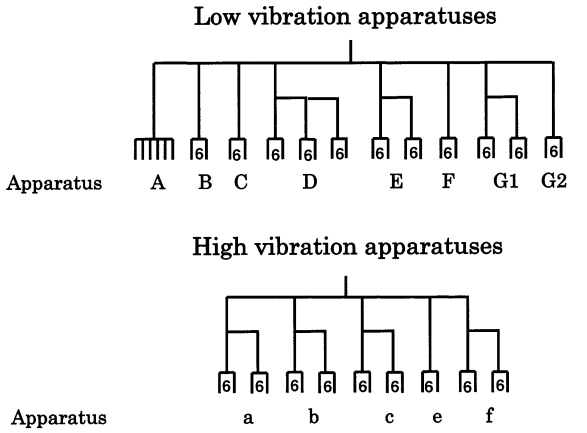

Fig. 2. Experimental design for evaluating the effect of vibration levels of the dissolution apparatus on the dissolution rate of EG using the rotating basket method. The number six means that six results were obtained in an experiment using each dissolution apparatus as in the experiment using apparatus A.

2.6. Estimation of intermediate precision and reproducibility of the pH of the test solution

Two operators in each participant laboratory independently prepared test solutions that contained 91.248 g of trisodium citrate dihydrate and 2.736 g of citric acid (anhydrous) in 6 l. Portions of the test solutions were sent to Laboratory A, where their pH values were measured at 24°C.

3. Results and discussion

In a previous study (Fujiwara et al., 1997), it was found that dissolution rates of EG measured by the rotating basket and paddle methods increased in a dissolution apparatus placed on a desk at a high vibration level. The degree of increase of in the dissolution rate of EG was slightly higher when the dissolution tests were conducted at 50 rpm, although the increase was also observed in dissolution testing conducted both at 100 rpm. Therefore, all dissolution tests were performed at 50 rpm. Because enteric-coating films usually show pH-dependent dissolution profiles, it was necessary to avoid variation in dissolution rates due to variation in pH values of the test medium used in the study. For this purpose, a large amount of concentrated test medium was prepared and the collaborators used it after diluting it by 15-fold without pH adjustment.

3.1. Results of EG obtained with the rotating basket method

Fig. 3a shows the correlation between vibration levels of the dissolution apparatus and the results of dissolution tests of EG using the rotating basket method at 50 rpm. The dissolution rate of cefalexin from EG measured by the rotating basket method at 50 rpm was markedly increased in dissolution apparatus at high vibration levels. According to this result, we defined dissolution ap-

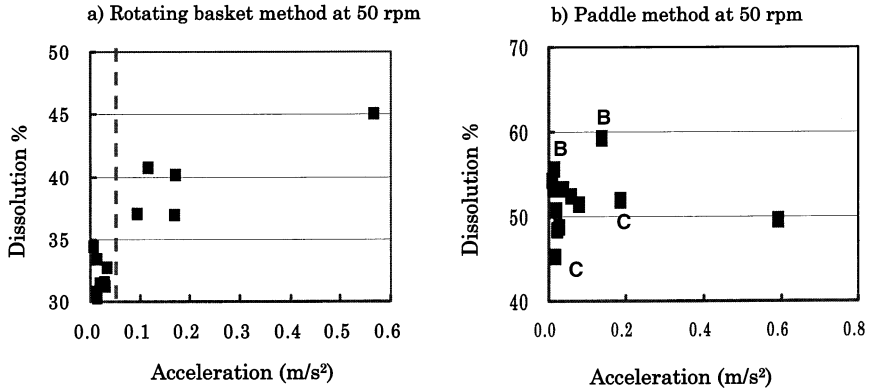

Fig. 3. Effects of vibration levels of the dissolution apparatus on the dissolution rate of EG. The vertical dotted line on graph (a) indicates 0.05 m/s^2 and B and C on the graph (b) indicate results obtained from laboratories B and C.

paratus at vibration levels lower than 0.05 as low vibration apparatus, and those at vibration levels higher than 0.05 as high vibration apparatus.

