

The effect of tablet splitting on the mass loss, uniformity, and stability: by hand or splitter?

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ABSTRACT

This study aimed to analyze and compare differences by split methods for scored tablets of different strengths and shapes. Five tablets with different strengths were subdivided using splitter, and by hand. The loss of weight, friability, the uniformity of dosage units, and stability were tested for whole tablets and tablets broken by hand and a splitter. All drug products showed greater weight loss and friability and smaller uniformity of dosage when broken by hand compared with the splitter. One mg tablets broken by hand and 8 and 16 mg rounded tablets subdivided by both hand and splitter did not satisfy content uniformity. All the products, except 8 and 16 mg rounded tablets, met the stability test criteria. Tablet subdividing by splitter is more appropriate, and these trends were more pronounced for non-rounded tablets with low strength. Hence, the lower-strength tablets require subdividing by a splitter.

Key words: splitting tablet, split methods, weight loss, content uniformity, stability

1. Introduction

Tablet splitting is practiced worldwide for various medications to provide an appropriate fractional dose, assess an individual patient's response to the drug, make swallowing easier, and for economic reasons (Dormuth et al., 2008; Rodenhuis et al., 2004; Stafford and Radley, 2002; Starling et al., 2015). However, the splitting of tablets at the dispensing stage can lead to a loss of weight from the whole tablet, increased friability, and a significant risk of weight nonuniformity of tablet fractions (Rosenberg et al., 2002). The change in weight uniformity can adversely affect dosage uniformity (Freeman et al., 2012). Moreover, at the point of ingestion, these tablet fractions may not have same stability profile as indicated by the manufacturer (Volpe et al., 2008). In particular, tablet splitting for drugs with a narrow therapeutic indices can lead to the administration of incorrect doses and possibly produce severe adverse reactions (Rodenhuis et al., 2004; Shah et al., 2010; Teng et al., 2002).

To ensure that the patient receives the correct dose, there is a need for the comprehensive examination of the quality of tablet fractions. The European Pharmacopoeia adopted tests

to confirm accuracy of split tablets in 2002. In the weight loss and content uniformity and dissolution tests, the subdivided tablets should meet the criteria for whole tablets and should be stable under long-term storage conditions. The result of splitting tablets is affected by the cutting method (Matuschka and Graves, 2001). The physical properties, shape, size, hardness, and scoring line also affect quality of the subdivided tablet (Abu-Geras et al., 2017; Elliott et al., 2014).

To date, several studies have evaluated the weight loss after the use of one or more tools such as knives, splitters, and razor blades for tablet splitting (Rosenberg et al., 2002; Cook et al., 2004; Tahaine and Gharaibeh, 2012; Verrue et al., 2011). In recent years, some studies have evaluated the uniformity of content, but the use of a single-split method (Hill et al., 2009) or the method of splitting is ambiguous (Zaid et al., 2013). Some studies involving scored tablets and various splitting methods have also evaluated either weight loss (Elliott et al., 2014; Teng et al., 2002) or content uniformity (Ciavarella et al., 2016). On the other hand, Volpe (Volpe et al., 2008) has tested stability differences between subdivided and whole gabapentin tablets and revealed that splitting of gabapentin tablets does not affect the stability.

Nonetheless, previous studies did not comprehensively evaluate the impact of splitting methods, strength, and shape of tablets when splitting. This study was aimed at comparing quality parameters, such as weight loss, friability, the uniformity, and stability of tablets split by means of a splitter and by hand in accordance with the FDA guidance and at testing how strength and shape of tablets when splitting affect the quality of subdivided tablets.

2. Materials and Methods

Materials

Our study drug products were five different medications in which we assessed the strength, shape, size (weight), and score line of the tablets. Each parameter was selected to evaluate the impact of manual and mechanical splitting on the content uniformity and stability of the subdivided tablets. The selected medications, which were all scored tablets, were risperidone 1 mg (Celltrion Pharm, Lot #168211, oblong), candesartan cilexetil 8 mg (Celltrion Pharm, Lot #152945, round) and 16 mg (Celltrion Pharm, Lot #158816, round), losartan potassium 50 mg (Celltrion Pharm, Lot #160215, oval), and gabapentin 600 mg (Celltrion Pharm, Lot #169046, oval). We intended to conduct a more in-depth study on the scored tablets, which, when split along the score line, were reported to better satisfy the dose variability and content uniformity criteria (Ciavarella et al., 2016).

