Disintegration Test to Measure Lot-to-Lot Variations of Vaginal Tablets

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Attempts were made to investigate the disintegration test for vaginal tablets. Disintegration tests were done for four different commercial vaginal tablets (three lots each) by the watch glass method and Japanese Pharmacopoeia (JP) disintegration method, and the resulting profiles were compared to those by the modified British Pharmacopoeia (BP) method on a point of lot-to-lot variation of the disintegration times. The disintegration time of every tablet by the modified BP method was longest, followed by the watch glass method, and finally by the JP disintegration method. The results for lot-to-lot differences in disintegration times by the modified BP method were similar to those by the watch glass method. However, such lot-to-lot differences as found by the modified BP method and watch glass method were not always observed by the JP disintegration method. It was concluded from these results that the modified BP method was most suitable for investigating lot-to-lot differences in the disintegration of vaginal tablets.

Keywords vaginal tablet; disintegration test; modified BP method; quality control; watch glass method; JP disintegration method

Although disintegration tests might originally be thought of as a general method to calculate an index for the bioavailability of drugs, the test is now also recognized as a control procedure to help produce uniform tablets.[1,2] The disintegration test for peroral tablets is always described in various Pharmacopoeias, but a test for vaginal tablets is not prescribed in either the Japanese Pharmacopoeia (JP) or the United States Pharmacopoeia. By contrast, the British Pharmacopoeia (BP) does state a disintegration test for vaginal tablets.[3] However, it is difficult to measure accurate individual disintegration times of tablets by the BP method.[4] Manufacturers in Japan have routinely applied the JP disintegration method and/or watch glass method[5] to vaginal tablets. Uniform disintegration is needed to ensure high quality control. We previously reported a modified BP disintegration method for vaginal tablets,[4] which gave accurate time and the process of disintegration of the tablets, and was applicable both to effervescent and non-effervescent vaginal tablets using the official limit prescribed in the BP.

In the present study, disintegration tests were done for four different commercial vaginal tablets (three lots each) by both the watch glass method and the JP disintegration method (JP method). The disintegration profiles resulting from these tests were compared to those produced by the modified BP method regarding lot-to-lot variation in disintegration times.

Experimental

Materials Samples from three lots of four commercial vaginal tablets made by different manufacturers were used (Table I). Since variations in diameter, length and thickness among all the tablets were very small, only the mean value is represented in Table I. The A, B and C tablets were effervescent, and the D tablet was non-effervescent. The manufacturer of the A tablet routinely used the watch glass method for the disintegration test. The manufacturers of the B and D tablets used the JP method. And the manufacturer of the C tablet used both the watch glass method and the JP method.[6] All tablets used in this experiment were adapted to their manufacturers' disintegration tests. All samples were packaged and stored in a dry place at room temperature, and the experiments were done immediately after opening the packages.

Modified BP Method The disintegration apparatus for vaginal tablets and the testing procedures were similar to those previously described[4]; the BP disintegration apparatus (Erweka, West Germany) was placed in a vessel containing distilled water at 37±0.5 °C. The water level was adjusted by the gradual addition of warm water until the perforations in the metal disc were just covered by a uniform layer of water. A tablet was placed on the center of the perforated plate and a guided plate (6 g) was placed on the tablet. The guided plate moved downward smoothly in a cylinder as the tablet disintegrated. The movement was recorded by a kymograph. When the tablet was completely disintegrated, the guided plate touched the surface of the perforated plate. At this point, the recording showed a horizontal line. The guided plate and kymograph (recording) are the differentiating factors in the BP method. The official limit for disintegration for the BP method was used in this experiment.

TABLE I. Vaginal Tablets Used in This Experiment

Tab.	Lot No.	Weight[a] (mg)	Diameter or length[b] (mm)	Thickness[b] (mm)
A1	B134	1696.8±15.8	24.7	6.4
A2	B164	1714.6±28.8	24.6	6.4
A3	B188	1698.0±15.6	24.6	6.5
B1	022Z	892.6± 7.8	15.1	4.4
B2	A26P	894.4±10.6	15.1	4.3
B3	E31L	891.9± 7.9	15.0	4.3
C1	EK03	942.4±13.4	15.0	4.0
C2	KP02	949.6± 7.9	15.0	4.0
C3	RAO3A	954.2±11.5	15.0	4.0
D1	5FWO1	1022.8± 5.7	15.1	4.9
D2	6FWO2	1042.4± 7.1	15.1	5.0
D3	706-93201	1030.5± 5.7	15.1	4.9

a) Mean±S.D., $N=10$. *b*) Mean value, $N=10$.