The mean percentage dissolution of cefalexin for six vessels at 30 min measured by the rotating basket method at 50 rpm obtained in all of the periods of the experimental design are shown in Table 2. The overall mean of the high vibration apparatus was about 7.4% higher than that of the low vibration apparatus. This difference was statistically tested on the assumption that a one-way layout was performed where the source of variation was the vibration level and one of the sources of residual error was the apparatus. Welch's test was applied because the variance of the two groups could not be assumed to be equal (JIS z 9049, Japanese Standards Association, Tokyo.). The observed difference in dissolution rates of EG between the two groups was statistically significant at ($p = 0.05$).

3.2. Results of EG obtained with the paddle method

The correlation between vibration levels of the dissolution apparatus and the percentage dissolution of cefalexin measured using the paddle method at 50 rpm is shown in Fig. 3b. In some laboratories (laboratories B and C), the dissolution rates of cefalexin from EG increased in the apparatus at high vibration levels; this is in accordance with the results reported previously (Fujiwara et al., 1997). However, the difference between the lowest and highest percentage dissolution of EG obtained from the low vibration apparatus was about 10% and this difference was larger than that observed using the rotating basket method. Thus, the results obtained in this collaborative study using the paddle method did not show a clear effect of vibration levels on dissolution rates of EG due to large variability between the apparatus.

During dissolution tests using the paddle method, about one half of EG was floating on the surface of the test solution, some had accumulated at the bottom of the vessels and the rest had dispersed in the test solution. Studies in our laboratory have shown that the amount of EG dispersed in the test solution is affected by the degree of deaeration of the test solutions. Therefore, the small difference in the degree of deaeration between the laboratories is considered as one possible reason for the large variation in dissolution rates of cefalexin between apparatus as measured by the paddle method, although the same method for deaeration was employed in this study.

3.3. Normal range of dissolution rates of EG measured by the rotating basket method at 50 rpm

The results shown in Table 2 suggest that by using dissolution rates of EG measured by the rotating basket method may be useful for evaluating the vibration levels of the dissolution apparatus. It is obvious by comparing Fig. 2a and 2b that use of either the rotating basket or paddle method did not affect the vibration levels of the apparatus. Therefore, if the vibration level of an apparatus is confirmed to be in the normal range using the rotating basket method, then confirmation by using the paddle method is unnecessary.

A dissolution calibrator requires specification limit(s) for percentage dissolution. The specification limits for dissolution rates of the individual vessels are given to the current USP dissolution calibrators. However, it is obvious by comparing Fig. 4a and 4b that the ability to discriminate high vibration apparatus was lower when results of the individual vessels were used than when a mean value for six vessels was used. The results of the individual vessels were more variable than the average values of six vessels because of errors that were due to factors other than vibration. When the purpose for validating a dissolution apparatus is to evaluate the verticality or shape of the vessels, or verticality of the shafts, the results obtained with individual vessels should be checked. On the other hand, an average value obtained from a dissolution apparatus can be also used for validation of its vibration level. Our results suggest that it is suitable to compare an average value with a specified limit when EG is used as a calibrator. For this reason, confidence limits of the average dissolution rates of EG for the low vibration apparatus were calculated.

Table 2
Summary of percentage dissolution of cefalexin from EG within 30 min measured by the rotating basket method at 50 rpm

Vibration level apparatus	Low								High				
	A	B	C	D	E	F	G1	G2	a	b	c	e	f
Experimental day													
1	31.56	33.35	30.74	31.16	31.46	32.70	34.42	30.29	45.02	40.75	40.09	36.92	37.02
2				32.14	30.23		33.06		47.83	36.46	35.53		36.85
3				33.42									
Apparatus mean	31.56	33.35	30.74	32.24	30.84	32.70	33.74	30.29	46.42	38.60	37.81	36.92	36.94
Group mean				31.93[a]							39.34		
Group S.D.				1.278							4.021		

[a] Significantly lower than the mean for the other group.

