dx.doi.org/10.14227/DT160409P29

Effect of Paddle-Shaft Position on the Dissolution Rate of Sodium Diclofenac Tablets and the Equivalence Assessment of a Generic Product

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ABSTRACT

Dissolution testing is useful for controlling the quality of oral products and rejecting bioinequivalent products. However, several sources of variability in dissolution tests can affect evaluations of quality. The purpose of this study was to investigate the effects of paddle-shaft position on the dissolution rates of a brand-name (BR) and four generic-equivalent (GE), rapid-release tablets of sodium diclofenac. The paddle was shifted 5 mm from the center of the vessel, and the dissolution profiles were compared with that obtained at the central position. Although the GEs had a wide range of variability and significantly different dissolution profiles, they were estimated to be equivalent to the BR when the paddle was set at the center of the vessel. The 5-mm-shifted position significantly increased the dissolution rates of all products with the result that some GEs did not meet the criteria for equivalence.

In conclusion, paddle position is potentially a cause of error in GE equivalence assessments. The paddle should be accurately positioned at the center of the vessel in dissolution tests for the equivalence assessment of GEs.

INTRODUCTION

The use of generic-equivalent (GE) drugs reduces medical and health-care costs. However, the market share of GEs in Japan is less than in other developed countries (*1*). While 96% of consumers supported GE usage in a questionnaire provided by the Japan Fair Trade Commission in September 2006 (*2*), 54% of physicians questioned their quality (*3*). Therefore, quality assurance is extremely important to eliminate anxiety about the usage of GEs in Japan.

GEs must be as safe and effective as brand-name medicines (BRs) and bioequivalent to BRs in human in vivo pharmacokinetic studies. Dissolution testing is a useful tool for the quality control of oral products, and it provides important information concerning bioequivalence. However, there are several sources of variability in dissolution testing such as temperature, pH (*4*, *5*), and aeration (*6*) of the test medium; rotation and agitation of the paddle shaft (*4*, *7*, *8*); sample position (*4*, *9*); sample storage conditions (*6*); and analytical methods (*10*), which potentially affect decision errors of quality evaluation. Qualification of the test apparatus and procedures is required. Therefore, it is necessary to develop a reliable and precise dissolution test method that is sensitive enough to detect slight differences between GE and BR. In this study, we investigated whether moving the paddle-shaft axis from the center affects the rate of dissolution. Precision glass vessels were used to exclude the effect of the vessel factor on tablet dissolution profiles. Sodium diclofenac in rapid-release tablets was chosen as the model drug and dosage form, because it is highly soluble in water, and its pharmacological effect appears so rapidly that the dissolution rate of the tablet may affect the therapeutic effect of the drug.

MATERIALS AND METHODS

Materials

Bulk powder sodium diclofenac was purchased as a standard material from Sigma Chemical Co. The drugs tested in this study were Voltaren as a reference and four GEs. All products were rapid-release dosage forms that

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Table 1. Tablets Used in the Study

Code	Brand Name	Package	Lot No.	Exp.	Company
BR	Voltaren Tab.	PTP	P0005	Nov 2008	CIBA-GEIGY(Japan)/ Novartis Pharma
GE1	Saffrac Tablets	PTP	112503	Nov 2007	NIPPON SHINYAKU
GE2	Sofarin	PTP	1703	Jan 2009	NIPPON CHEMIPHAR
GE3	DAISPAS Tab.	PTP	SP06311	Aug 2008	Fuso Pharmaceutical Industries/Daito Pharmaceutical
GE4	BOLABOMIN	PTP	3052	Jan 2008	MERCK HOEI/ Tsuruhara Pharmaceutical

contained 25 mg of sodium diclofenac. Information on these tablets is summarized in Table 1. These drugs are all currently on the market in Japan. All were stored at room temperature before use, and the testing was performed before product expiration.

Dissolution Tests

Dissolution tests were carried out by the paddle methods listed in the *JP 15* (*11*) and the *Japanese Orange Book* (*12*). A dissolution apparatus (NTR-VS6P, Toyama Sangyo Co. Ltd., Osaka, Japan) fitted with an autosampler (TCP-61C) was used. Performance qualification (PQ) was accomplished by the USP Performance Verification Test (PVT) with USP prednisone calibrator tablets. Pure water obtained from a reverse-osmosis membrane water system was kept at 45 °C to deaerate for 2 h before use. The position of a tablet dropped at the bottom of the vessel was determined visually. Each test was conducted with a set of six tablets at 50 rpm using 900 mL of deaerated water at 37 ± 0.5 °C.

