

The Applications of the Content Uniformity Test and the Weight Variation Test on Process Validation Tests of Multiple Ingredient Preparations

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The new criteria for the weight variation test and the content uniformity test in general tests were revised in the Japanese Pharmacopoeia thirteenth edition (JPXIII), and both tests are used to determine the uniformity of dosage units. The weight variation test, if the content of an ingredient could be directed in the assay reported in JP13, replaces the content uniformity test. Although over-the-counter (OTC) drugs, for example medicine for coughs, are guaranteed to content uniformity, the applications of these tests have not been thoroughly investigated.

We investigated whether one of the effective ingredients could be used as an indicator for the content uniformity of an OTC drug. The indicator was chosen by reason of the very small quantity compared to the others such as anhydrous caffeine in the case of cough medicine. When the mixing process was incomplete and the weight variation test was passed, the content uniformity of anhydrous caffeine in tablet varied in relative standard deviation and could not be guaranteed by this test, though both tests were passed as to the other ingredients. One ingredient such as anhydrous caffeine could not be used as a representative indicator for the other ingredients to confirm the content uniformity. And the content uniformity test could not be replaced by the weight variation test when the content uniformity of the mixed powder had not been confirmed. To guarantee the content uniformities of all effective ingredients of OTC drugs, the content uniformities in the mixing process should be confirmed respectively.

Key words content uniformity test; weight variation test; cough medicine; mixing process; *k* value; process capability

The new criteria for the weight variation test and the content uniformity test were revised in general tests in the Japanese Pharmacopoeia thirteenth edition (JPXIII)^{1,2}; in particular, the weight variation test was regarded to be used in place of the content uniformity test when the method directed in the assay is used for determination. It is very important for guaranteeing the quality of the medicines that the individual content of each effective ingredient in the medicine is consistent. Although the applications^{2,3} of both tests to over-the-counter (OTC) drugs, such as medicine for coughs, anti-febrile and *etc.*, are not studied enough, the content uniformity of the ingredients in the all preparations are usually guaranteed by both tests which are used to determine the uniformity of dosage units.

If each ingredient in the preparation is not mixed uniformly such as tablets, capsules, and injections to be dissolved or suspended before use, the content uniformity of the respective ingredients can not be evaluated by the weight variation test only. Because the real content uniformity is not concordant with the results in the weight variation test in which the acceptance value is estimated from the content average and the fluctuation of the weights by the assay, the result will be passed in the weight variation test even if the mixing is not enough.

In this study, we inspected whether the weight variation test is displaced relative to the content uniformity test for the content uniformities of OTC drugs obtained from several factories. For example, OTC drugs containing anhydrous caffeine (CF), acetaminophen (AA) and ethenzamide (EB), which are well known as the constituent drugs for cough medicine in Japan, were investigated with both tests using a CF assay. The adaptabilities of the weight variation test and the content uniformity test were carried out as practical applications on the OTC drugs, on the process validation,

which were performed in regard to the mixing process, compressing process and packaging process in making the OTC drugs process, simultaneously. We investigated whether the content uniformity could be guaranteed using CF as the prove because the ratio of CF to all ingredients was small, and whether it needed to assure by each ingredient.

Experimental

Apparatus An HPLC instrument (Hitachi 655A) was used with autoinjector, detector, integrator and an octadecylsilanized silica gel column. Volumetric flasks and volumetric pipets were standard grade of Japanese Industrial Standard.⁴

Reagents and Chemicals Methanol was HPLC grade (Kishida Chemicals). CF was purchased from Yamanouchi Pharmaceutical Co., Ltd. and was recrystallized. The other reagents were guaranteed reagent grade (Nacalai Tesque). CF, AA and EB as reference standard (STD) for HPLC assay were determined to be 100.1, 100.3 and 99.4% pure, respectively.

Samples The OTC drugs for cough medicine containing CF were supplied by four pharmaceuticals in Gifu Prefecture in Japan (A—D). The samples of each OTC drug were collected from a mixing process, a compressing process and a packaging process.

