Original Article

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Selection of generic preparations of famotidine orally disintegrating tablets for use in unit-dose packages

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ABSTRACT: Changes in the hardness, dissolution, and the disintegration time of brand name and generic preparations (6 preparations) of famotidine orally disintegrating tablets were investigated. Tablets had been stored in a thermo-hygrostat-controlled environment set to simulate the home conditions of patients up to 8 weeks after unit-dose packaging. Among the tablets in unit-dose packaging prepared immediately after blister packs (BP) were opened, one generic had decreased hardness to less than 2.0 kg after 1 week, 55.1% of its initial hardness value, and a shorter disintegration time of about 1/5 of its initial disintegration time. Generics met the standard for dissolution 8 weeks after unit-dose packaging. The decrease in hardness after unit-dose packaging is presumed to be associated with additives, and particularly the types and amounts of binding agents, but evidence of this association was lacking. The hardness noted in drug interview forms (IFs) and the state of sales of bulk tablet packages must be determined to facilitate the selection of generics that remain hard even after unit-dose packaging.

Keywords: Unit-dose packaging, generics, tablet hardness, famotidine orally disintegrating tablet

1. Introduction

The "2008 Patient Survey" by the Ministry of Health, Labor, and Welfare listed "estimated numbers of patients receiving medical treatment for major diseases"; of these, about 520,000 persons were found to be receiving medical treatment for gastric or duodenal ulcers (*1*). Drug treatment for these conditions mainly involves histamine H_2 receptor antagonists (H_2RAs), which inhibit gastric acid secretion, and proton pump inhibitors (PPIs) (*2*). Orally disintegrating tablets of these drugs are also widely used by elderly patients and patients with difficulty swallowing.

A neighboring medical institution consulted the current authors about orally disintegrating tablets of famotidine as an H_2RA to determine if generics were as susceptible to disintegration after unit-dose packaging as their brand name counterparts. Otori *et al*. studied brand name and 4 generic preparations of famotidine orally disintegrating tablets subjected to Accelerated Testing as described in the Stability Testing Guidelines, and they reported differences in stability and sensory evaluations over the long term (*3*).

Harada *et al*. evaluated disintegration properties using a newly proposed disintegration test featuring a rotating shaft and rotation speed, and they reported that this test helped to estimate the actual disintegration time in humans (*4*). Tokuyama *et al*. measured dissolution of brand name and generic preparations and compared their degree of bitterness; they reported that there were large variances in the intensity of bitterness; they found that some generics were significantly more bitter than their brand name counterparts (*5*). As mentioned earlier, many studies of famotidine orally disintegrating tablets have been conducted. However, no studies compared changes in the hardness, dissolution, and disintegration time of brand name and generic tablets after unit-dose packaging. Therefore, the current study compared the hardness, dissolution, and disintegration time up to 8 weeks after unit-dose packaging of brand name and generic preparations. This study also evaluated the criteria for famotidine orally disintegrating tablets for use in unit-dose packaging.

2. Materials and Methods

2.1. *Materials*

A brand name preparation (Gaster® D tablet 10 mg: Astellas Pharma Inc.) and 6 generic preparations (A-F) of famotidine orally disintegrating tablets were used. Of the 10 generics that were commercially available at the

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start of this study (September 2011), 6 were selected because they came in smaller packages, facilitating purchase by medical institutions, and because they had different combinations of binding agents as additives (*6-8*). Differences in the additives in brand name tablets and the 6 generics are shown in Table 1. The paper used for unit-dose packaging was E Ueda Cello-Poly (polyethylene laminated cellophane; thickness, 0.04 mm; transparent packaging paper: MEG Co.).