Precision glass vessels, which have uniform bottom curvature and inner surface regularity (Takao Manufacturing Co., Ltd., Kyoto, Japan), were used to minimize the vessel figure factor (*13*, *14*). The vessels have an inner diameter of 100.06 ± 0.08 mm in the cylinder and a radius of 50.03 ± 0.08 mm in the hemispheric portion. They provide test results that are reproducible and less variable. The dissolution apparatus was adjusted to a horizontal position using a level gauge. The paddle shafts were set at the center of the vessels (center position) and the position was confirmed using a center gauge (Toyama Sangyo Co., Ltd., Osaka, Japan).

To investigate the influence of their positions, the paddles were moved 5 mm from the center along the vessel bottom (5-mm-off position). We had already carried out a pilot study that showed a significant difference in the dissolution rate of the calibrator tablet between the center and 3-mm-shifted paddle conditions. To detect the clear effect of the shifted paddle position, we moved the paddle 5 mm (Figure 1).

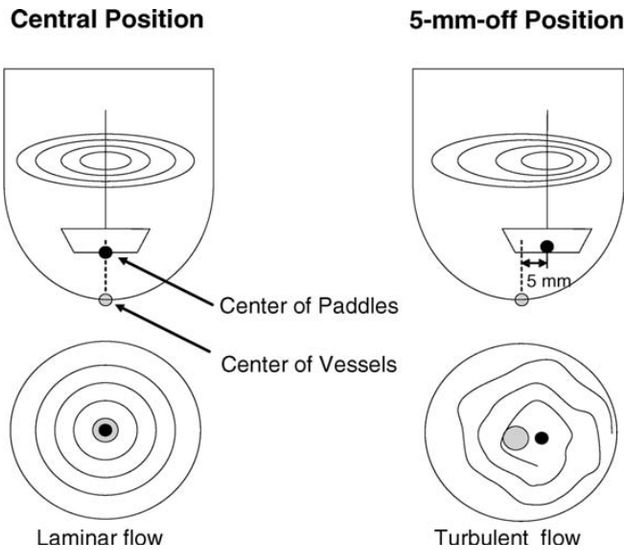


Figure 1. Schematic diagram of deviation in the paddle-shaft position and medium flow in the vessels.

Sampling and Measurement of the Sodium Diclofenac Solution

Samples were collected at 3, 6, 9, 12, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, and 80 min and filtered using polyester fiber, 20–30 µm (F72, Toyama Sangyo Co., Ltd., Osaka, Japan). The initial volume was maintained by the addition of water. Sodium diclofenac concentrations were determined using a UV spectrophotometer (UV-2550, Shimadzu Co. Ltd., Kyoto, Japan) at 276 nm. Absorbance values were converted to percent dissolved values using a standard curve.

Acceptance Criterion for Dissolution Tests

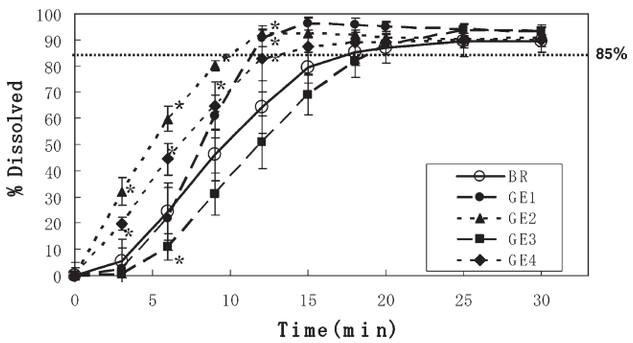
The acceptable mean percent dissolved at 20 min is 85% or more in the *Japanese Orange Book* (*12*).

Acceptance Criteria for Equivalence of Dissolution Profiles

To evaluate differences in dissolution patterns between BR and GEs, f_2 values were calculated. This factor is a logarithmic transformation of the sum of the squared error

$$f_2 = 50 \cdot \log\left\{\left[1+1/n\sum_{i=1}^{n}\left(T_i - R_i\right)^2\right]^{-0.5} \times 100\right\}$$

where T_i is the test data (mean percent dissolved value of the GE) at time point i, R_i is the reference data (mean percent dissolved of BR) at time point i, and n is the



* Significantly different from that of BR ($P < 0.05$).