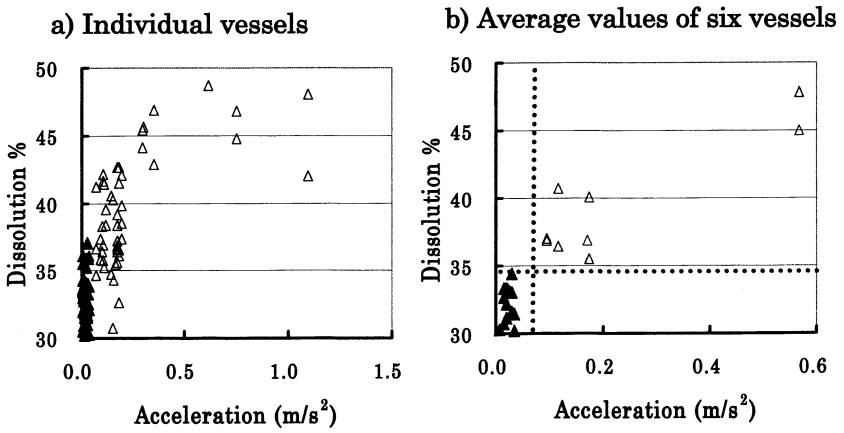

Fig. 4. Correlation between vibration levels of vessels and dissolution rates of EG. ▲ Results of low vibration apparatus and △ results of high vibration apparatus.

Table 3 is the analysis of variance (ANOVA) table of percentage dissolution of EG measured by the rotating basket method at 50 rpm using low vibration apparatus. Variability due to the apparatus in the ANOVA table almost has the same meaning as the variability due to the laboratories in this collaborative work, because each laboratory had one dissolution apparatus at a low vibration level except laboratory G (Table 1). In order to get an accurate description, 'apparatus' and not 'laboratory' was used as the source of variation.

Using the results shown in the ANOVA table (Table 3), a specification limit for percentage EG dissolution was calculated as follows. The result (x) of dissolution testing obtained from a vessel can be expressed by the following equation.

$$x = \mu + b + c + e$$

Where μ,e,c and b are a true value, the residual error of each vessel, part of the between-experimentals error which can not be explained by e, and part of the between-apparatus error which can not be explained by c + e, respectively. The variances of c and b are expressed as σ_c^2 and σ_b^2. Expected variances (E(v)) for each source of variation in the unbalanced nested design that was employed in this study are shown in Table 3 (Ojima, 1984). The variances of between-vessels error, between-experimentals error and between-apparatus error are also termed as variances under repeatability condition, intermediate condition and reproducibility condition and are expressed as σ_r^2, σ_{RW}^2 and σ_R^2, respectively.

Intermediate and reproducibility variances in percentage dissolution of the average of six vessels can be calculated by the following equations (JIS z 8042, Japanese Standards Association, Tokyo.).

$$\sigma_{RW}^2(\text{mean}) = \frac{\sigma_r^2}{6} + \sigma_c^2$$

$$\sigma_R^2(\text{mean}) = \sigma_b^2 + \sigma_{RW}^2$$

The estimated repeatability standard deviations in percentage dissolution of EG at 30 min measured by the rotating basket method at 50 rpm was 1.91%. The estimated intermediate and reproducibility standard deviations for the average mean were 1.03 and 1.38%, respectively.

Because vibration gives energy to dissolution systems and high vibration levels never cause a decrease in dissolution, we should consider only the upper limit of the normal dissolution rate. The upper limits of percentage dissolution of EG for the average percentage dissolution obtained from low vibration apparatus were calculated based on reproducibility, assuming that the dissolution test results have a normal distribution with an estimated mean and standard deviation. Upper limits of percentage dissolution of EG with confidence coefficients of 90, 95 and 99% were 33.8, 34.3 and 35.2%, respectively.

Table 3
Analysis of variance of results obtained by the rotating basket method at 50 rpm using low vibration apparatus

Source of variation	Sum of square	Degree of freedom	Mean square	E(v)
Apparatus	95.6372	7	13.6625	$\sigma_r^2+6\sigma_c^2+8.71\sigma_b^2$
Experiment	25.4228	4	6.3557	$\sigma_r^2+6\sigma_c^2$
Repeatability	219.6108	60	3.6602	σ_r^2
Total	340.6707	71		

3.4. Ability of EG discriminating high vibration apparatus

The dissolution results obtained from all experiments using high vibration apparatus were compared with the upper limits of percentage dissolution of EG. As shown in Table 4, all high vibration apparatus used in this study were rejected by the 90% confidence limits and eight out of nine readings were rejected by the 95 and 99% confidence limits. These results suggest that EG has excellent ability to detect high vibration apparatus.

