

Mass Variation Tests for Coating Tablets and Hard Capsules: Rational Application of Mass Variation Tests

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The mass variation test is a simplified alternative test version of the content uniformity test. In the case of coating tablets and capsules, the mass variation test is principally applied to test the inner cores or fillings containing the active ingredient. However, some exceptions exist in pharmacopoeias. The effects of tablet coating and capsule shell on the results of the mass variation test were studied. The mass variation of outer crusts (coatings, capsule shells) and inner cores (core tablets, fillings) was measured separately in several products. The effects of coating on weight variability were very large for sugar-coated tablets. Relative standard deviation (RSD) of the formulation weight (RSD_w) of sugar-coated tablets (2.73%) was larger than that of plain tablets (0.77%). The cause of the large RSD_w is the large variation the weight of sugar-coating accounting for 44% of formulation weight. In the case of film-coated tablets, the effect of coating weight on the mass variation test was very small because the rate of coating in comparison to the whole weight was small. In the case of hard capsules, the usage of whole formulation weight resulted in underestimation of variations of filling weight. The differences between dosage forms in the applicability of the mass variation test are caused by differing weight proportions and variability of the outer coatings or shells. To avoid the underestimation of mass variation for hard capsules, a corrected acceptance value is useful. For all the dosage units, the mass variation test can principally be applied to determine which mass is expected to be proportional to the content of the active ingredient. However, some modification of acceptance values enables application of the mass variation tests to inapplicable cases, such as when the RSD of drug concentration (RSD_c) is larger than 2%.

Key words mass variation; content uniformity; coating tablets; hard capsules; Japanese Pharmacopoeia

To assure the therapeutic utility of dosage units such as tablets, capsules, and solids in single-unit containers, the drug content of each unit in a lot should be distributed in a narrow range around the label strength. For this purpose, there are two tests in pharmacopoeias, the content uniformity test and a simplified alternative test, the mass variation test. The latter can be applied when the variability of drug content is proportional to that of the mass of products as follows: (1) a solution in which active ingredient is perfectly dissolved, (2) solids of active ingredient containing no added substances, (3) freeze-dried solid prepared from true solutions in the final containers, (4) concentration RSD (RSD_c) in the final dosage units is not more than 2%. In the first three cases, the mass of formulation is expected to be perfectly proportional to the content of the active ingredient. In the fourth case, the mass of formulation is regarded as proportional to the content of the active ingredient. In our previous study,¹⁾ the mixing homogeneity at 2% of RSD_c was sufficient to maintain the consumer's risk of mass variation test at a low level, the same as in the content uniformity test. The consumer's risk means the risk that consumers purchase defective products. We set the consumer's risk at 5%, and set the quality of defective product at 10% RSD of the content (RSD_D).

In the case of coating tablets and capsules, the mass variation test is principally applied for inner cores or fillings containing active ingredient. However, the mass variation test is applied to film-coated tablets but not for sugar coated tablets in most pharmacopoeias. At the same time, only in the Japanese Pharmacopoeia, the Mass Variation Test can be applied for hard capsules using whole weight including the capsule shell. The difference among dosage forms in the applicability is based on the natures of the outer crusts of the for-

mulations. However, the applicability of mass variation tests have been decided empirically, and no practical data about the mass variation test of the dosage forms are available. In this study, we investigated the effect of coatings and capsule shells on the results of the mass variation test using the test results of products released in Japan, and assessed the adequacy of application of the mass variation test to coating tablets and capsules.