2.2. *Measurement of hardness*

The hardness of famotidine orally integrating tablets was measured immediately after blister packs (BPs) were opened. The tablet hardness in unopened BPs was also measured 2, 4, and 8 weeks after storage in BPs in a thermo-hygrostat (Emviros: Tokyo, at a temperature of 27°C (± 0.5°C) with a humidity of 55% (± 3%)). Unit-dose packaging took place immediately after BPs were opened, and tablets were stored in a thermo-hygrostat at the same temperature with the same humidity, and hardness was measured after 1, 2, 4, and 8 weeks of storage. The hardness of 10 tablets of each preparation was measured under the same conditions at each measurement point using a Monsanto hardness tester (Tablet Hardness Meter Type A, 15 kg: Fuji Rikakogyo Co., Ltd.), and the mean was determined. The temperature (27°C) and humidity (55%) used for the thermo-hygrostat in this study were determined based on measurements from the homes of 10 teachers and students of the University. The temperature and humidity of places where drugs were stored in the home were measured 3 times a day over 3 days from September 1 to 10, 2008. The mean temperature and humidity were used, as shown in Table 2.

Table 1. List of additives in famotidine orally disintegrating tablets

Additive		Original brand product	Generic products					
			A	B	C	D	E	F
Cornstarch	binder				○	○		
Crystalline cellulose	binder			○	○			
Dextrin	binder					○		
Ethyl acrylate, methyl methacrylate polymer	binder		○					
Ethylcellulose	binder	○			○			○
Hydroxypropyl cellulose	binder							○
Hydroxypropyl starch	binder			○				
Hydroxyproryl methylcellulose 2910	binder		○					
D-Mannitol	binder	○	○		○		○	○
Methylcellulose	binder		○					
Povidone	binder			○				
Aspartame		○	○	○	○	○	○	○
Anhydrous silicic acid						○		
Calcium silicate							○	
Calium stearate		○						
Cetyl alcohol		○			○			○
Cyclodextrin		○						
β-Cyclodextrin			○					
Ethyl vanillin								○
Fragrance		○	○		○	○	○	○
Glucono-σ-lactone			○					
Gum arabic						○		
Lactose hydrate				○		○		
Light anhydrous silicic acid					○			
Magnesium stearate			○	○	○	○	○	
Magnesium aluminometasilicate			○					
Maltitol starch syrup								○
L-Menthol			○	○	○	○	○	
Polyoxyethylene nonylphenyl ether			○					
X-Povidone			○	○	○		○	
Powder candy		○						
Sodium lauryl sulfate		○			○			○
Sodium stearyl fumarate								○
Starch syrup			○					
Synthesis aluminum silicate				○				
Talc			○			○		○
Triacetin		○			○			○
Vanillin								○
Be non-sealed tablet		○	○		○	○	○	○
Be hardness in IF			○	○		○	○	○

Data are shown as the combination of binding agents as additives in brand name tablets and 6 generic (A-F) tablets.

Table 2. The mean temperature and humidity of the place where drugs were stored in the homes of 10 volunteers

Cooperator	A	B	C	D	E	F	G	H	I	J	Mean
Temperature max. (°C)	28	27	28	27	28	28	29	28	29	29	
Temperature min. (°C)	24	24	24	25	24	24	26	26	26	26	
Temperature mean (°C)	26	26	26	26	26	26	28	27	28	28	26.5
Humidity max. (%)	68	65	76	62	64	75	61	60	60	55	
Humidity min. (%)	42	44	49	48	41	57	47	44	45	45	
Humidity mean (%)	55	55	63	55	53	66	54	52	53	50	55.4

2.3. *Measurement of the dissolution rate*

The dissolution rate of famotidine orally disintegrating tablets was measured immediately after BPs were opened and 1, 2, 4, and 8 weeks after storage in unit-dose packages in a thermo-hygrostat at the same temperature and humidity as noted earlier. Dissolution was measured according to Japanese Pharmaceutical Codex, Part III using the second method of the dissolution test (the paddle method) with a medium volume of 900 mL, temperature of 37 ± 0.5°C, and paddle rotation rate of 50 rpm. The medium was 0.05 mol/L acetic acid/sodium acetate buffer, measurement was performed at each measurement time using 5 tablets, and the mean value was used. Samples (5 mL) were collected 1, 2, 5, 10, 20, and 40 min after measurement started and analyzed using an ultraviolet and visible spectrophotometer (JASCO V-650 Spectrophotometer: JASCO Co., Tokyo, Japan) at a wavelength of 266 nm.