Watch Glass Method According to the disintegration test for contraceptive phenylmercuric acetate tablets,[5] a tablet was placed on the center of a watch glass 11 cm in diameter, which floated on a water bath at 37±0.5 °C. Warm distilled water (4 ml per 1 g tablet weight) was poured on the tablet. The tablet was touched with the tip of a finger every 30 s. The complete disintegration of the tablet was defined as the point when tablet-residue consisted only of a soft or frothy mass with no solid core offering resistance to fingertip pressure.

JP Method According to the JP XI disintegration test, a tablet disintegration tester (Kayagaki, Japan) was used. For effervescent tablets (A, B and C tablets), a plastic disc was used to prevent the tablet from floating on the water, and for the non-effervescent one (D tablet), the test was done without the disc.

Results and Discussion

The disintegration times of A, B, C and D tablets, which were measured by the modified BP method, watch glass

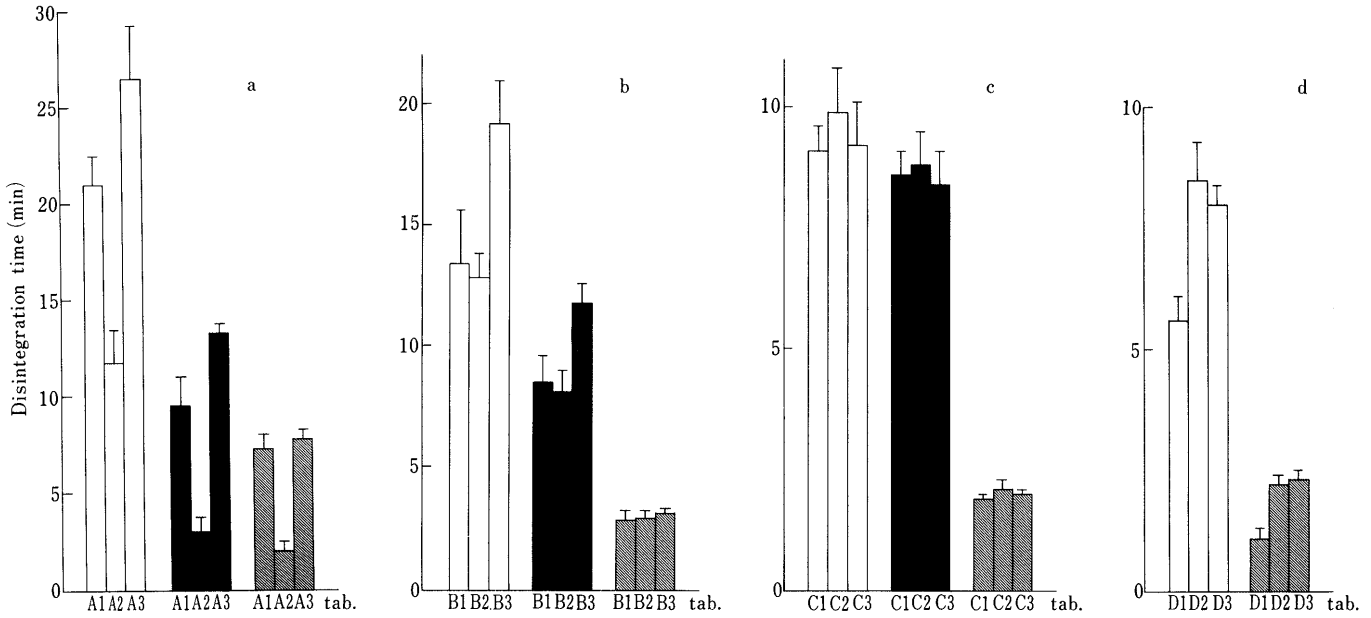

Fig. 1. Disintegration Times of Four Vaginal Tablets (Three Lots Each) Measured by Various Methods

Figs. 1a, b, c and d show the results for tabs. A, B, C and D, respectively. □, modified BP method; ■, watch glass method; ▨, JP method (tabs. A, B and C were tested with a disc and tab. D without a disc.). Each value represents the mean ± S.D. of 6 experiments.