Reference standards purchased from USP were used in the test for drug content and content uniformity. The Ezy dose tablet cutter (Apothecary Products Inc.), which can be easily purchased at global and Korean online shopping malls, was selected as the splitter. In the analysis process, the following reagents were used: acetonitrile (JT Baker, HPLC grade), ammonium hydroxide solution (Sigma Aldrich, ACS reagent), trifluoroacetic acid (Samchun, Extra-pure grade), hydrochloric acid (Samchun, Extra-pure grade), phosphoric acid (Sigma Aldrich, Extra-pure grade), and potassium hydroxide (Sigma Aldrich, Extra-pure grade). Purified water was obtained by means of a Milli-Q water purification system (Integral 15, Millipore).

2.1. Equipment and chromatographic conditions

For content evaluation, a 1260 infinity HPLC system from Agilent was used to quantify the test samples in accordance with United States Pharmacopeia (USP)-NF monograph (United States Pharmacopeia and National Formulary, 2016) (Appendix 1).

Methods

2.2. Physical characteristics

The shapes and scoring lines of the five types of tablets under study were verified visually. Twenty pre-separated tablets were randomly selected, and the diameter and thickness of each tablet were individually measured by means



Figure 1. Tablet splitter (Apothecary Products Inc.®)

of a Vernier caliper (Mitutoyo, ID-C1012X) and a tablet breaking-force tester (ERWEKA, TBH225WTD). The data variation was determined via calculation of averages.

2.3. Tablet splitting

Tablets were split by two methods: by hand of a 31-year-old female laboratory technician (hand size: height 17.0 cm; width 7.5 cm), using the muscular strength of the thumb and index finger grabbing each side of the scoring line, but not by using a fingernail; when a splitter (Apothecary Products Inc.®) was employed, the lid of the splitter was lifted, the tablet was placed on the V-shaped holder and divided into two pieces by increasing the force applied to the lid (Figure 1).

Any mishandled tablets broken into more than two pieces were excluded from the experiment (two tablets each of Candesartan cilexetil 8 and 16 mg, all the incidents occurred in the case of hand breaking).

2.4. Loss of weight

In accordance with the FDA guidance, 15 randomly selected tablets from each product were individually weighed on an analytical balance (Sartorius Inc., ED224S, Germany) with 0.1-milligram precision before and after the splitting process. The loss of weight was calculated via the following formula:

$$\begin{aligned} \text{Loss of weight (\%)} &= \frac{\{\text{Weight of whole tablet (mg)} - \text{weight of both half tablets (mg)}\}}{\text{Weight of whole tablet (mg)}} \\ &\times 100 (\%) \end{aligned}$$

The average, standard deviation, and minimum/maximum of the weight loss were calculated. To comply with the FDA guidance, the individual loss of weight should be less than 3.0%.

2.5. Friability test

Three repeated measurements of the whole tablets and tablet fractions were performed for the evaluation of friability.

For risperidone, candesartan, and losartan, the tablet specimens collected were approximately 6.5 g. Ten presplit tablets and 20 postsplit tablets were selected for gabapentin. The friability of tablets was measured in a Copley friabilator (FRV2000, UK). The friabilator was operated at a speed of 25 rpm for 100 turns. The final result was calculated by means of the following formula after three repeat measurements:

$$\text{Friability (\%)} = \frac{\{\text{weight of tablets before test (mg)} - \text{weight of tablets after test (mg)}\}}{\text{weight of tablets before test (mg)}} \times 100 (\%)$$

The acceptance criterion was that the maximum mean weight loss in the test does not exceed 1.0% according to the USP.