Theoretical Background In the case of coated tablets and capsules, a formulation consists of two parts: one is the outer covering crusts such as a coating or capsule shell, and the other is the inside core such as core tablets or fillings which usually contain the active ingredient. Therefore, the variations in the whole formulation mass consist of mass variations of these two parts. The relationship of weights of the whole formulation, outer crusts (coating, capsule shell) and inner core (core tablet, filling) are described below,

$$w = w_o + w_i \quad (1)$$

where w , w_o and w_i are the individual weight of whole formulation, outer and inner, respectively. Assuming that the individual formulations make up a manufacturing lot, mean and variance of the lot are described as

$$\mu_w = \mu_{w_o} + \mu_{w_i} \quad (2)$$

$$\sigma_w^2 = \sigma_{w_o}^2 + \sigma_{w_i}^2 \quad (3)$$

where μ_w , μ_{w_o} and μ_{w_i} are the mean weight of whole formulations, outer crusts and inner cores, respectively, and σ_w^2 , $\sigma_{w_o}^2$ and $\sigma_{w_i}^2$ are variances in the weight of whole formulations, outer crusts and inner cores, respectively. The lot relative standard deviation (RSD) of whole weight is calculated as below.

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Table 1. Variation in Weight of Whole Formulation, Outer Crusts and Inner Core of Commercial Products

Dosage forms	Sugar-coated tablets	Film-coated tablets ^{a)}	Hard capsules ^{b)}	Plain tablets
No. of companies	10	29	10	37
No. of brands	14	56	14	93
No. of lots	42	168	42	279
Formulation weight (min-max)				
Whole (mg)	157.9 (74.6—303.9)	143.9 (48.2—309.4)	248.1 (86.7—446.8)	159.3 (48.9—999.1)
Inner core (mg)	87.2 (44.9—149.6)	80.0 ^{a)}	221.3 (58.3—370.3)	—
Outer crusts (mg)	70.7 (29.7—173.9)	6.7 ^{a)}	48.0 (28.4—76.6)	—
Proportion of outer crust (%)	44.0 (25.1—57.2)	7.7 ^{a)}	20.6 (17.1—32.8)	—
Expected lot RSD (%)				
<i>RSD_w</i>	2.73 (1.00—5.66)	0.85	1.06 (0.60—1.74)	0.77 (0.32—1.65)
<i>RSD_{wI}</i>	1.05 (0.44—3.21)	0.62 ^{a)}	1.16 (0.67—2.09)	—
<i>RSD_{wO}</i>	6.09 (1.79—12.68)	8.10 ^{a)}	2.01 (1.59—2.37) ^{b)}	—
Content uniformity (%)				
<i>RSD_D</i>	1.63	1.34	1.56	1.26

a) Simultaneous weighing of precoated inner tablets was done for one brand, 3 lots. b) Individual capsule shells were weighed for 4 brands, 12 lots.

$$RSD_w = \frac{\sigma_w}{\mu_w} = \frac{\sqrt{\sigma_{wO}^2 + \sigma_{wI}^2}}{\mu_{wO} + \mu_{wI}} \tag{4}$$

From Eqs. 2, 3 and 4, lot RSD of the inner core weight is

$$RSD_{wI} = \frac{\sigma_{wI}}{\mu_{wI}} = \frac{\sqrt{\sigma_w^2 - \sigma_{wO}^2}}{\mu_w - \mu_{wO}} \tag{5}$$

and also, the RSD of the outer crust weight is

$$RSD_{wO} = \frac{\sigma_{wO}}{\mu_{wO}} = \frac{\sqrt{\sigma_w^2 - \sigma_{wI}^2}}{\mu_w - \mu_{wI}} \tag{6}$$

In the case of plain tablets, the following equation is effective,¹⁾

$$RSD_D^2 = RSD_w^2 + RSD_C^2 \tag{7}$$

where *RSD_D* and *RSD_C* are the lot RSDs of dose and concentration, respectively. However, in the case of coating tablets or hard capsules, an ordinary formulation contains an outer coat consisting of an inactive ingredient. Therefore, dose uniformity is described as follows.

$$RSD_D^2 = RSD_{wI}^2 + RSD_{CI}^2 \tag{8}$$

where *RSD_{CI}* is a lot RSD of the concentration of the core containing the active ingredient.