2.4. *Measurement of disintegration time*

Famotidine orally disintegrating tablets were stored under the same conditions as in the hardness and dissolution rate experiments, and the disintegration time was measured after 1, 2, 4, and 8 weeks. In accordance with the Disintegration Test of the Japanese Pharmacopoeia used to measure the disintegration time of brand name drugs, water was used as a medium, and a disintegration tester (NT-1HM Toyama Disintegration Tester: Toyama Sangyo Co., Ltd. Osaka, Japan) was operated at 37 ± 2°C. Measurement was performed at each measurement time using 6 tablets, and the mean was determined.

3. Results

3.1. *Hardness*

All generics except generic B were harder than the brand name tablets immediately after BPs were opened. The hardness of brand name and generic tablets stored in unopened BPs in a thermo-hygrostat at a temperature of 27°C ± 0.5°C with a humidity of 55% ± 3% for 8 weeks is shown in Figure 1, and the hardness of tablets stored in unit-dose packages prepared immediately after BPs were opened in a thermo-hygrostat at the same temperature with the same humidity for 8 weeks is shown in Figure 2. Figure 1 indicates that the hardness of brand name tablets decreased by 13.4%. Similarly, the hardness of other preparations decreased less than 20%. As shown in Figure 2, the hardness of brand name tablets decreased by 5.4% while that of generic B decreased by 55.1% (hardness < 2 kg) after 1 week. After 2, 4, and 8 weeks, generic B was softer than brand name tablets, and some tablets of generic B had disintegrated during measurement.

3.2. *Dissolution rate*

The dissolution rate for brand name and generic tablets 1, 2, 5, 10, 20, and 40 min after measurement started is shown in Figure 3. Figure 3 indicates that the dissolution rate of all tablets reached nearly 100% 10 min after measurement started. The dissolution rate was evaluated within 10 min after measurement started. The dissolution rate for brand name and generic tablets after storage for 2, 4, and 8 weeks following unit-dose packaging is shown in Figures 4-6, respectively. These figures indicate that generic E had the slowest dissolution. Generics B and C had faster dissolution than other tablets.

3.3. *Disintegration time*

The disintegration time of tablets stored in unopened BPs and in unit-dose packages throughout the 8-week storage period compared to when measurement started is shown in Figures 7 and 8, respectively. These figures indicate that the disintegration time of most tablets stored in unit-dose packages began to decrease after one week. Disintegration time decreased to about 1/5 after one week for generic B in particular in comparison to when BPs were opened.

4. Discussion

As noted earlier, this study was initiated because a neighboring medical institution consulted the current authors regarding "the susceptibility to disintegration of generic preparations of famotidine orally disintegrating tablets after unit-dose packaging in comparison to brand name preparations". The hardness of brand name tablets and 6 generic preparations (A-F) was measured immediately after unit-dose packaging and also 8 weeks later. One week after the storage of tablets at a temperature of 27°C ± 0.5°C with a humidity of 55% ± 3% following unit-dose packaging,

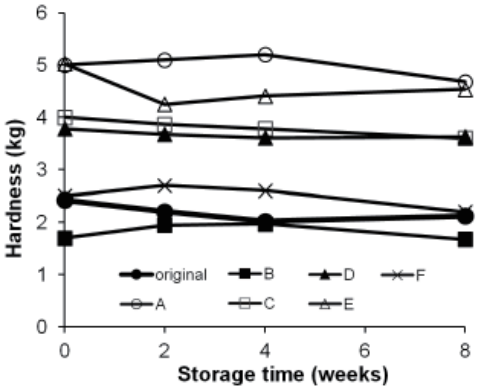

Figure 1. Hardness of famotidine orally disintegrating tablets stored in BPs. Data are shown as the mean for 10 tablets measured at each measurement point using a Monsanto hardness tester. Brand name, ●; generic A, ○; generic B, ■; generic C, □; generic D, ▲; generic E, △; generic F, ×.