2.6. Uniformity of dosage units

The whole and split tablets were tested for content uniformity in accordance with the general chapter of the United States Pharmacopeia (USP 40) Uniformity of Dosage Units <905> (United States Pharmacopeia and National Formulary, 2016), which is a requirement of the FDA Guidance for Industry on tablet scoring. Risperidone 1 mg, candesartan 8 mg, and candesartan 16 mg were tested in accordance with the content uniformity test methods: should contain 25 mg of an active ingredient and constitute less than 25% by weight of the dosage-form unit. Losartan 50 mg and gabapentin 600 mg were evaluated in accordance with the weight variation test method: should contain 25 mg or more of an active ingredient and constitute 25% or more by weight of the dosage-form unit. Thirty samples were randomly chosen, and the acceptance value was calculated based on the individual content results from the first 10 specimens using the following formula:

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

where M is a reference value; \bar{X} is a mean of individual contents; k , acceptability constant; s , sample standard deviation.

Twenty tablets (20 parts of the 10 subdivided tablets) were further analyzed if the acceptance value did not meet the 85–115% range.

2.7. Drug content

Twenty tablets, selected from whole tablets and split either by hand or with the splitter, were used in the content test in accordance with the Content Assay Method of the United States Pharmacopeia (USP)-NF Tablets. For content evaluation, an Agilent 1260 Infinity HPLC system was used to quantify the test samples in accordance with the proxy United States Pharmacopeia (USP)-NF monograph (United

States Pharmacopeia and National Formulary, 2016) (Appendix 1). The acceptance criteria were applied in accordance with the content test for each tablet.

2.8. Dissolution test

According to the USP-NF monograph (tablet) (United States Pharmacopeia and National Formulary, 2016), the dissolution test was performed on 12 tablets of each drug selected from whole and split tablets, complying with the guidance recommendation. The sample solution was taken at a predetermined time, and the result was evaluated from the dissolution rate [% Wd (dissolution amounts (mg)) / Wt (theoretical amounts (mg))] after one whole tablet or half of a tablet of each drug was placed into the dissolution vessel. Compliance criteria were set at a dissolution rate [% Wd (dissolution amounts (mg)) / Wt (theoretical amounts (mg))] of Q+5% or more from each sample.

2.9. Stability test

For each drug, five tablets were selected from the whole tablets and were split by hand or machine (splitter) in high-density polyethylene containers and stored in a controlled environment (25°C ± 2°C/60% ± 5% relative humidity) in a stabilized chamber (Lab Fine Ltd., FLT-1207S, Korea) for 90 days in accordance with the FDA Guidance. The tablets were tested for drug contents, dissolution, and the individual test results were determined and compared with the specification of the tablet after a 90-day interval.

3. Results

3.1. Physical characteristics of products

In the comparison of the drug content by weight in the various study drug products, tablets with 1 mg risperidone had an active pharmaceutical ingredient content of approximately 1% of the tablet weight, compared with 73.1% for the tablets with 600 mg gabapentin. Tablets with 600 mg gabapentin had the highest breaking force with 19.52 ± 2.83 kp; candesartan 8 and 16 mg tablets had lower breaking force of 7.89 ± 2.31 kp and 7.65 ± 1.51 kp, respectively (Table 1).

3.2. Loss of weight and friability of products

All drug products showed greater weight loss when subdivided by hand compared with using a splitter. The percentage weight loss for hand split candesartan 8 and 16 mg was 3.74% and 3.55%, respectively, which exceeded the proposed limit of the FDA guidance; the values obtained using the splitter, 2.44% (for 8 mg tablets) and 2.12% (for 16 mg tablets), satisfied the acceptance criteria (less than 3%). Gabapentin tablets, which had the largest weight, showed superior properties in terms of weight loss compared with other tablets (hand splitting: maximum loss rate, 0.27%; by using a splitter, maximum loss rate, 0.19%). The split tablets showed increased friability (%) compared with whole tablets. The hand split tablets showed higher friability (%) compared

Table 1. Tablet characteristics of study drugs: risperidone, candesartan cilexetil, losartan potassium, and gabapentin.