Calculation of Acceptance Values The acceptance values are used as criteria of the mass variation test in JP14,²⁾ and are calculated from the standard deviation of drug content estimated and the deviation of mean content from label claims^{3,4)} as follows.

$$\text{acceptance value} = |M - A| + ks$$

M: label claim (100.0%), unless otherwise specified in the individual monograph

A: content of active ingredient (% of label claim) determined as described under Assay

*x*₁, *x*₂ ··· *x*_{*n*}: individual estimated contents of the units tested

$$x_i = w_i \times A / \bar{W}$$

*w*₁, *w*₂ ··· *w*_{*n*}: individual weights of the units tested

\bar{W} : mean of individual weights (*w*₁, *w*₂ ··· *w*_{*n*})

n: sample size (number of units in a sample)

k: acceptability constant, *k*=2.2 when the sample size is 10, and *k*=1.9 when the sample size is 30

s: standard deviation of the sample

$$s = \sqrt{\frac{\sum_{i=0}^n (x_i - A)^2}{n-1}}$$

Experimental

Forty-nine pharmaceutical companies participated in this study.^{1,5)} All products studied were released in Japan and details of the sources of the products are described in ref. 1. Ten units each were sampled from individual lots. All the brands of sugar-coated tablets were tested using two types of samples; one is a pre-coated plain tablet sampled from production lines, another is a finished sugar-coated tablet. Pre-coated plain tablets of film-coated tablets were tested for one brand.

Measurements were done by the individual manufacturers. The assay methods used were HPLC and UV absorption methods. Analytical precision was below 2.5% of relative standard deviation. The mean and S.D. of drug content, formulation weight and concentration (w/w%) of the active ingredient were calculated for each 10 units in a lot, and were used for obtaining the acceptance values of JP14, as described above. Details of the test procedure of each dosage form in the same as in ref. 1.

Results and Discussions

Effect of Crusts on *RSD_w* in Commercial Products.

Sugar-Coated Tablets Generally, the mass variation test is not applied for sugar-coated tablets because it has been believed that the sugar coating largely affects the variation in tablet weight, and the mass variation may not correctly reflect the content variation. To examine the effect of coatings on the mass variation test, two types of samples were tested: one is a pre-coated plain tablet sampled from production lines, another is a sugar-coated tablet as a final product. In all the dosage forms, sugar-coated tablets showed the largest *RSD_w* (Table 1). The mean *RSD_w* of commercial sugar-coated tablets (2.73%) is about three times those of plain (0.77%) and film-coated (0.85%) tablets, whereas the *RSD_{wI}* of the pre-coated plain tablets (1.05%) is close to the *RSD_w* of plain tablets. This means that the mass variation test of sugar-coated tablets overestimates the uniformity of mass by using the whole weight instead of the core weight containing active ingredients. In Fig. 1, the *RSD_w* of sugar-coated tablets correlated well with the *RSD_{wO}* of sugar coatings, but not with the *RSD_{wI}* of the core tablets. Coating materials accounted for 44% of the sugar-coated tablets in weight, and showed 6% of *RSD_{wO}* (Table 1). It was concluded that the large *RSD_w* of sugar-coated tablets was, as has been believed,

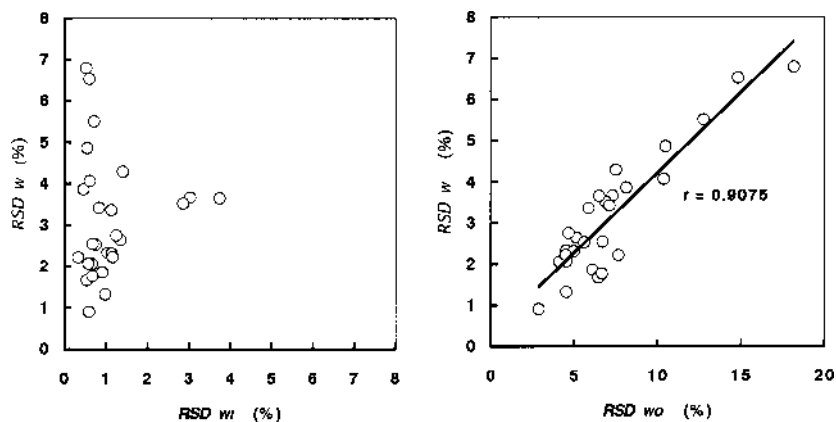


Fig. 1. Relationships between Whole Formulation and Core Tablets or Coating in Weight RSD of Sugar-Coated Tablets