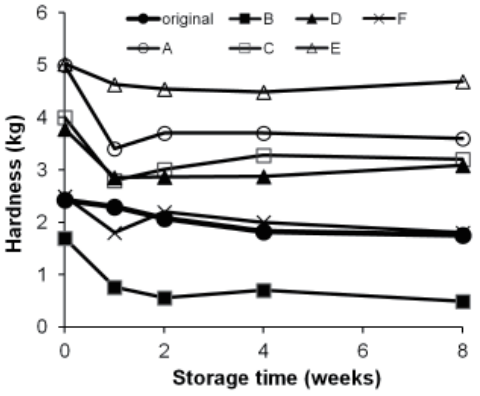

Figure 2. Hardness of famotidine orally disintegrating tablets stored in unit-dose packages. Data are shown as the mean for 10 tablets measured at each measurement point using a Monsanto hardness tester. Brand name, ●; generic A, ○; generic B, ■; generic C, □; generic D, ▲; generic E, △; generic F, ×.

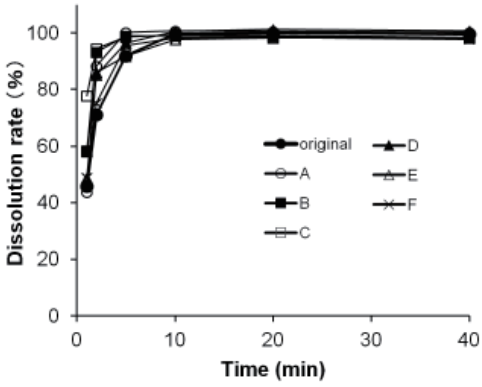

Figure 3. Dissolution rate of famotidine orally disintegrating tablets immediately after BPs were opened (0-40 min). Data are shown as the mean for 5 tablets measured at each measurement point using an ultraviolet and visible spectrophotometer. Brand name, ●; generic A, ○; generic B, ■; generic C, □; generic D, ▲; generic E, △; generic F, ×.

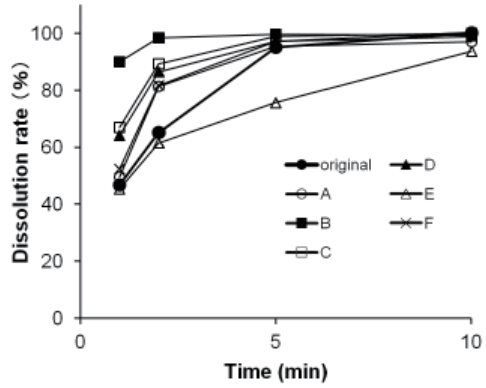

Figure 4. Dissolution rate of famotidine orally disintegrating tablets after storage for 2 weeks following unit-dose packaging (0-10 min). Data are shown as the mean for 5 tablets measured at each measurement point using an ultraviolet and visible spectrophotometer. Brand name, ●; generic A, ○; generic B, ■; generic C, □; generic D, ▲; generic E, △; generic F, ×.

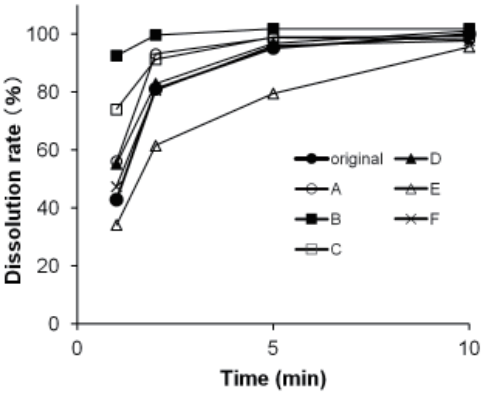

Figure 5. Dissolution rate of famotidine orally disintegrating tablets after storage for 4 weeks following unit-dose packaging (0 - 10 min). Data are shown as the mean for 5 tablets measured at each measurement point using an ultraviolet and visible spectrophotometer. Brand name, ●; generic A, ○; generic B, ■; generic C, □; generic D, ▲; generic E, △; generic F, ×.