TABLE II. Comparison of Disintegration Methods for Vaginal Tablets[a]

	A1 *vs.* A2	A2 *vs.* A3	A1 *vs.* A3	B1 *vs.* B2	B2 *vs.* B3	B1 *vs.* B3
Modified BP method	$p<0.01$	$p<0.01$	$p<0.01$	ND	$p<0.01$	$p<0.01$
Watch glass method	$p<0.01$	$p<0.01$	$p<0.01$	ND	$p<0.01$	$p<0.01$
JP method	$p<0.01$	$p<0.01$	ND	ND	ND	ND

	C1 *vs.* C2	C2 *vs.* C3	C1 *vs.* C3	D1 *vs.* D2	D2 *vs.* D3	D1 *vs.* D3
Modified BP method	ND	ND	ND	$p<0.01$	ND	$p<0.01$
Watch glass method	ND	ND	ND			
JP method	ND	ND	ND	$p<0.01$	ND	$p<0.01$

a) Statistically analyzed results as shown in Fig. 1 by the Student's *t*-test. ND = not determined.

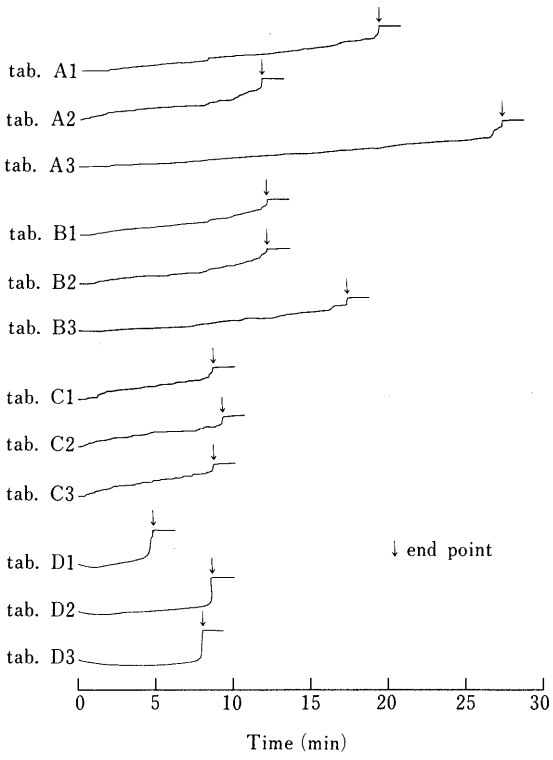

Fig. 2. Disintegration–Time Profiles of Vaginal Tablets Recorded by the Modified BP Method

Arrows show the end-point of disintegration.

method and JP method, are represented in Figs. 1a, b, c and d, respectively. In general, the disintegration time of each type of tablet by the modified BP method was longest, followed by the watch glass method, and finally the JP method. Lot-to-lot (inter-lot) differences in the disintegration times of the tablets are summarized in Table II. Their intra-lot variations (S.D./mean value; %) are about 5—20%, and the values are nearly similar, regardless of the method.

Disintegration times of the three lots of A tablets were significantly different between tabs. A1 and A2, and between tabs. A2 and A3 for every disintegration method. However, significant differences which were similar between A1 and A3, as found by the modified BP method and the watch glass method, were not observed in the JP method. In the case of the B tablets, significant differences between B1 and B3, and B2 and B3 were found by the modified BP method and watch glass method. However, differences were not observed by the JP method. In the case of the C tablets, no significant differences in disintegration times were found among the methods. In the case of the D tablets, disintegration times were significantly different between D1 and D2, and D1 and D3 by the modified BP method and

the JP method.

Figure 2 shows the disintegration time profile for each tablet recorded by the modified BP method.

These results by the modified BP method for lot-to-lot differences in disintegration times agreed with the results of the watch glass method. However, especially for effervescent tablets such as A and B, the lot-to-lot differences found through the modified BP method and the watch glass method were not always observed using the JP method. The reason for a lack of significant difference for the JP method might be that the method uses a strong disintegration medium with relatively high agitation. The strong medium and high agitation could cause such rapid disintegration that the method is unable to provide intricate disintegration profiles. The JP method is surely useful for quality control of peroral tablets, but it may not be suitable to test the disintegration time of vaginal tablets. Another problem is that the watch glass method can be used only for effervescent vaginal tablets, and it is possible for different workers to disagree upon the point at which complete disintegration is reached using this method.

By contrast, the modified BP method gives a clear end-point for disintegration and it can be applied both to effervescent and non-effervescent vaginal tablets using the official limit prescribed in the BP. Furthermore, the modified BP disintegration method is currently the only one to record both the total disintegration time and the course of disintegration. Therefore, the modified BP method may be the most useful for the quality control of vaginal tablets. It could be applied as a quality control system in pharmaceutical companies as well as in hospitals.

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