caused by the large weight variability of sugar coatings. Therefore, it is difficult to apply the mass variation test to sugar-coated tablets as a releasing test. However, the mass variation test can be applied to pre-coated plain tablets as an in-process test.

Film-Coated Tablets Though the film-coated tablets showed a high RSD_{WO} of 8%, their RSD_W was as low as that of plain tablets (Table 1). The reason for the low RSD_W of film-coated tablets was the rather small proportion of coating materials. The film-coated tablets contained about 8% coating material whereas sugar-coated tablets contained almost 50% coating materials. In most pharmacopoeias, the mass variation test is applicable for film-coated tablets but not for sugar-coated tablets. The difference between the two types of coated tablets is the effect of the coating crusts on mass variation. The adequacy of the application of a mass variation test for film-coated tablets was supported by the result that the film coating had little effect on the mass variation.

Hard Capsules The mass variation test of commercial capsules showed slightly smaller RSD_W than RSD_{WI} (Table 1). In contrast, sugar-coated and film-coated tablets showed larger RSD_W than RSD_{WI} . The capsule shell accounted for 20% of the formulation weight and showed relatively small RSD_{WO} (2.01%). The noticeable difference between a hard capsule and coated tablets was the considerably small mass variation of the outer shells. Because of the very low variability of capsule shell weight, the JP Mass Variation Test uses the whole capsule weight in the first step of the test, whereas mass variation tests of other pharmacopoeias use only the filling weight. Our results showed that the mass variation is possibly underestimated by using the whole weight of capsules instead of the filling weight. The variance in whole formulation weight is the sum of variances of the inner core and outer crust weights. Therefore, the S.D. of the whole formulation weight is theoretically larger than the S.D. of the filling weight. However, the mass variation test evaluates the RSD_W but not the S.D. of weight. Accordingly, the calculated RSD_W was reduced by the addition of the shell's weight to filling weight. To avoid the underestimation by the mass variation, the corrected RSD_W should be evaluated as described in the previous other section.

Relationship between RSD_W , RSD_{WO} and Proportion of Outer Crusts Our results showed that if the whole formulation weight is used to determine inner core weight, mass

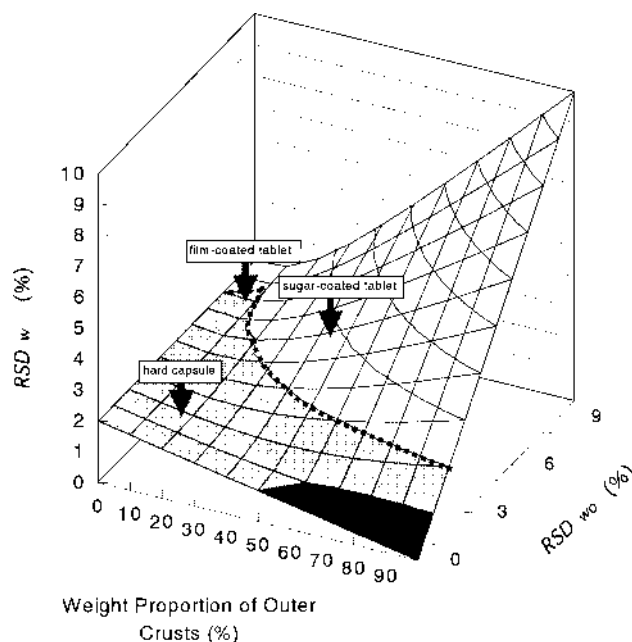


Fig. 2. Contour Plots of Estimation Quality of Mass Variation Test

Gray and dark gray areas show the underestimation, light gray areas show the overestimation in mass variation tests using whole formulation weight. Broken line shows the just-estimated boundary. RSD_W was calculated by Eq. 12 under the condition of the RSD_{WI} assumed to be 2.0%.