Figure 2. Dissolution profiles of diclofenac at the central position. The dotted line represents the acceptance criterion (85% in 20 min) for diclofenac tablets specified by JP 15. The results are expressed as the mean ± SD (n = 6).

number of time points (n = 3 at 15, 30, and 40 min). The factor is 100 when the reference and test profiles are identical and approaches zero as the dissimilarity increases. In the guideline for bioequivalence studies of generic products (*15*), products are judged to be equivalent in dissolution rate when the average dissolution from the reference product reaches 85% between 15 and 30 min; the average dissolved amount from the test product does not deviate by more than 15% from that of the reference product at two time points when the average amounts dissolved from the reference product are around 60 and 85%. When f_2 is used, the value should not be less than 42. This guideline is similar to "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (*16*).

Statistical Analysis

To compare the BR and GE dissolution data, a one-way analysis of variance (ANOVA) was carried out followed by the Tukey-Kramer multiple-range test or Scheffe's F-test (*17*). To determine whether there were any differences between the central and 5-mm-off positions, Student's t-test was used. When the data did not show a normal distribution, the homogeneity of variances, Welch's t-test, was performed. The differences were considered significant at $P < 0.05$.

RESULTS

Dissolution Characteristics at the Central Position

Dissolution profiles of BR and GEs obtained when the paddle was positioned at the center of the vessel are shown in Figure 2. The profiles show wide variability and significant differences among the products, especially during the early phase of dissolution (0–15 min). GE2 and GE4 started dissolving quickly with 20–30% dissolved at 3 min, whereas BR, GE1, and GE3 showed a delay in dissolution.

Table 2. Percent Dissolved, Judgment, and f_2 Factor for Sodium Diclofenac Products

	% Dissolved at 20 min[a]	% Dissolved at 12 min[b]	% Dissolved at 18 min[b]	f_2 factor[c]	Judgment
	(mean ± SD)				
BR	87.1 ± 4.3	64.3 ± 10.0	85.4 ± 5.9	62.9 ± 4.5	Pass
GE1	94.9 ± 2.3	90.9 ± 8.2	95.8 ± 2.6	50.0 ± 4.8	Pass
GE2	90.9 ± 1.1	92.4 ± 1.9	91.9 ± 1.2	55.2 ± 2.2	Pass
GE3	88.4 ± 4.1	51.0 ± 10.1	82.1 ± 6.6	60.5 ± 15.2	Pass
GE4	89.0 ± 8.1	82.6 ± 12.6	89.2 ± 9.0	58.1 ± 10.3	Pass

Acceptance criteria:
[a] 85% dissolution within 20 min.
[b] Mean % dissolved of GEs does not deviate by more than 15 percentage points from that of BR at time points when the mean % dissolved of BR is around 60% and 85% (12 min and 18 min).
[c] f_2 value of 42.

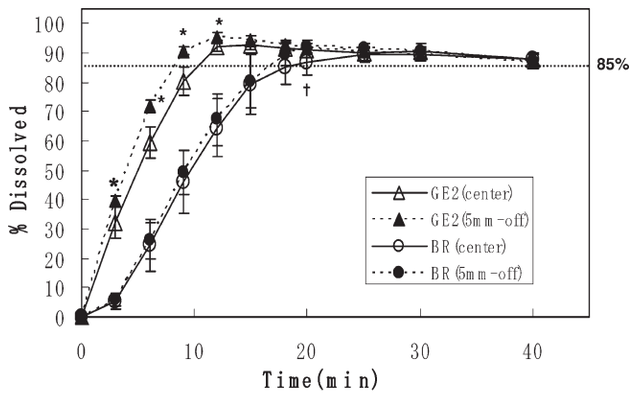
At 3 and 6 min, the order based on mean values was GE2 > GE4 > BR > GE1 > GE3. After 6 min, the dissolution of GE1 accelerated, and the order at 15 and 18 min was GE1 > GE2 > GE4 > BR > GE3. At 20 min, each product was over 85% dissolved, as shown in Table 2. Therefore, all products met the acceptance criterion (85% dissolution within 20 min). The f_2 values calculated using the 15-, 30-, and 40-min time points in the dissolution tests carried out at the central position are listed in Table 2. The f_2 values of all products were greater than 42, and all products were judged equivalent to BR.

The mean percent dissolution of BR (central position) was 64.3 ± 10.0% at 12 min and 85.4 ± 5.9% at 18 min (Table 2). At 12 min, GE1, GE2, GE3, and GE4 were 90.9 ± 8.2%, 92.4 ± 1.9%, 51.0 ± 10.1%, and 82.6 ± 12.6% dissolved, respectively (Table 2). GE3 was 51.0 ± 10.1% dissolved, a value that does not deviate by more than 15% (49.3–79.3%) from that of BR (64.3%), meeting the equivalence criterion. However, the mean dissolution rates of GE1, GE2, and GE4 at 12 min deviated from that of BR by more than 15%.