HPLC Assay The HPLC mobile phase was prepared by mixing purified water, methanol and acetic acid (80:20:1) followed by filtration through a 0.2 μ m membrane filter (Advantec Toyo). A three μ l aliquot of the solution was injected onto the column and the absorption of peak was monitored at 280 nm. The internal standard (IS) solution was prepared with theophylline (21.67 mg) dissolved into the mobile phase for CF 25 mg. STD solution was prepared for CF, AA and EB by weighing the quantity corresponding to the dosage and were dissolved in the HPLC mobile phase.

Sampling Methods (1) Mixing Process. A batch of mixed ingredients was separated into five parts almost equally from the top to the bottom of the mixer. The mixed powder as the test sample was weighed according to the weight of its dosage three times a part respectively from each part. At this time, the test samples obtained from the mixed powders on the A, B, C and D were expressed as Am, Bm, Cm and Dm, respectively. The Am, Bm, Cm and Dm were powdered sufficiently with a mortar. Each powder was weighed accurately corresponding to the weight of one tablet into 100 ml volumetric flask. The forty ml of the IS solution and HPLC mobile phase were added into volumetric flasks, mixed well and the drug mixture dissolved by ultrasonic producer for 15 min. And then it was diluted with the

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Table 1. The Lists of Combination of Effective Ingredients in Cough Medicines

Component	Cough medicine							
	A		B		C		D	
	content (mg)	content (%)	content (mg)	content (%)	content (mg)	content (%)	content (mg)	content (%)
Anhydrous caffeine	150.0	3.13	75.0	3.13	100.0	3.33	104.0	2.04
Acetaminophen	600.0	12.50	900.0	37.50	—	—	900.0	17.65
Chlorpheniramine maleate	—	—	7.5	0.31	9.0	0.30	7.5	0.15
Tipecidine hibenazate	—	—	75.0	3.13	—	—	—	—
<i>dl</i> -Methylephedrine hydrochloride	—	—	60.0	2.50	75.0	2.50	—	—
Potassium guaiacolsulfonate	—	—	240.0	10.00	—	—	—	—
Thiamine disulfide	—	—	24.0	1.00	—	—	—	—
Ethenzamide	1000.0	20.83	—	—	—	—	—	—
Dihydrocodeine phosphate	—	—	—	—	30.0	1.00	—	—
Noscapine	—	—	—	—	60.0	2.00	—	—
Ephedra herb extract	—	—	—	—	—	—	660.0	12.94
Glycyrrhiza extract	—	—	—	—	—	—	340.0	6.67
Ginseng extract	—	—	—	—	—	—	350.0	6.86
Cinnamon bark extract	—	—	—	—	—	—	600.0	11.76

Content (mg): weight of dosage in a day, content (%): proportion against the dosage in a day.

mobile phase to make 100 ml, and filtered through a 0.2 μm membrane filter. The filtrate was the test sample solution for HPLC assay. (2) Compressing Process. The whole compressing time was divided among five almost equally from the starting to the ending of the compressing the tablets with the batch Thirty tablets were left out and three tablets were used for the assay from each part. The test samples obtained from the compressed tablets on the A, B, C and D were expressed as Ac, Bc, Cc and Dc, respectively. The Ac, Bc, Cc and Dc were weighed accurately and were dropped into 25 ml volumetric flasks. Then ten ml of the IS solution and HPLC mobile phase were added into volumetric flasks. The following procedures were performed in a similar manner to above. (3) Packaging Process. Thirty tablets were collected from packaged tablets on the A, B, C and D, which were expressed as Ap, Bp, Cp and Dp, respectively. The Ap, Bp, Cp and Dp were tested according to the assay on the letter of manufacturing approval of the drug. Briefly, the assay for CF, AA and EB for Ap and Cp were performed as previously described, respectively.⁵⁻⁷ The assay for Bp and Dp was performed with an HPLC assay using an octadecylsilanized silica gel column.