variation is overestimated for sugar-coated tablets, underestimated for capsules and just estimated for film-coated tablets (Table 1). These differences are caused by the difference in the relative weight of outer coatings or shells compared to the whole weight of the products and its variability. Figure 2 shows the relationship between RSD_W , RSD_{WO} and the proportion of the outer coating. When μ_W is 1, from Eq. 4, RSD_W is

$$RSD_W = \frac{\sigma_W}{1} = \sqrt{\sigma_{WO}^2 + \sigma_{WI}^2} \tag{9}$$

From Eqs. 5 and 6, the following equations are introduced.

$$\sigma_{WO} = RSD_{WO} * \mu_{WO} \tag{10}$$

$$\sigma_{WI} = RSD_{WI} * (1 - \mu_{WO}) \tag{11}$$

From Eqs. 9, 10 and 11, the relationship between RSD_W , RSD_{WO} and the proportion of the outer coatings is

$$RSD_w = \sqrt{RSD_{w0}^2 \mu_{w0}^2 + RSD_{w1}^2 (1 - \mu_{w0})^2} \tag{12}$$

Figure 2 shows the relationship of Eq. 12 under the condition of the RSD_{w1} assumed to be 2.0%. The position of formulation on the contour map in Fig. 2 could indicate the applicability of the mass variation test. The light gray area in Fig. 2 shows overestimation results, and the gray and dark gray areas show the underestimation results for mass variation tests using whole formulation weight. The broken line in Fig. 2 shows the just-estimated boundary between under- and over-estimation. When the RSD_{w0} is smaller than 2.0%, RSD_w is always lower than RSD_{w1} , regardless of the proportion of the coating weight. Therefore, the mass variation is possibly underestimated by using the whole weight of hard capsules, which showed about 2% of RSD_{w0} . The average proportion of the coating weight of the sugar-coated tablets was 44%, and RSD_{w0} was larger than 4%. The position of sugar-coated tablet in Fig. 2 shows that the mass variation test possibly overestimated RSD_{w1} under this condition. In the case of film-coated tablets, the average proportion of the coating weight of film-coated tablets was 7.7%, and RSD_{w0} was 8.1%; Fig. 2 also shows that the mass variation test of film-coated tablets occurs in the vicinity of the just estimated boundary, though the RSD_{w0} is very large. In conclusion, the applicability of coated tablets and capsules depends on the proportion of coating to the whole formulation weight, since there are variations of weight in the coatings, as shown in Fig. 2.

Adaptive Usage of Mass Variation Tests. Usage of Modified Acceptability Constant The mass variation test can principally be applied for formulations in which the mass is expected to be proportional to the content of the active ingredient. In our previous study,¹⁾ from the standpoint of consumer's risk, it was shown that the RSD_C of a product should be below 2% to apply the mass variation test for content uniformity tests. However, even if the product showed an RSD_C higher than 2%, it is possible to apply the mass variation test with some modification without an increase in consumer's risk. The modification would be to increase the acceptability constant k (ordinarily 2.2 and 1.9 for the sample size of 10 and 30, respectively) used to calculate the acceptance values for a mass variation test in JP14.²⁾