API	Strength (mg), lot number	Weight (mg) \pm SD [‡] (N=20)	Dimensions (mm) [†] , (N=20)				Shape	Scored mark	Hardness (kp) [†] \pm SD [‡] (N=20)
			Width \pm SD [‡]	Length \pm SD [‡]	Length/width ratio	Thickness \pm SD [‡]			
Risperidone	1.0, 168211	103.1 \pm 1.09	4.07 \pm 0.13	8.71 \pm 0.22	2.14	2.83 \pm 0.31	Oblong	1-sided	8.87 \pm 1.26
Candesartan cilexetil	8.0, 152945	135.2 \pm 0.85	6.65 \pm 0.32	6.65 \pm 0.34	1.0	3.20 \pm 0.27	Round	1-sided	7.89 \pm 2.31
	16.0, 158816	150.9 \pm 1.25	7.03 \pm 0.20	7.03 \pm 0.25	1.0	3.39 \pm 0.40	Round	1-sided	7.65 \pm 1.51
Losartan potassium	50.0, 160215	103.0 \pm 0.91	5.50 \pm 0.23	10.30 \pm 0.37	1.87	6.73 \pm 0.14	Oval	1-sided	10.90 \pm 3.24
Gabapentin	600.0, 169046	820.6 \pm 1.98	9.01 \pm 0.23	17.32 \pm 0.20	1.92	6.75 \pm 0.33	Oval	1-sided	19.52 \pm 2.83

Abbreviations: API, active pharmaceutical ingredient; mg, milligram; mm, millimeter; kp, kilopond.

[†] Average value of 20 measurements[‡] Standard Deviation**Table 2. Comparative analysis of the loss of weight and friability for a half-tablet between non-mechanical and mechanical methods.**

API	Strength (mg)	Specification		Whole tablet (N=15)	Half tablet (N=30) by hand				Half tablet (N=30) by a tablet splitter			
		items	Criteria		Mean \pm SD [†]	Max	Min	Result	Mean \pm SD [†]	Max	Min	Result
Risperidone	1.0	Loss of weight (%)	Less than 3.0%	n/a	0.57 \pm 0.48	1.54	0.10	Pass	0.35 \pm 0.43	1.43	0.00	Pass
		Friability (%)	NMT 1.0%	0.15	0.24 \pm 0.05	0.30	0.17	Pass	0.22 \pm 0.05	0.28	0.15	Pass
Candesartan cilexetil	8.0	Loss of weight (%)	Less than 3.0%	n/a	2.01 \pm 0.66	3.74	1.25	Fail	1.15 \pm 0.57	2.44	0.07	Pass
		Friability (%)	NMT 1.0%	0.39	0.99 \pm 0.01	1.00	0.97	Pass	0.65 \pm 0.07	0.74	0.57	Pass
	16.0	Loss of weight (%)	Less than 3.0%	n/a	1.93 \pm 0.54	3.55	1.51	Fail	1.06 \pm 0.52	2.12	0.07	Pass
		Friability (%)	NMT 1.0%	0.40	0.98 \pm 0.01	1.00	0.96	Pass	0.63 \pm 0.06	0.70	0.55	Pass
Losartan potassium	50.0	Loss of weight (%)	Less than 3.0%	n/a	0.40 \pm 0.28	0.96	0.06	Pass	0.24 \pm 0.15	0.58	0.06	Pass
		Friability (%)	NMT 1.0%	0.25	0.45 \pm 0.01	0.65	0.27	Pass	0.38 \pm 0.10	0.50	0.25	Pass
Gabapentin	600.0	Loss of weight (%)	Less than 3.0%	n/a	0.13 \pm 0.09	0.27	0.01	Pass	0.06 \pm 0.07	0.19	0.00	Pass
		Friability (%)	NMT 1.0%	0.09	0.15 \pm 0.07	0.25	0.09	Pass	0.14 \pm 0.07	0.24	0.08	Pass

Abbreviations: API, active pharmaceutical ingredient; NMT, not more than; mg: milligram.