3.5. Reproducibility of preparation of the test solution

The pH range of the test solutions for EG dissolution testing prepared by 14 operators was 6.48–6.50 (mean 6.49; the intermediate precision 0.0038; reproducibility 0.0067) and a 99% confidence interval was 6.47–6.51. The dissolution tests for EG were performed by the rotating basket method at 50 rpm using test solutions adjusted to a pH of 6.47 and 6.51. The observed percentage dissolution of EG in 30 min was 31.6% at pH 6.47 and 36.0% at pH 6.51, respectively. The interpolated percentage dissolution of EG at 95% upper and lower confidence limits of pH of the test solutions were 33.4 and 34.7%. The difference in dissolution rates of EG between the low and high vibration apparatus was larger than those obtained between the lower and upper pH limits of pH of the test solution. Therefore, EG may work well in the evaluation of vibration levels of the dissolution apparatus, although its dissolution rate is pH-dependent.

The results of the dissolution tests obtained here were slightly higher than the results shown in previous sections. Both results cannot be compared directly because methods for preparing the test solutions were different in both experiments.

3.6. Correlation between dissolution rates and vibration levels assessed in various modes

As shown in Fig. 5, acceleration showed the highest correlation with the dissolution rate of EG as measured by the rotating basket method, while the disposition showed the lowest correlation. When vibration levels of the apparatus were assessed on acceleration, the assessment of vibration at the edge of the vessels was more discriminatory than that at the front panel of the driving device (shaft). The correlation between vibration levels and percentage dissolution of EG did not depend on whether the vibration levels in either the horizontal or vertical directions were measured.

The particle sizes of EG were large enough to remain in the basket during dissolution testing. In some laboratories it was found that EG spread more widely along the wall of the basket or accumulated more loosely in the basket of the high vibration apparatus. This may lead to a larger effective surface area of EG in high vibration apparatus than in the low vibration apparatus. Energy of vibration may be conveyed to the dissolution medium from the dissolution apparatus. In contrast to velocity and acceleration, disposition of vibration does not correlate directly with the energy. Thus, acceleration and velocity may correlate with dissolution rates of EG more than disposition does. Our results suggest that it is appropriate to access vibration levels on acceleration at the edge of the vessels.

Table 4
Abilities of EG and the USP calibrators to discriminate high vibration apparatus

Apparatus	a	a	b	b	c	c	e	f	f
Experimental day[a]	1	2	1	2	1	2	1	1	2
EG rotating basket (50 rpm)	Rejected (×) or accepted (○) by testing								
90% Upper limit	×	×	×	×	×	×	×	×	×
95% Upper limit	×	×	×	×	×	○	×	×	×
99% Upper limit	×	×	×	×	×	○	×	×	×
USP	Number of vessels rejected								
Disintegrating type: Paddle (50 rpm)	0		5		0		0	0	
Non-disintegrating type: Paddle (50 rpm)	0		0		0		0	0	
Non-disintegrating type: Rotating basket (50 rpm)	5		0		0		0	0	

[a] Experiments for EG were repeated in some laboratories but experiments for USP calibrators were not repeated.

3.7. Results of USP calibrators

The average values for percentage dissolution of prednisone and salicylic acid from USP calibrators in six vessels at 30 min was measured using the rotating basket and paddle methods at 50 rpm (Table 5). There was no significant difference in percentage dissolution of prednisone from disintegrating type calibrator tablets between the low and high vibration groups measured by the paddle methods at a significance level of 0.05. Although the dissolution rates of prednisone from the USP calibrator measured by the rotating basket method seemed to be slightly higher in the high vibration apparatus than in the low vibration apparatus, the difference was not significant. It has been reported that vibration effects showed higher dissolution rates with a larger standard deviation of the USP salicylic acid tablets (non-disintegrating type) by the paddle method at 100 rpm (Gray, 1997). However, there was no significant increase in the mean and standard deviation in the percentage dissolution of salicylic acid from USP dissolution calibrator tablets by using the paddle method at 50 rpm in this study. The results obtained with salicylic acid as measured by the rotating basket method at 50 rpm were not compared because of the large amount of abnormal data. An abnormally low dissolution rate was obtained when a large bubble (an air pocket) appeared between a tablet and the upper surface of the basket.