As shown in Eq. 7, dose uniformity (RSD_D) consists of mass variation (RSD_w) and mixing homogeneity (RSD_C). If the RSD_C can be determined in advance, the appropriate limit (L_w) for RSD_w can be set according to the specified limit (L_D) for RSD_D :

$$RSD_D \leq L_D \tag{13}$$

$$RSD_w \leq L_w \tag{14}$$

The acceptance value of the content uniformity test in JP14 is

$$\text{acceptance value} \leq |M - \bar{X}| + ks \tag{15}$$

and

$$s = \bar{X} \cdot RSD_D \tag{16}$$

where \bar{X} is the mean of content. From Eqs. 13, 15 and 16, the criterion of the test is described as:

$$|M - \bar{X}| + k\bar{X} \cdot RSD_D \leq L \tag{17}$$

where L is the specification limit of the test (normally 15.0). Eq. 17 can be changed to

$$RSD_D \leq \frac{L - |M - \bar{X}|}{k\bar{X}} \tag{18}$$

From Eqs. 13 and 18, the following relationship is introduced:

$$L_D = \frac{L - |M - \bar{X}|}{k\bar{X}} \tag{19}$$

then

$$L_D = L'/k \tag{20}$$

where

$$L' = \frac{L - |M - \bar{X}|}{\bar{X}} \tag{21}$$

From Eqs. 7 and 13, the following relationships are introduced:

$$\sqrt{RSD_w^2 + RSD_C^2} \leq L_D \tag{22}$$

$$RSD_w^2 + RSD_C^2 \leq L_D^2 \tag{23}$$

$$RSD_w \leq \sqrt{L_D^2 - RSD_C^2} \tag{24}$$

and from Eqs. 14 and 24, the relationship between L_D and L_w is described as follows:

$$L_w = \sqrt{L_D^2 - RSD_C^2} \tag{25}$$

When modified acceptability constant k' is used for the mass variation test, the acceptance value is

$$\text{acceptance value} = |M - A| + k' s_w \tag{26}$$

and

$$s_w = A \cdot RSD_w \tag{27}$$

The same steps as in Eqs. 16 to 19 about L_D, L_w are given as:

$$L_w = \frac{L - |M - A|}{kA} \tag{28}$$

Because A is almost the same as \bar{X} , from Eqs. 21 and 28, L_w is

$$L_w = L'/k' \tag{29}$$

and from Eqs. 20 and 25 L_w is also:

$$L_w = \sqrt{L'^2 / k'^2 - RSD_C^2} \tag{30}$$

accordingly, from Eqs. 29 and 30 the relationship between k and k' is described as follows:

$$k' = \frac{L'}{\sqrt{L'^2 / k^2 - RSD_C^2}} \tag{31}$$

$$k' = k \frac{L'}{\sqrt{L'^2 - k^2 RSD_C^2}} \tag{32}$$

When $A = \bar{X}$ and A is almost the same as M ($=100$), Eq. 21 gives:

$$L' = L/100 \tag{33}$$

then Eq. 32 is changed as follows:

$$k' = k \frac{L}{\sqrt{L^2 - k^2 100^2 RSD_C^2}} \quad (34)$$

The calculated k' is shown in Table 2. The k' increases following RSD_C increases. When the RSD_C is less than 2%, the same acceptability constant as the content uniformity test can be used for the mass variation test. Additionally, modified constant k' allowed us to apply the mass variation test under the condition of RSD_C being higher than 2%. Figure 3 shows the relationships of the acceptance values between content uniformity and mass variation tests for tested commercial plain and film-coated tablets. When the same acceptability constants k (2.2) as in JP14 were used for content uniformity and mass variation tests, the acceptance constants of the mass variation test is always lower than those of the content uniformity test, and correlation between the two values was therefore not as high. When the modified acceptability constants k' corresponding to individual RSD_C 's for the mass variation test were used instead of ordinary one, the correlation between the two values was very high (Fig. 3). Therefore, as a quality control routine, if the RSD_C is known previously, the mass variation test can be used as a content uniformity test by using modified acceptability constants k' .

Usage of Intact Whole Hard Capsules As described above, the mass variation is possibly underestimated by using the whole weight of the capsules instead of the filling weight. To avoid the underestimation of mass variation, corrected individual estimated contents of the units should be used. This can be achieved by first determining the mean capsule shell weight using empty capsules, and then weighing individual

whole capsules. In calculating of acceptance value, individual estimated contents of the units tested (see the paragraph of calculation of acceptance values) are obtained as below:

$$x_i = A \times (w_i - \bar{W}_O) / (\bar{W} - \bar{W}_O) \quad (35)$$

where \bar{W}_O is the mean capsule shell weight. The criterion for intact hard capsules was the same as the ordinary JP mass variation test. The burdensome procedure of taking off the capsule shells in the mass variation test can be avoided by using the corrected acceptance values.