[†] Standard Deviation

with the use of the tablet splitter. Nonetheless, all drug products satisfied the proposed FDA guidance limit (1.0%). Gabapentin tablets had the lowest friability (hand split: 0.15%; using the tablet splitter: 0.14%; Table 2).

3.3. Uniformity of dosage units

The all tablets complied with the test: not more than one of the individual concentrations of the 30 units was outside 85–115% of the average content and no values were outside the limits of 75–125% of the average content. The acceptance value of mean content uniformity for all split tablets was higher than that of whole tablets. The uniformity of the dosage unit for tablets split by hand was lower compared with the use of the splitter. The mean content uniformity of hand-

split risperidone tablets was 16.7, which exceeded the FDA guidance (less than 15), whereas the value obtained using the splitter (10.3) satisfied the FDA guidance criteria (less than 15).

All candesartan tablets exhibited unacceptable content uniformity when splitting was done by the splitter (31.5 for 8 mg tablets, 17.6 for 16 mg tablets) and by hand (46.7 for 8 mg tablets, 16.1 for 16 mg tablets). Losartan and gabapentin tablets satisfied the uniformity test when split by hand and using the splitter (Table 3).

3.4. Dissolution test

According to the FDA guidance, the subdivided tablets must meet the dissolution test criteria of the original product.

Table 3. Uniformity of dosage units of study drugs: risperidone, candesartan cilexetil, losartan potassium, and gabapentin.

API	Strength (mg)	Specification items	Whole Tablet (N=10)	Half tablet by hand (N=20)	Half tablet by a tablet splitter (N=20)
Risperidone	1.0	Method	CU	CU	CU
		Number of units	10	30	30
		AV †	1.9	16.7	10.3
		Result	Pass	Fail	Pass
Candesartan cilexetil	8.0	Method	CU	CU	CU
		Number of units	10	10	10
		AV †	2.4	46.7	31.5
		Result	Pass	Fail	Fail
	16.0	Method	CU	CU	CU
		Number of units	10	30	30
		AV †	1.8	16.1	17.6
		Result	Pass	Fail	Fail
Losartan potassium	50.0	Method	WV	WV	WV
		Number of units	10	10	10
		AV †	1.6	14.2	14.0
		Result	Pass	Pass	Pass
Gabapentin	600.0	Method	WV	WV	WV
		Number of units	10	10	10
		AV †	0.6	12.8	9.4
		Result	Pass	Pass	Pass

Abbreviations: API, active pharmaceutical ingredient; CU, content uniformity; WV, weight variation; mg, milligram.

† AV: Passance value (Criteria: maximum AV is not more than 15.0)

On the other hand, the subdivided tablets of candesartan 8 (min value by hand: 73%, min value by a tablet splitter: 82%) and 16 mg (min value by hand: 82%, min value by a tablet splitter: 81%) failed to meet the dissolution test criteria immediately after splitting, regardless of the tablet splitting method. The other three products met the dissolution test criteria of the original product.

3.5. Stability test

On the basis of the standard deviation of all five products, there was no dissolution loss during storage for 3 months immediately after the split. Tablets satisfying the dissolution test criteria immediately after the split also satisfied the 3-month stability test standard (Table 4).

4. Discussion

Our study conducted comprehensive examination of many qualities of subdivided tablets (that have different strength and shape) depending on the split method. To confirm the quality impact of a subdivided tablet, the content uniformity test (risperidone and candesartan cilexetil) by the validated HPLC method and the weight variation test (losartan and gabapentin) of the subdivided tablets were carried out using

the splitter or hand. As a result, it was confirmed that the value of content uniformity is larger when a tablet is divided by hand (except for 16 mg candesartan); therefore, it was subdivided more uniformly when a splitter was used. Friability was also tested to determine the level of quality risk during storage and transportation of the subdivided tablets; this parameter for all subdivided tablets was in accordance with the FDA's standard. In a stability comparison between whole tablets and subdivided tablets, all products, except candesartan cilexetil 8 and 16 mg rounded tablets, met the stability test criteria with both tablet splitting methods, and stability was dependent on the initial stability test results regardless of the splitting method.