Results and Discussion

Sample Sizes and *k* Values The samples were taken from the mixing process (powder), the compressing process (uncoated tablet), and the packaging process (uncoated or coated tablet). As the controls for the mixing process and the compressing process will influence the quality of the last product, the content uniformity test is performed in the mixing process and the compressing process for guaranteeing the quality of the medicine. In this study, the mixing uniformity of the effective ingredient was evaluated with the fluctuations of fifteen values (*n*=15) which were obtained from five layers and with three values per layer (*n*=3) on the mixed powder. Fifteen values were similarly obtained from the compressing process.

The acceptability constant “*k* values” are adopted as 2.2 and 1.9 on the content uniformity test and the weight variation test when the sample sizes are 10 and 30, respectively, according to JPXIII.¹ This *k* value is determined assuming that the consumer’s risk is approximately 5%.^{2,8} If the sample size is not 10 or 30, both tests can be applied with the *k* value which is determined from the operating characteristic curve statistically, in this study, as the sample size was 15, the *k* value was adopted 2.0.^{2,9}

There are 140 kinds of preparations for OTC cough medi-

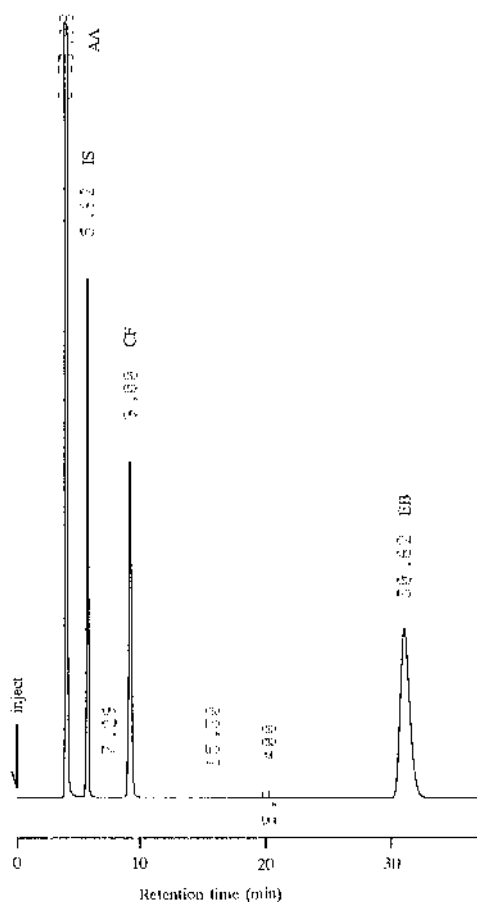


Fig. 1. Liquid Chromatogram of A

Chromatography was carried out on a 655A HPLC instrument (Hitachi) with 851-AS autoinjector (JASCO), SPD-6AV UV-VIS spectrophotometric detector (Shimadzu) and D-2500 Chromato-Integrator (Hitachi).

Peaks: AA=acetaminophen, IS=internal standard (theophylline), CF=anhydrous caffeine, EB=ethenzamide.

Column, TSK gel ODS-80TM (Tosoh), 150×4 mm i.d.; mobile phase, purified water-methanol-acetic acid (80:20:1, v/v); flow-rate, 1.0 ml/min; column temperature, 40 °C; detection, UV (280 nm).

cine for adults in the third edition of the OTC ENCYCLOPEDIA,¹⁰ and CF or caffeine monohydrate, AA and EB CF,

which are included in 92 (119), 89 (125) and 26% (36 kinds), are well known ingredients of OTC drugs for cough in Japan. CF or caffeine monohydrate is included in almost all OTC drugs for cough, and it may be able to be used to prove the content uniformity. The components list of the four kinds of medicine (A—D) used in this study are shown in Table 1. CF, AA and EB were contained 2—3 (in A—D), 10—40 (in A, B and D), and 20% (in A), respectively. The concentration of CF was a smaller proportion against the others than that of AA and EB in each of the four products. The content uniformity of CF, which is an indicator, in a mixed powder will be able to indicate the mixing conditions of other components, because the quantity of CF is very small and its mixing uniformity may be not enough compared with the mixing uniformities of the other effective ingredients.