At 18 min, GE1, GE2, GE3, and GE4 were 95.8 ± 2.6%, 91.9 ± 1.2%, 82.1 ± 6.6%, and 89.2 ± 9.0% dissolved, respectively. The mean rates of dissolution for GE1, GE2, GE3, and GE4 did not deviate by more than 15% (70.4–100.4%) from that of BR (85.4%), meeting the equivalence criterion. Therefore, GE3 met both of the criteria.

Effect of 5-mm Shaft Offset on the Dissolution Profile

Figure 3 illustrates the dissolution profiles for BR and GE2. The 5-mm-offset condition increased the rate of dissolution. Table 3 gives the percent dissolution up to 20 min at the central and 5-mm-off positions. The same phenomenon was observed for all products until 12 min, with GE2 and GE4 showing significant increases in the 5-mm-off condition.



* Significantly different from that of the central position for GE2 ($P < 0.05$).
† Significantly different from that of the central position for BR ($P < 0.05$).

Figure 3. Dissolution profiles of diclofenac at the central and 5-mm-off positions for BR and GE2. The dotted line represents the acceptance criterion (85% in 20 min) for diclofenac tablets specified by JP 15. Results are expressed as the mean ± SD (n = 6).

However, even in the 5-mm-off condition, all products passed the criterion of 85% dissolution at 20 min, and the f_2 values of GEs were also equal to or greater than 42 (data not shown). The mean percent dissolution of BR at 12 min was 67.4 ± 8.9%, higher than that at the center (Table 3). The value for GE3 at 12 min was 51.0% at the central position, which deviated by more than 15% from that of BR in the 5-mm-offset condition (52.4–82.4%) (Table 4). When the results obtained at the central position were used, GE3 was judged to be equivalent to BR. But based on the results obtained at the 5-mm-off position, GE was judged to be not equivalent to BR. Therefore, the paddle position affected the quality evaluation.

Effect of 5-mm Offset on the Difference in Percent Dissolved

Tables 3 and 5 show the effects of paddle position on the difference in percent dissolution between BR and GE products. The mean values for BR were compared with those for GEs at the center and 5-mm-off positions, with (+) denoting a significant difference and (-) denoting no significant difference. The effect of offsetting the shaft could be detected when the result at the center changed.

The difference in dissolution between GE and BR under accurate conditions was checked. For GE1, there was a significant difference at 12 min. For GE2 and GE4, there were significant differences at 3, 6, 9, and 12 min. For GE3, there was a significant difference at 6 min, as shown in Tables 3 and 5.

The dissolution of BR at the central position was significantly different from that of GE1 at 9, 18, and 20 min and GE3 at 6 min at the 5-mm-off position, as shown in Table 3.

Compared with the result for BR at the 5-mm-off position, the results for GE3 at 9 min and for GE4 at 9 and 12 min at the central position were changed (Table 5). At the 5-mm-off position, the results for GE1 at 9 min and

Table 3. Comparison of Percent Dissolved of Generic Products with Those of Brand Product

	BR		GE1		GE2		GE3		GE4	
	center	5 mm	center	5 mm	center	5 mm	center	5 mm	center	5 mm
3 min										
%	5.3	5.8	2.6	5.9	32.1*†	39.4*†	0.3	0.7†	19.7*†	21.2*†
SD	2.8	2.1	1.6	2.8	5.2	1.7	1.0	1.1	2.6	4.3
6 min										
%	24.4	26.1	21.7	34.1	59.7*†	71.9*†	11.0*†	16.5	44.5*†	48.6*†
SD	8.7	6.1	7.7	9.9	5.4	2.0	4.9	8.5	6.1	4.2
9 min										
%	46.0	49.3	60.8	74.3*†	80.2*†	90.7*†	31.2†	37.6	64.6*	70.7*†
SD	10.8	7.6	12.0	8.7	4.9	1.4	8.0	8.1	9.3	4.2
12 min										
%	64.3	67.4	90.9*†	94.8*†	92.4*†	95.2*†	51.0	56.4	82.6*	87.9*†
SD	10.0	8.9	8.2	5.0	1.9	1.5	10.1	8.0	12.6	4.4
18 min										
%	85.4	89.6	95.8	96.8*	91.9	92.8	82.1	81.7	89.2	93.9
SD	5.9	4.1	2.6	0.9	1.2	1.7	6.6	7.6	9.0	2.7
20 min										
%	87.1	92.0	94.9	95.6*	90.9	91.7	88.4	86.3	89.0	93.1
SD	4.3	2.3	2.3	0.8	1.1	1.7	4.1	6.8	8.1	2.5

* Significantly different from mean dissolved rate (%) of BR (central position).
† Significantly different from mean dissolved rate (%) of BR (5mm-off position).