Splitting (by either method) increased weight variation compared with whole tablets; this result is consistent with the findings of other study (Fahelbom et al., 2016; Habib et al., 2014; Helmy, 2015). The use of the splitter yielded more uniform tablets and led to lower weight loss than breaking by hand did, in agreement with findings by others (Cook et al., 2004). This may be because breaking by hand may not exert uniform pressure on tablets, thus producing jagged cut lines and thereby creating greater weight variation in comparison with the use of a splitter (Fahelbom et al., 2016; Habib et

Table 4. Stability test of study drugs: risperidone, candesartan cilexetil, losartan potassium, and gabapentin.

API	Strength (mg)	Specification		Whole tablet (Initial, N=10)	Half tablet (Initial, N=20)		Whole tablet (3 months, N=10)	Half tablet (3 months, N=20)	
		Items	Criteria		By hand [†]	By a tablet splitter [‡]		By hand [†]	By a tablet splitter [‡]
Risperidone	1.0	Assay (%)	90.0–110.0	101.4	99.2	100.7	101.5	98.4	100.6
		Dissolution (%) [§]	NLT 80%	94.0 ± 1.7	93.0 ± 7.2	94.0 ± 4.6	92.0 ± 1.5	93.0 ± 7.5	93.0 ± 4.2
		Min / Max		91.0 / 96.0	84.0 / 102.0	86.0 / 98.0	90.0 / 94.0	83.0 / 102.0	86.0 / 98.0
		Result		Pass	Pass	Pass	Pass	Pass	Pass
Candesartan cilexetil	8.0	Assay (%)	90.0–110.0	99.0	97.2	97.4	99.8	98.3	96.0
		Dissolution (%) [§]	NLT 85%	98.0 ± 0.9	89.0 ± 9.9	91.0 ± 6.1	98.0 ± 1.0	88.0 ± 9.9	89.0 ± 7.1
		Min / Max		96.0 / 99.0	73.0 / 98.0	82.0 / 98.0	97.0 / 99.0	73.0 / 98.0	82.0 / 97.0
	16.0	Assay (%)	90.0–110.0	100.0	98.4	98.7	99.8	97.1	98.7
		Dissolution (%) [§]	NLT 85%	98.0 ± 0.8	94.0 ± 9.2	96.0 ± 11.6	98.0 ± 1.0	93.0 ± 8.6	95.0 ± 9.5
		Min / Max		97.0 / 99.0	82.0 / 104.0	81.0 / 108.0	96.0 / 99.0	83.0 / 102.0	82.0 / 107.0
		Result		Pass	Fail	Fail	Pass	Fail	Fail
		Result		Pass	Fail	Fail	Pass	Fail	Fail
Losartan potassium	50.0	Assay (%)	95.0–105.0	100.5	97.3	98.1	102.8	100.4	102.5
		Dissolution (%) [§]	NLT 80%	99.0 ± 1.4	98.0 ± 4.4	96.0 ± 5.0	97.0 ± 1.2	100.0 ± 4.8	97.0 ± 5.6
		Min / Max		97.0 / 100.0	93.0 / 103.0	92.0 / 102.0	95.0 / 99.0	94.0 / 107.0	91.0 / 103.0
		Result		Pass	Pass	Pass	Pass	Pass	Pass
Gabapentin	600.0	Assay (%)	90.0–110.0	99.4	99.6	101.3	101.1	99.9	101.2
		Dissolution (%) [§]	NLT 85%	96.0 ± 0.5	99.0 ± 6.0	94.0 ± 5.0	95.0 ± 0.5	98.0 ± 3.5	94.0 ± 3.3
		Min / Max		95.0 / 96.0	91.0 / 106.0	90.0 / 103.0	94.0 / 95.0	93.0 / 102.0	90.0 / 99.0
		Result		Pass	Pass	Pass	Pass	Pass	Pass

Abbreviations: API, active pharmaceutical ingredient; Min: minimum; Max, maximum; NLT, not less than; mg, milligram.