Analytical Validations of the HPLC Assay As the precision of the assay for use should be confirmed when the fluctuations of the content uniformity of the effective ingredients are mentioned, the validation of the HPLC analytical method was evaluated with regard to CF, AA and EB according to the validation of analytical procedures in general information in JPXIII. The behavior of the retention time of A on the HPLC column is shown in Fig. 1.

Ingredients other AA, IS, CF and EB were not detected or not separated. The chemical compounds in the extracts of the crude drugs were not assayed and did not interfere with the assay of these ingredients since they are detected before 3 min. This HPLC method has been validated according to validation of analytical procedures in general information in JPXIII as previously described.¹¹⁾ The resolutions of AA against IS, CF and EB, IS against CF and EB, and CF against EB is 8.8, 20.7, 38.8, 13.3, 36.6 and 27.8, respectively. The number of theoretical plates for AA, IS, CF and EB is 7800,

12900, 13800 and 11300, respectively. Their tailing factors are 97.1, 90.9, 92.5 and 96.3, respectively. Their capacity factors are 0.89, 1.68, 3.28 and 12.19. The linearity and range of CF were confirmed at the maximum concentration in a time of the last product in the four products. The concentrations of AA and EB showed good linearity similar to that of CF. The peak area of the STD solutions were almost unchanged, when the STD solutions were assayed before and after determinations of CF in the test solutions. This HPLC analytical method was well validated for the assay of CF. Recovery tests were performed for all of the test solutions obtained from the mixing process and the compressing process, and the recoveries of CF were about 100% for all determinations, because this test was performed to ensure the confidence of ingredient content, which was estimated values in the assay, in the extracted solution.

Process Validation by Content Uniformity Test and Weight Variation Test Tablets are usually prepared in a procedure composed of weighing process, mixing process, tablet making process (compressing and coating) and packaging process. The ingredients and fillers were confirmed by the inspections of the papers recording their weight data. Thus, their weights were almost 100% against the weighing quantities of the manufacturing direction.

(1) Process Validation about Mixed Powders: The contents of the ingredients of Am—Dm are shown in Table 2. Each content average except for CF of Am was in the lower limit (90%) or the upper limit (110%) of the quantity control. But one of the content average of CF of Am was 123.0% and exceeded the upper limit of the quantity control and its relative standard deviation (R.S.D.) was 7.77%. An index of process capability (Cpk)¹²⁾ is used to indicate the fluctuation of the process against the lower limit and the upper limit. The