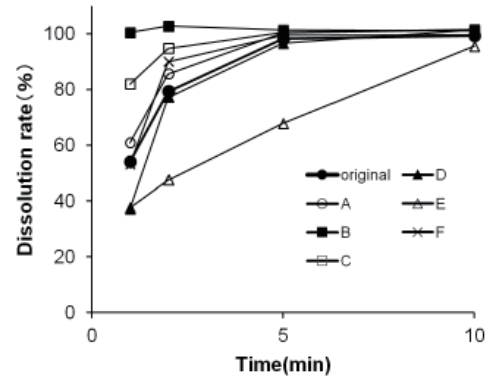

Figure 6. Dissolution rate of famotidine orally disintegrating tablets after storage for 8 weeks following unit-dose packaging (0-10 min). Data are shown as the mean for 5 tablets measured at each measurement point using an ultraviolet and visible spectrophotometer. Brand name, ●; generic A, ○; generic B, ■; generic C, □; generic D, ▲; generic E, △; generic F, ×.

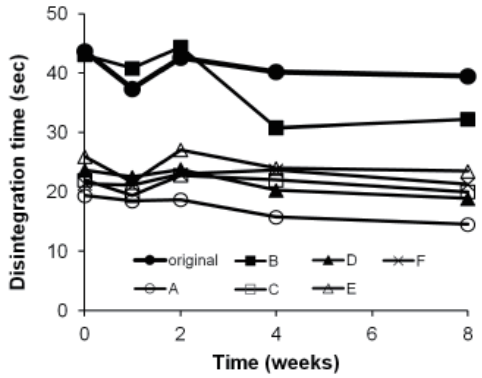

Figure 7. Disintegration time of famotidine orally disintegrating tablets 8 weeks after storage in BPs. Data are shown as the mean for 6 tablets measured at each measurement point using a disintegration tester. Brand name, ●; generic A, ○; generic B, ■; generic C, □; generic D, ▲; generic E, ∆; generic F, ×.

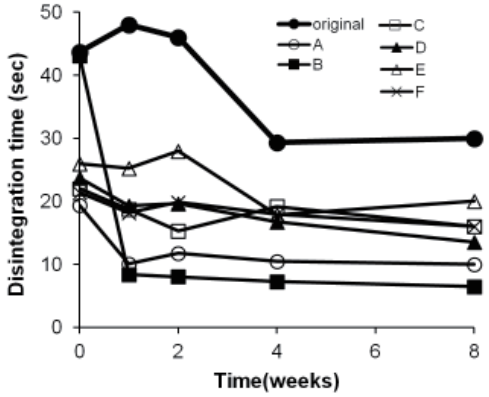

Figure 8. Disintegration time of famotidine orally disintegrating tablets 8 weeks after storage in unit-dose package. Data are shown as the mean for 6 tablets measured at each measurement point using a disintegration tester. Brand name, ●; generic A, ○; generic B, ■; generic C, □; generic D, ▲; generic E, ∆; generic F, ×.

brand name tablets and generic E had a 5.4 and 7.8% decrease in hardness, respectively, but generic B had a 55.1% decrease. The "stability date for uncovered tablets and capsules" proposed by the Japanese Society of Hospital Pharmacists (standard criteria in August 20, 1999) defines the "presence of a change (nonstandard)" in hardness as a change of 30% or more in hardness or a hardness value < 2.0 kg. The results of this study show that generic B was nonstandard when unit-dose packaging was done under the conditions noted earlier. Unless pharmacists give patients instructions regarding the most appropriate method of drug storage to prevent moisture absorption by tablets stored in unit-dose packages (*9*), the hardness of generic B may decrease and the potential for its disintegration may increase, resulting in a decrease in patient compliance. The decrease in the hardness of generic B may have been due to increased moisture absorption after BPs were opened. Although bulk tablet packages of generic B are not commercially available, caution is necessary since unit-dose packages are often prepared in clinical practice. The environmental conditions for storage in this study were a temperature of 27°C and a humidity of 55% given the general conditions at patients' homes. However, tablet hardness may further decrease with seasonal changes in the storage environment or changes in the storage location in the home. Therefore, patients need to be given instructions regarding methods of drug storage.