[†] Using hand, [‡] Using tablet splitter, [§] %: Wd (dissolution amounts (mg)) / Wt (theoretical amounts (mg)), Number of samples = 6, Mean ± Standard deviation

al., 2014). Weight loss (e.g., for 1, 8, and 16 mg tablets) was greater in low-strength products of relatively smaller physical sizes. Among them, when round tablets were broken by hand, the weight loss criterion was not met. Considering the factors affecting the tablet splitting with the score line suggested by Steen (2010) (van der Steen et al., 2010), the above finding must be due to the low diameter/width ratio of the round tablet compared to the oblong tablet. The small round tablets made splitting difficult and thus created the biggest weight variation among all the drugs analyzed; this result is similar to the findings of another study (Ciavarella et al., 2016).

We showed that subdivided tablets, whether by hand or using the splitter, had markedly higher dose variability and acceptance values of content uniformity than did the whole tablets, in line with the findings of a U.S. study (Ciavarella et al., 2016). Round tablets with low strength did not satisfy the content uniformity criteria regardless of the splitting method (by hand or splitter). Although splitting of scored tablets is approved by the FDA as efficacious and safe, tablets with a small size or low proportion of an active pharmaceutical ingredient are generally not suitable for splitting because the half-tablet weights of the divided scored tablets often do not pass the dose content uniformity tests (Mosena and Van der

Merwe, 2009). Other than that, tablets with high strength and the shape of a large oval met the criteria. Similar to the results of other studies (Helmy, 2015; Hill et al., 2009; Zaid et al., 2013), this finding might be due to the following principle: the larger the weight loss ratio, the greater is the variation in content.

As a result of the stability test on five products, no significant changes occurred in the dissolution profiles between the initial test and a test after 90 days. On the other hand, the low-strength (candesartan cilexetil 8 and 16 mg) round tablets broken by hand did not meet the weight loss criteria and failed the dissolution test from the initial stage. In other words, the subdivided tablets satisfying the stability test criteria at the initial stage passed the stability test after 90 days. These results are similar to and different from the findings of another stability test (Volpe et al., 2008) and highlight the importance of accurate splitting.

Unlike that in previous studies, in the present study, we analyzed the results comparatively in relation to study objects, i.e., based on the strength and shape of tablets and splitting methods (a splitter or hand) in contrast from the previous studies. Tablets from low strength (1 mg) to high strength (600 mg) were selected to determine the effect of differences

in tablet strength. Products (candesartan cilexetil 8 and 16 mg) of different strengths were also selected to determine quality differences for tablets of different strengths containing the same drug. Risperidone, which was especially selected to find effects of low strength (lowest strength [1 mg] among risperidone formulations), met the standard (<3.0%) of weight loss regardless of splitting methods. Nonetheless, the method using the splitter satisfied the guidance criteria (less than 15 AV) only on the uniformity of dosage. In contrast, tablets (losartan potassium, and gabapentin) with strength above 50 mg showed the same performance on both weight loss and uniformity tests regardless of the splitting method in this study. Therefore, through our study design, we proved that the splitting method could result in a quality issue when tablets of low drug strength or low tablet weight were subdivided. On the other hand, quality evaluation results of two strengths (8 and 16 mg) of candesartan cilexetil were the same in all tests of subdivided tablets. These results mean that tablet shape (round, length/width ratio = 1.0) of candesartan cilexetil caused inaccurate tablet splitting, in agreement with other studies (van der Steen et al., 2010). Only candesartan cilexetil (8 and 16 mg) tablets also did not meet the stability test criteria with both tablet-splitting methods. The reason why candesartan cilexetil tablets failed to meet the dissolution test criteria immediately after splitting when considering the results of a gabapentin study (Volpe et al., 2008) is that stability of subdivided tablets depended on the initial result when splitting.