Table 2. Determination of Ingredient Contents in Four OTC Drugs

OTC drug component		Am			Bm		Cm	Dm	
		CF	AA	EB	CF	AA	CF	CF	AA
1st layer	1-1	107.63	98.45	104.00	93.65	106.87	94.55	92.23	95.71
	1-2	107.77	98.41	104.64	94.59	106.13	96.98	95.14	98.21
	1-3	105.80	98.11	104.91	93.45	106.76	96.71	94.95	98.09
2nd layer	2-1	108.93	98.34	97.16	96.56	106.04	95.82	93.70	95.89
	2-2	109.30	97.20	106.42	96.08	106.09	95.97	95.22	96.28
	2-3	103.24	97.16	106.20	93.97	106.88	96.54	94.36	95.47
3rd layer	3-1	95.34	99.35	101.36	93.99	108.30	95.62	96.25	96.52
	3-2	101.20	99.10	102.26	94.26	106.06	95.96	95.37	96.29
	3-3	102.69	97.87	102.53	94.89	105.50	95.56	95.66	96.03
4th layer	4-1	111.73	97.57	105.08	93.65	104.71	93.56	95.39	96.34
	4-2	106.02	99.65	103.59	93.07	108.60	95.05	94.94	96.11
	4-3	109.60	97.51	98.41	94.69	104.25	96.08	95.67	95.56
5th layer	5-1	121.62	97.15	105.57	97.43	104.86	95.22	96.61	94.01
	5-2	122.74	96.24	104.17	97.51	103.08	95.49	95.30	96.64
	5-3	124.61	96.00	101.15	97.58	102.27	94.59	95.49	95.90
Average (%)		109.2	97.9	103.2	95.0	105.8	95.6	95.2	96.2
S.D.		8.49	0.90	0.99	1.55	1.35	0.56	0.60	0.69
R.S.D. (%)		7.77	0.92	0.96	1.63	1.28	0.58	0.64	0.72
Maximum value (%)		122.99	98.77	104.52	97.50	106.62	96.98	95.79	97.34
Minimum value (%)		99.74	96.46	102.05	93.80	103.40	93.56	94.42	95.52
Upper limit of standard		110.0	110.0	110.0	110	110	110.0	110.0	110.0
Lower limit of standard		90.0	90.0	90.0	90	90	90.0	90.0	90.0
Cpk		0.39	3.71	3.36	2.15	2.47	5.98	5.51	4.83

Am, Bm, Cm and Dm : mixed powder obtained from the mixing process on the A, B, C and D, respectively. CF: anhydrous caffeine, AA: acetaminophen, EB: ethenzamide, S.D.: standard deviation, R.S.D.: relative standard deviation. Cpk: an index of process capability. S.D., R.S.D., maximum and minimum values, and Cpk were calculated using the values of the respective content averages of 5 layers.

Table 3. The Content Uniformity Test and the Weight Variation Test as to the Anhydrous Caffeine Content of the Four OTC Tablet

Samples	Ac			Bc			Cc			Dc			
	Weight of tablet (mg)	Individual content (%)	Estimated content (%)	Weight of tablet (mg)	Individual content (%)	Estimated content (%)	Weight of tablet (mg)	Individual content (%)	Estimated content (%)	Weight of tablet (mg)	Individual content (%)	Estimated content (%)	
I	1-1	303.01	107.81	104.41	204.36	101.24	99.89	239.02	96.95	95.90	396.25	93.31	93.83
	1-2	304.04	109.32	104.77	201.87	100.26	98.68	240.91	99.18	96.66	402.58	98.25	95.33
	1-3	303.83	103.30	104.70	203.33	98.63	99.39	243.38	98.63	97.65	401.52	94.07	95.08
II	2-1	296.55	100.56	102.19	198.83	97.19	97.19	247.33	100.20	99.23	397.22	91.30	94.06
	2-2	300.76	100.57	103.64	200.48	97.80	98.00	256.73	105.34	103.00	404.04	95.83	95.67
	2-3	300.35	110.15	103.50	201.95	98.37	98.72	252.83	102.60	101.44	409.38	96.42	96.94
III	3-1	299.39	93.05	103.17	199.73	96.67	97.63	254.66	100.60	102.17	391.22	93.16	92.61
	3-2	303.25	117.86	104.50	197.12	96.64	96.36	250.23	99.87	100.40	397.27	95.59	94.07
	3-3	298.93	97.10	103.01	202.68	97.32	97.32	254.26	101.26	102.01	402.46	94.16	95.30
IV	4-1	302.58	110.69	104.27	198.31	96.32	96.94	255.61	100.94	102.55	401.34	95.00	95.04
	4-2	298.61	96.78	102.90	200.08	97.44	97.80	262.27	103.31	105.23	400.56	96.15	94.85
	4-3	302.44	109.81	104.22	203.93	99.63	99.68	257.52	102.31	103.32	407.17	96.78	96.42
V	5-1	294.97	92.32	101.64	202.53	98.45	99.00	254.74	101.80	102.20	397.41	94.27	94.10
	5-2	299.62	95.73	103.25	200.40	98.64	97.96	254.29	101.76	102.02	401.77	95.32	95.14
	5-3	304.24	109.92	104.84	201.59	100.26	98.54	256.23	101.84	102.80	403.29	94.35	95.50
Average	300.84	103.7	103.7	201.15	98.3	98.3	98.3	252.00	101.1	101.1	400.90	94.9	94.9
S.D.	2.83	7.71	0.98	2.11	1.49	1.03	1.03	6.58	2.03	2.64	4.53	1.70	1.07
R.S.D. (%)	0.94	7.44	0.94	1.05	1.51	1.05	1.05	2.61	2.01	2.61	1.13	1.79	1.13
Acceptance value	—	19.09	—	—	4.65	—	—	—	5.17	—	—	8.48	—
Weight variation	—	5.62	—	—	3.74	—	—	—	6.38	—	—	7.22	—