Conclusion

Differences in the applicability of the mass variation test are caused by differences in the proportion and variability of the weight of outer crusts. It is difficult to apply the mass variation test instead of content uniformity test to sugar-coated tablets, which contain a large amount of coating. In contrast, the mass variation test can be applied to film-coated tablets because the proportion of coating to whole weight was relative small. The JP Mass Variation Test, which uses the whole capsule weight in the first step of the test, underestimates the variability in drug content because it fails to separately calculate the contribution of the shell weight to the results. To avoid the underestimation of mass variation, a corrected acceptance value is useful. Although the mass variation test can principally be applied to formulate weight when the mass is expected to be proportional to the content of active ingredient, some modification of acceptance values enables us to apply the mass variation tests to instances of more variable drug concentration.

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References

- 1) Katori N., Aoyagi N., Kojima S., *Chem. Pharm. Bull.*, **49**, 1412—1419 (2001).
- 2) Japanese Pharmacopoeia 14 ed. (2001).
- 3) Katori N., Aoyagi N., Kojima S., *JP Forum*, **4**, 71—92 (1995).
- 4) Katori N., Aoyagi N., Kojima S., *USP Pharmacopeial Forum*, **23**, 5325—5333 (1997).
- 5) Nakanishi A., Tonooka H., Suzuki S., Ohtani S., Okuda H., Kato M., *Iyakuhin Kenkyu*, **32**, 27—33 (2001).

Table 2. Modified Acceptance Constants for Mass Variation Test

RSD_C	L_D	L_W	k ($n=10$)	k' ($n=10$)
1.0	15.0	14.8	2.2	2.2
2.0	15.0	14.3	2.2	2.3
3.0	15.0	13.5	2.2	2.4
4.0	15.0	12.1	2.2	2.7
5.0	15.0	10.2	2.2	3.2
6.0	15.0	7.12	2.2	4.6
7.0	15.0	<0	2.2	—

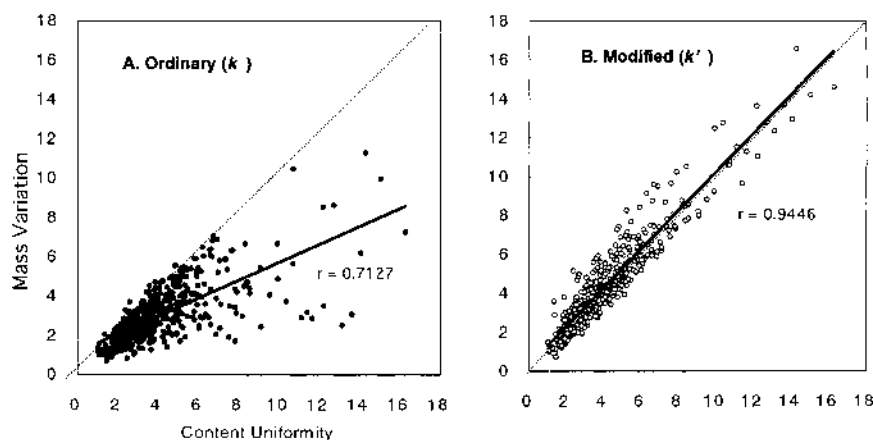


Fig. 3. Relationships of Acceptance Values between Content Uniformity and Mass Variation Tests for Plain and Film-Coated Tablets

(a) Acceptance values obtained by using the same acceptability constants k (2.2, JP14 first step) among the two tests. (b) Acceptance values of mass variation test are obtained by using modified acceptability constants k' (shown in Table 2). Solid lines show the regression lines, and broken lines show the $Y=X$ equation lines.