The tests results obtained at 50 rpm were compared with the specification limits provided for the USP calibrators (Table 4). The USP disintegrating type calibrator (prednisone) rejected only the high vibration apparatus in laboratory B. However, it failed to reject other high vibration apparatuses. It can be said from our experience that the current USP prednisone tablet is sensitive to the verticality of vessels and the verticality of stirring shafts. Therefore, there was probably a problem with alignment of the stirring shafts in the high vibration apparatus of in laboratory B.

The validation using USP salicylic acid tablets (non-disintegrating type) by the paddle method completely failed to reject the high vibration apparatus used in this study. However, five vessels in the highest vibration apparatus used in this study (the apparatus in laboratory A) were rejected by USP salicylic acid tablets measured by the rotating basket method. Therefore, it can be concluded that the dissolution rate of the USP salicylic acid tablet measured by the rotating basket method at 50 rpm is sensitive to the vibration levels of the dissolution apparatus, although its sensitivity is not as high as that seen with EG's.

These results suggest that the current USP calibrators are not as sensitive as EG to the variation in vibration levels of the dissolution apparatus.

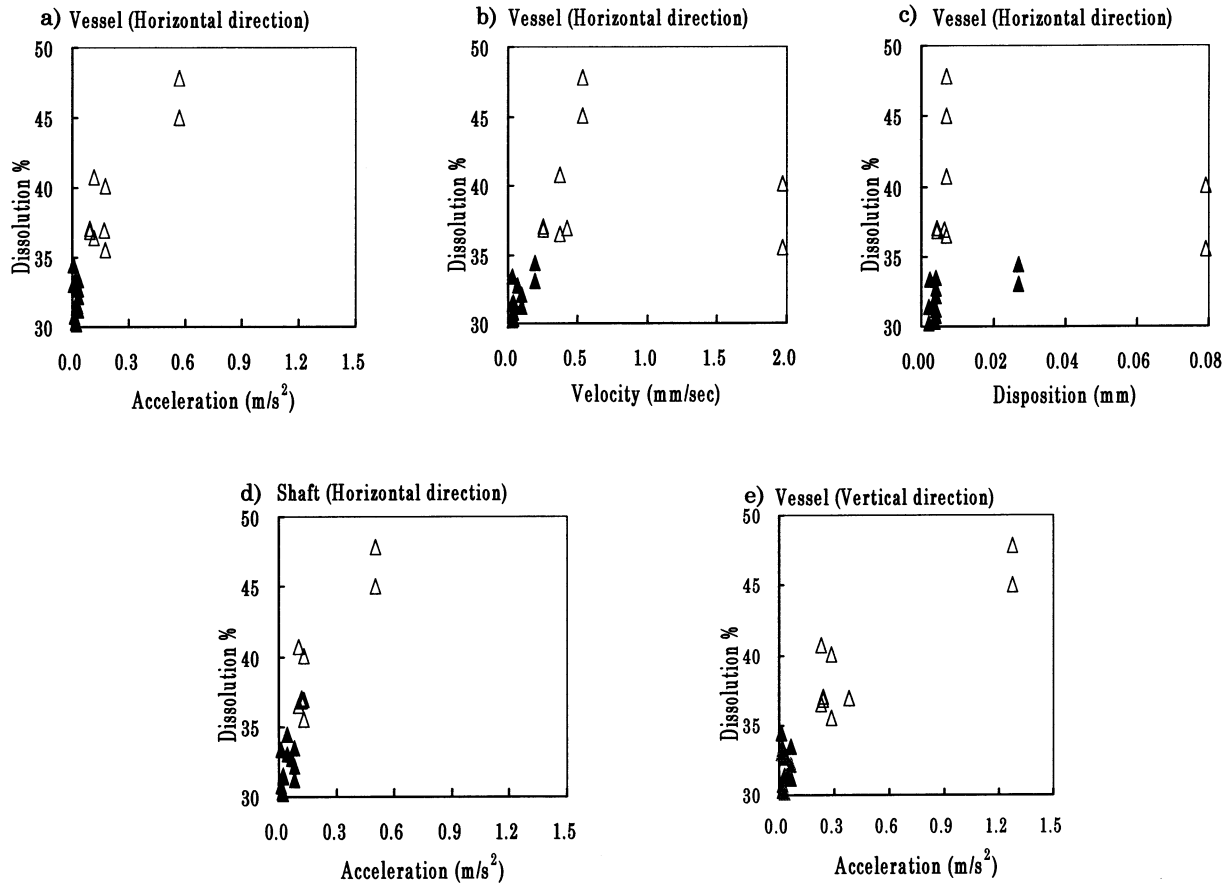

Fig. 5. Effect of evaluation methods of vibration levels on the correlation between vibration levels and dissolution rates of EG measured by the rotating basket method at 50 rpm. ▲ Results of low vibration apparatus and △ results of high vibration apparatus.

4. Conclusion

A dissolution calibrator for the evaluation of vibration levels of the dissolution apparatus may be considered unnecessary, as they can be measured using vibration meters. However, there is diversity in mechanisms for evaluation of vibration levels and estimated values for vibration levels of the dissolution apparatus will vary from machine to machine. In addition, the observed values for vibration levels may be affected by the placement of pickup. Before vibration levels for dissolution apparatus were measured by a VM-7000, participants had measured the vibration levels using their own vibration meters. Values between 0.05 and 3 for low vibration apparatus and values between 0.4 and 10 for high vibration apparatus were obtained. This does suggest that it is difficult to assess absolutely vibration levels of the dissolution apparatus using vibration meters. This is exactly why we need a dissolution standard for evaluating whether the vibration level of a dissolution apparatus is within the normal range.