Ac, Bc, Cc and Dc: compressed tablets obtained from the compressing process on the A, B, C and D respectively. Individual content (%): the value assayed individually. Estimated content (%): the value calculated from the average of individual content in a sample unit, the average of tablet weight and individual weight of tablet. S.D.: standard deviation, R.S.D.: relative standard deviation.

Table 4. The Weight Variation Test in the Last Product

OTC drug Component	Ap			Bp (Sugar coated tablet)			Cp			Dp		
	Weight of tablet (mg)	Estimated content (%)	Individual content (%)	Weight of tablet (mg)	Estimated content (%)	Individual content (%)	Weight of tablet (mg)	Estimated content (%)	Individual content (%)	Weight of tablet (mg)	Estimated content (%)	Individual content (%)
Content average (%)	—	107.13	CF	—	—	CF	—	—	CF	—	—	CF
Sample	Weight of tablet (mg)	Estimated content (%)	Estimated content (%)	Weight of tablet (mg)	Estimated content (%)	Estimated content (%)	Weight of tablet (mg)	Estimated content (%)	Estimated content (%)	Weight of tablet (mg)	Estimated content (%)	Estimated content (%)
1	300.73	106.4	100.9	405.03	98.8	99.3	262.67	96.2	96.2	422.07	99.5	98.3
2	303.14	107.3	101.7	366.43	99.6	89.8	264.83	97.0	97.0	413.04	97.4	96.2
3	301.61	106.7	101.2	422.67	102.9	103.6	250.71	91.8	91.8	425.13	100.2	99.0
4	304.96	107.9	102.3	407.31	100.2	99.8	259.10	94.9	94.9	423.15	99.8	98.5
5	299.15	105.9	100.4	430.54	98.3	105.5	264.99	97.1	97.1	409.94	96.7	95.4
6	301.95	106.9	101.3	411.70	99.2	100.9	258.80	94.8	94.8	414.54	97.7	96.5
7	302.88	107.2	101.6	420.00	102.2	102.9	256.52	94.0	94.0	420.93	99.3	98.0
8	302.75	107.1	101.6	398.73	97.0	97.7	263.92	96.7	96.7	431.08	101.6	100.4
9	305.75	108.2	102.6	409.99	100.5	100.5	256.28	93.9	93.9	421.27	99.3	98.1
10	304.40	107.7	102.2	395.02	100.0	96.8	255.48	93.6	93.6	426.81	100.6	99.4
Average	302.73	107.1	101.6	406.74	99.5	99.7	259.33	95.0	95.0	420.80	99.2	98.0
S.D.	1.99	0.71	0.67	17.83	4.34	4.37	4.73	1.73	1.73	6.54	1.54	1.52
Acceptance value	—	8.7	3.1	—	10.6	9.9	—	8.8	—	—	4.2	5.4

Ap, Bp, Cp and Dp: packaged tablets, CF: anhydrous caffeine, AA: acetaminophen, EB: ethenzamide. Content average: percent of component content, tested according to the assay on the letter of manufacturing approval of the drug. Estimated content: calculated value with the content average of component and individual weight of tablet in manufactured good. S.D.: standard deviation, acceptance value: the value is for the weight variation test.