We comprehensively compared the impact of splitting by means of a splitter and by hand on the quality of split tablets in accordance with the FDA guidance and revealed the influence of strength and shape of tablets on the quality of subdivided tablets. This study has several limitations. First, we did not consider all possible physical characteristics of tablets that can have an influence on tablet splitting. Future studies should further analyze the quality of split tablets according to other physical characteristics by selecting different tablets manufactured by various companies for the same compound. Second, the characteristics of the splitter were not completely determined. Therefore, our results may only be accurately interpreted to represent the splitter used in this study. Nevertheless, the effect of the splitter type may be expected to be minimized because the splitter selected was the most commonly used one in the world market. Finally, variations based on the characteristics of users could not be determined, because a single individual performed both the manual and mechanical splitting processes to minimize the influence of skill on the splitting process. Therefore, our results should be interpreted by considering that the same tester split tablets using the same splitter in the same way.

5. Conclusion

This study verified that the strength and shape of a tablet

and splitting method also affect the weight loss, uniformity, and stability of split scored tablets. Tablet splitting using the splitter resulted in a smaller loss of weight and better content uniformity than did splitting by hand, and these trends were more pronounced for tablets with low strength. Stability of subdivided tablets was also dependent on the accuracy of splitting with less weight loss. Taken together, these findings suggest that tablets with lower strength that require splitting should be split by means of a splitter.

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Appendix 1. HPLC conditions, the mobile phase, flow, and flow rate for the study drugs: risperidone, candesartan cilexetil, losartan potassium, and gabapentin.

API	Test items	HPLC condition						
		column	Mobile phase (M.P.)	WL (nm)	Inj.v (µL)	Flow	Flow rate (mL/min)	
Risperidone	UOD/Dissolution	C18, 4.6 × 150 mm, 5 µL	PW:ACN:TFA (65:35:0.1)	237	50.0	Isocratic	1.5	
	Assay	C18 (L1), 4.6 × 150 mm, 5 µL	A: PW:ACN:TFA (80:19.5:0.1) Adjusted with NH ₄ OH to pH 3.0 B: PW:MeOH:TFA (61:39:0.1) Adjusted with NH ₄ OH to pH 3.0	275	20.0	Gradient	2.5	
						Time (min)	M.P-A	M.P-B
						0-8	100	0
						8-16	100→0	0→100
						16-20	0	100
						20-21	0→100	100→0
						21-30	100	0
Candesartan cilexetil	Dissolution	C8 (L7), 4.6 × 150 mm, 5 µL	ACN:TFA:PW (550:1:450)	254	50.0	Isocratic	1.5	
	Assay/UOD	C8 (L7), 4.6 × 150 mm, 5 µL, 30°C	ACN:TFA:PW (550:1:450)	282	10.0	Isocratic	1.5	
Losartan potassium	Dissolution	C18 (L1), 4.0 × 250 mm, 5 µL	ACN:0.1% phosphoric acid (40:60)	254	20.0	Isocratic	1.0	
	Assay/UOD	C8 (L7), 3.9 × 150 mm, 5 µL, 25°C	A: ACN: phosphate buffer (15:85) B: ACN *phosphate buffer: 1.25 mg/mL of monobasic potassium phosphate and 1.5 mg/mL of dibasic sodium phosphate in water	250	10.0	Gradient	1.0	
						Time (min)	M.P-A	M.P-B
						0	80	20
						10	40	60
						11	80	20
						15	80	20
Gabapentin	Dissolution/ Assay/UOD	C8 (L7), 4.6 × 250 mm, 5 µL	1.2 g of monobasic potassium phosphate in 940 mL of water. Adjust with 5 N KOH to pH 6.9 and then add 60 mL ACN	210	50.0	isocratic	1.2	

Abbreviations: API, active pharmaceutical ingredient; HPLC, high-performance liquid chromatography; WL, wavelength; mm, millimeter; µL, microliter; Inj. v, injection volume; mL, milliliter; min, minute; UOD, uniformity of dosage units; PW, purified water; ACN, acetonitrile; TFA, trifluoroacetic acid; MeOH, methanol.