Table 4. Effect of Paddle Position on Acceptance Criteria for Equivalence of Dissolution Profiles

		BR	
		Center	5 mm off
	Center	64.3% (49.3–79.3%)	67.4% (52.4–82.4%)
GE1	90.9%	NE	NE
GE2	92.4%	NE	NE
GE3	51.0%	E	NE
GE4	82.6%	NE	NE

E: equivalent to BR
NE: not equivalent to BR

Table 5. Effect of Paddle Position on Dissolution Rates for BR and GE Products

	3 min	6 min	9 min	12 min	18 min	20 min
BR (Center) vs GE (Center)						
GE1	–	–	–	+	–	–
GE2	+	+	+	+	–	–
GE3	–	+	–	–	–	–
GE4	+	+	+	+	–	–
BR (Center) vs GE (5 mm off)						
GE1	–	–	– → +	+	– → +	– → +
GE2	+	+	+	+	–	–
GE3	–	+ → –	–	–	–	–
GE4	+	+	+	+	–	–
BR (5 mm off) vs GE (Center)						
GE1	–	–	–	+	–	–
GE2	+	+	+	+	–	–
GE3	–	+	– → +	–	–	–
GE4	+	+	+ → –	+ → –	–	–
BR (5 mm off) vs GE (5 mm off)						
GE1	–	–	– → +	+	–	–
GE2	+	+	+	+	–	–
GE3	– → +	+ → –	–	–	–	–
GE4	+	+	+	+	–	–

+ Significantly different from mean dissolved rate (%) of BR.
– Not significantly different from mean dissolved rate (%) of BR.

for GE3 at 3 and 6 min were changed. The shift in position affected the statistical significance between GE and BR. The experiments suggest that the position of the paddle affects the evaluation of quality and bioequivalence.

DISCUSSION

Recent dissolution variance studies conducted by the United States Pharmacopeia (USP) suggested glass vessels and apparatus to be a major cause of variability in results. An irregular inner shape altered the flow dynamics and could disturb the conical shape formed by tablet particles, resulting in extensive variation in data. Tanaka et al. (*13*) reported that precision glass vessels (*14*), which have no apparent deviation of actual interior vessel shape, gave reproducible and less variable results, regardless of the vessel and position.

The purpose of the present study was to clarify the effects of paddle position on dissolution test results and to develop an accurate method of testing based on reported studies. Therefore, precision glass vessels were used to reduce variability. The effect of paddle position on dissolution testing of GEs was investigated by comparing results between the center and an eccentric position. The dissolution rates for the central and 5-mm-off positions were significantly different, with the latter being significantly higher than the former (Table 3). The results are consistent with previous reports (*9*, *18–20*), since the rate of dissolution increased significantly when the shaft was offset 2–10 mm from the central axis of the vessel. The increase in dissolution rate could be explained by the difference in agitation force at the position used. The fluid flow at the center of the vessel is laminar with the slowest and weakest flow. As the position moves away from the center, the fluid resistance may increase and make a turbulent fluid flow, which can also cause the dissolution rate to increase (*8*, *19*).

Early on, Cox and co-workers at FDA (*18*) emphasized the necessity of a laminar, nonturbulent fluid flow in the dissolution vessel. Kaneniwa et al. (*21*) reported differences in the dissolution process between laminar and turbulent fluid flows. The study suggested that the active energy of dissolution is greater for turbulent than for laminar fluid flow. This could be one of the reasons for the intrabatch variation in the dissolution rates of solid oral dosage forms. The 5-mm-off position leads to significant differences in the dissolution rates of GE and BR and affects the quality evaluation of GEs (Table 4). This study suggests that the paddle shaft should be adjusted accurately to the center of precision glass vessels in dissolution tests. The *JP* requirement that the rotating shaft and axis of the dissolution vessel coincide within ±2 mm defines centering.

CONCLUSIONS

The 5-mm-off position significantly increased the dissolution rate of all tablets with the result that some GEs did not meet the criteria for equivalence. The paddle position should be accurately adjusted to the center of the vessel in dissolution tests for GEs. Further studies are being conducted to understand the influence of paddle movement on both the hydrodynamics within the vessel

and the amount of drug dissolved during dissolution testing. The results of such studies may lead to more specific tolerance guidelines for variability.

ACKNOWLEDGMENTS

This work was supported by grants from MEXT.HAITEKU (2004–2008). The authors would like to thank Toyama Sangyo Co., Ltd. and Takao Manufacturing Co., Ltd. for experimental materials.

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