Cpk value of 1.33 or above expresses that the process capability is sufficiently controlled, and a value of less than 1.00 expresses that the process is not controlled enough. The values of CF, AA and EB in Am were 0.39, 3.71 and 3.36, respectively. The mixing conditions of CF in Am was not enough, though the mixing conditions of AA and EB in Am were sufficiently. All of the Cpk values of effective ingredients in Bm, Cm and Dm were more than 1.33, and their mixing process performed successfully.

In spite of the fact that weights of the ingredients and fillers of Am—Dm were confirmed by inspections by each manufacturer, the averages of the contents were not always 100%. The difference between the content before mixing and the content estimated by the assay does not come from an error in the assay, because the assay used was validated and the results of the recovery tests were almost 100%. As the values of the contents and their averages were estimated from three determinations of the assay and the resulting 5 averages, it might be needed to investigate the sampling inspection, for example the number of test samples or number of parts-separation.

The R.S.D. value of CF in Am (7.8%) was more than four times those of the others (0.6—1.6%). The mixing condition of CF in Am was worst among all ingredients of the four medicines [significant difference ($p < 0.05$)]. When CF is used as an indicator for the process validation test in these multiple ingredient preparations, the content of CF should have a close relationship with the other ingredients. The correlation coefficients between CF and AA (0.785) in Am, and CF and AA (0.724) in Bm were found, but the correlations between CF and EB (0.0800), AA and EB (0.172) in Am, and CF and AA (0.0787) in Dm were not good. Thus, CF could not be an indicator for mixing conditions, since CF was not always well correlated to the others.

(2) Process Validation for Uncoated Tablets: When the acceptance values of the weight variation test or the content uniformity test are less than or equal to 15.0%, each test is passed. The acceptance values of CF in Ac reveal that the

content uniformity test (19.09) was not agreeable but the weight variation test (5.62) was passed (Table 3). The S.D. value of the weight variation test of CF in Ac (0.98) is smaller than that of the content uniformity test of CF in Ac (7.71). The acceptance value of the weight variation test was calculated from the average of the content concentrations and its S.D. value while the acceptance value of the content uniformity test was calculated with individual content concentration and its S.D. value. When the S.D. value of the weights of tablets are so small to pass weight variation test of that tablets, even if its mixing was not done enough. As to CF, the S.D. values of content uniformity test were similar to that of weight variation test as Bc, Cc and Dc, both tests were passed (Table 3). The weight variation test could not be substituted for the content uniformity test when the mixing process was performed enough as CF in Ac. Although the S.D. values of the weight variation test of EB in Ac (0.95) are smaller than that of the content uniformity test of EB in Ac (5.84), the content uniformity test was passed. The other values of the weight variation test, except for CF in Ac and EB in Ac, are similar to those of the content uniformity test, and both tests were passed (data not shown). As the differential evaluations of both tests were observed in Ac, CF could not be used as an indicator.

(3) Process Validation about Last Products: The last products except Bp were not coated, and the weight variation test was applied to them (Table 4). As the acceptance values of them were less than 15.0%, the weight variation tests were passed. Although the Bp are sugar coated and thus the weight variation test can not be applied, the value was less than 15.0% and the test was passed when the test was applied.

Relationship between Content Uniformity Test and Weight Variation Test We tried to investigate whether CF, which is a very small quantity compared to the others, could be used as an indicator for guaranteeing the content uniformity of OTC drugs. The relationship of acceptable values between the weight variation test and the content uniformity test of the tablets on the compressing processes is shown in