In the dissolution test, the dissolution of brand name and generic tablets differed during the first 10 min. When tablets were stored in unit-dose packages, the dissolution rates of generics B and C tended to increase compared to other preparations after 2-8 weeks, but the dissolution rate of generic E tended to decrease. However, all tablets had dissolution of 85% or more within 15 min, so there may be no dissolution problems even after unit-dose packaging according to the criteria of the Guidelines for Bioequivalence Studies of Generics (*10*).

In recent years, the dissolution test has been performed prior to the disintegration test (*11*). In the current study, disintegration tests were performed to ensure drug quality. In Japan, there are no established public criteria for the disintegration time of oral fast-disintegrating tablets. In the U.S., the U.S. Pharmacopoeia (USP) recommends 30 sec or less as the disintegration time in the disintegration test (*12*). In the current study, some took slightly more than 30 sec to disintegrate. However, the disintegration time of generic B stored in unit-dose packages decreased to about 1/5 after 1 week, affecting storage.

Based on these results, unit-dose packaging of brand name or generic (A-F) orally disintegrating tablets of famotidine causes no bioequivalence problems in terms of dissolution. The hardness of one of the generics became nonstandard and its disintegration time decreased to about 1/5, which may cause "susceptibility to disintegration" in a clinical setting. Since factors for the evaluation of the bioequivalence of brand name preparations do not include hardness or the disintegration time, generics that are susceptible to disintegration over time are on the market. When generics are used, pharmacists should be fully aware of their characteristics.

Preparations used in the current study were chosen assuming that additives, and particularly binding agents, affect hardness and are associated with disintegration. However, brand name and generic B tablets had few similarities. The generic was softer and its disintegration time decreased to about 1/5 when stored in unit-dose packages. Brand name tablets contained ethylcellulose and D-mannitol as binders while generic B contained three different binders: crystalline cellulose, hydroxypropyl starch, and povidone. Generic E (which had only a slight decrease in hardness when stored in unit-dose packages) did not contain ethylcellulose. No association between binders

and hardness was noted because binder intensity will vary from preparation to preparation depending on the amount, type, and number of binders. However, package inserts and drug interview forms (IFs) provide no information on the additives contained. As shown in Table 1, brand name and generic tablets differed substantially in terms of the additives they contained, so their formulations may differ. When selecting generics in a clinical setting, a drug's susceptibility to disintegration may thus be difficult to assess based only on a description of its additives.

In this study, the hardness of every preparation decreased 1 week after unit-dose packaging when tablets were stored at a temperature and humidity simulating those at a patient's home. Therefore, other types of tablets should be selected for patients who do not need orally disintegrating tablets. Changes in the hardness of all of the tablets in this study were within 20% when they were stored in unopened BPs, presenting no problems. The description of hardness should be confirmed in the IF when these preparations are used after unit-dose packaging, and tablets should not have decreased hardness to $\leq$ 2.0 kg or $\geq$ 30% change in hardness compared to when the BP is opened. Table 1 suggests that a lack of commercially available bulk tablet packages may result in use of preparations with softer tablets. This aspect can be considered when selecting generics in a clinical setting.

The discussion in this study is based on the latest IFs from September 2011. This study was planned in August 2008, but additives in generics A and F changed. Bulk tablets of generic F also became available commercially. Pharmacists must obtain the latest drug information and utilize that information when selecting generics.

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