It was found in this study that the current USP prednisone tablet (disintegrating type) was not sensitive to the variation in vibration levels of the dissolution apparatus, although it is sensitive to the verticality and shape of vessels and the eccentricity of the shafts. USP will be considering another formulation of a disintegrating type calibrator tablet (prednisone) after exhaustion of

Table 5
Dissolution test results of USP calibrators obtained by the paddle and rotating basket methods using low and high vibration aparatus

Type	Dissolution method	Dissolution percentage (mean ± S.D.)		Result of *t*-test
		Low vibration level	High vibration level	
Disintegrating type	Paddle	43.90 ± 2.26	44.74 ± 3.29	N.S.
	Rotating basket	16.52 ± 5.56	19.16 ± 2.53	N.S.[a]
Non-disintegrating type	Paddle	16.92 ± 1.21	16.76 ± 2.15	N.S.
	Rotating basket	—[b]	—[b]	

[a] Welch's test was performed because of unequal variances.
[b] Averages and S.D. were not calculated because of many abnormally low values due to appearance of air pockets.

the supply of current USP disintegrating type calibrator tablets, (Lot L, Moore and Cox, 1997). It has been reported that the candidate for USP disintegrating type calibrator tablet is useful for testing apparatus alignment and medium degassing, but that its sensitivity to vibration levels of the apparatus is unclear. While the current USP non-disintegrating type calibrator tablet (salicylic acid) showed slight sensitivity to vibration by the rotating basket method at 50 rpm, it is was not suitable as a calibrator because of the low sensitivity and high frequency of getting abnormal data as a result of the appearance of an air pocket.

Thus, the current USP calibrators and the candidate for the disintegrating type tablet do not work well as calibrators in detecting high vibration levels of the dissolution apparatus. The results of this collaborative study showed that EG was sensitive to variation in vibration levels of the apparatus and could discriminate high vibration apparatus from low vibration apparatus. Therefore, EG could be useful as a standard for validation unseen vibration of the dissolution apparatus and it may complement the USP disintegrating type calibrator candidate which is sensitive enough for evaluating degree of deaeration, and verticality of stirring shafts and the vessels of a dissolution system.

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