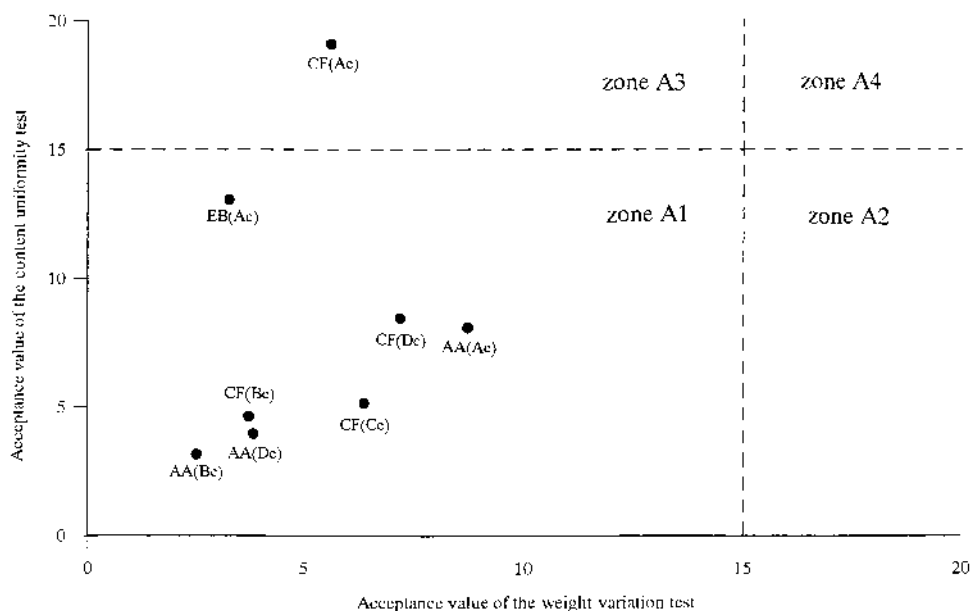


Fig. 2. The Relationship of the Acceptance Values between the Weight Variation Test and the Content Uniformity Test

CF: anhydrous caffeine, AA: acetaminophen, EB: ethenzamide, Ac, Bc, Cc and Dc: tablets obtained from the compressing process on A, B, C and D, respectively.

Fig. 2. The requirements are met if the acceptance values in both tests are less than or equal to 15.0%. The acceptance values of CF in Ac is plotted over the limit line of the content uniformity test and on the left side of the limit line of the weight variation test. The fluctuation of tablet weight will influence the acceptance value of the weight variation test, and the fluctuation in the mixing process will influence the acceptance value of the content uniformity test. When the plot is in zone A1, both tests are agreeable and it means that the mixing process and the compressing process are satisfactorily performed. In zone A2, although the mixing process is satisfactory, the compressing process is inadequate. In zone A3, the mixing process is inadequate but the compressing process is satisfactory. In zone A4, both the mixing process and the compressing process are inadequate. CF of Ac is plotted in zone A3, although AA and EB of Ac are plotted in zone A1. Therefore CF could not be used as a representative indicator for the other ingredients. For guaranteeing the content uniformity of the OTC drug, the content uniformities of all ingredients should be confirmed.

In conclusion, the applications of both tests were performed with the validated HPLC assay to OTC drugs containing CF for four kinds of tablets. Although all of the ingredients should be assayed and tested essentially, we tried to determine whether CF could be used as an indicator for the content uniformity test and the weight variation test, because the weight of CF is quite small. But CF could not be used as an indicator. As the mixing process and the tablet making process are important for guaranteeing the quality of medicine, we sampled from the mixed powders, the uncoated tablets and the final products in each process. Then the contents of the effective ingredients in the mixing powder and the uncoated tablet were assayed, and the content uniformities could be confirmed by testing with the content uniformity test. At present, the weight variation test is regarded in place of the content uniformity test, therefore the weight variation test was carried out for the uncoated tablet obtained from compressing process. We have had one experience

where uncoated tablets did not pass the content uniformity test, in spite of passing the weight variation test. This result means that the content uniformity of the ingredients in the tablets can not be assured with only the agreement of the weight variation test for the tablets. In the case of the tablet composed of various effective ingredients, it is necessary for guaranteeing the content uniformity of the tablets not only to pass the weight variation test of the last products but also to confirm the content uniformity in the mixing process.

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