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International Journal of Pharmaceutics 250 (2003) 99–109
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Measurement of agitation force in dissolution test and mechanical destructive force in disintegration test

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Received 22 April 2002; received in revised form 16 August 2002; accepted 7 September 2002

Abstract

The purpose of this study was to investigate the effect of the agitation force and mechanical destructive force on the drug dissolution of a tablet in the paddle rotation dissolution test and in the disintegration test. The agitation in the paddle method and the mechanical destructive force in the disintegration test were considered to be conclusive factors for drug dissolution. The dissolution rate of planar-constant-release tablets increased with increasing paddle rotation speed and increased with increasing distance from the center of the vessel bottom. Separately, the fluid resistance (agitation force) in the vessel was measured using a modified paddle method apparatus equipped with a fluid resistance sensor. The fluid resistance was 0.03×10^{-3} N/(64 mm^2) when the paddle rotation speed was 50 rpm at a position 4 mm away from the center. A considerable position-dependent change in agitation force intensity was seen with the fluid resistance sensor. The impulsive force (mechanical destructive force) in the disintegration test apparatus was measured using a modified basket-rack assembly with a strain gauge transducer. The fluid resistance was measured using the basket-rack assembly with a different sensor probe and amplifier. The impulsive force applied by the auxiliary disk was 0.31 N and the fluid resistance at the bottom of the basket-rack assembly was 1.66×10^{-3} N/(64 mm^2).

Keywords: Dissolution test; Disintegration test; Agitation force; Fluid resistance; Destructive force

1. Introduction

Dissolution test is generally conducted as a product quality control but it is expected that it may also be used as a prognostic tool that can evaluate the bioequivalence of solid oral dosage forms (Ogata et al., 1979; Shah et al., 1992; Lozano et al., 1994). The dissolution rate of a dosage form is considered to correlate with the dissolution test conditions. Among the test conditions, hydrodynamic property (agitation force) is

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0378-5173/02/$ - see front matter
PII: S0378-5173(02)00535-5

an important factor in determining the dissolution behavior of the dosage form.

Ogata et al. evaluated the agitation force intensities of eight dissolution test methods using sugar-coated tablets, which had a dissolution lag time (Ogata et al., 1979). They obtained only a rank order relationship among the dissolution test methods. Although the effect of the agitation force on the dissolution rate was previously studied using various types of dissolution test vessels (Underwood and Cadwallader, 1976), a direct measurement of the agitation force intensity has not been conducted yet. Moreover, in the paddle method, the tablets often do not stay right under the paddle axis and so their dissolution behavior changes depending on the tablet position. This dissolution rate variance may be explained by the difference in agitation force intensity.

To make the dissolution test a better prognostic tool to evaluate the in vivo performance of oral dosage forms, we need to understand the relationship between the agitation force on the dosage forms in dissolution testing and their dissolution rates. In the present study, the paddle method was investigated because the method was the most commonly used dissolution test method. The effect of the paddle rotation speed and the tablet position on the dissolution rate was evaluated using a non-disintegrating planar-constant-release (PCR) tablet. Then, the agitation force intensities at the bottom of the vessel were directly measured with a baffle sensor as fluid resistance. The fluid resistance that the dosage forms received in the vessel was numerically evaluated.

Disintegration test is a general in vitro test for the evaluation of oral solid dosage forms. However, it is rarely used as a drug-release evaluation method (Stavchansky et al., 1980; Nishimura et al., 1984; Bhagavan and Wolkoff, 1993), because the disintegration test simply reflects the size reduction rate of solid dosage forms. It does not directly reflect the drug release rate. Nevertheless, the disintegration test is a characteristic test method whereby a mechanical destructive force is exerted on solid dosage forms. It is known that oral solid dosage forms receive mechanical destructive forces in the gastrointestinal (GI) tract of human and animals (Hamaguchi et al., 1995; Katori et al., 1995). These forces were previously evaluated (Kamba et al., 2000). If the destructive force in the disintegration test were close to that in the human GI tract, the test may simulate in vivo drug release. Such a test would be useful to evaluate the controlled-release formulations, and enteric-coated tablets, for instance. Therefore, the destructive force in the disintegration test was measured to compare with the force in the GI tract.

The impulsive force generated by the collision between the disk and the tablet was measured using a modified basket-rack assembly with an L-shaped rod sensor. The fluid resistance was measured using the basket-rack assembly with a baffle-plate sensor. The effects of the two forces on the disintegration profile of enteric-coated tablets were investigated in the present study.

2. Materials and methods

2.1. Materials

Benzoic acid was purchased from Koso Chemical (Japan). Ethyl cellulose, carnauba wax, low-substituted hydroxypropylcellulose, microcrystalline cellulose, magnesium stearate, polyethyleneglycol 6000, Eudragit S100 and talc used were of pharmaceutical excipient grade.

2.2. Manufacturing process of the PCR tablet

The core tablet was composed of 100 mg of benzoic acid. The insoluble outer layer was made from a mixture of 180 mg of ethyl cellulose and 20 mg of carnauba wax (Fig. 1a). An oil press (Riken Seiki, Japan) was used with flat punches and a die (diameter 7 mm) to prepare the core tablet. The compression force was 9.8 kN/punch. The core tablet was press-coated with the outer-layer powder using the oil press. The diameter of the press-coated PCR tablet was 9 mm. The compression

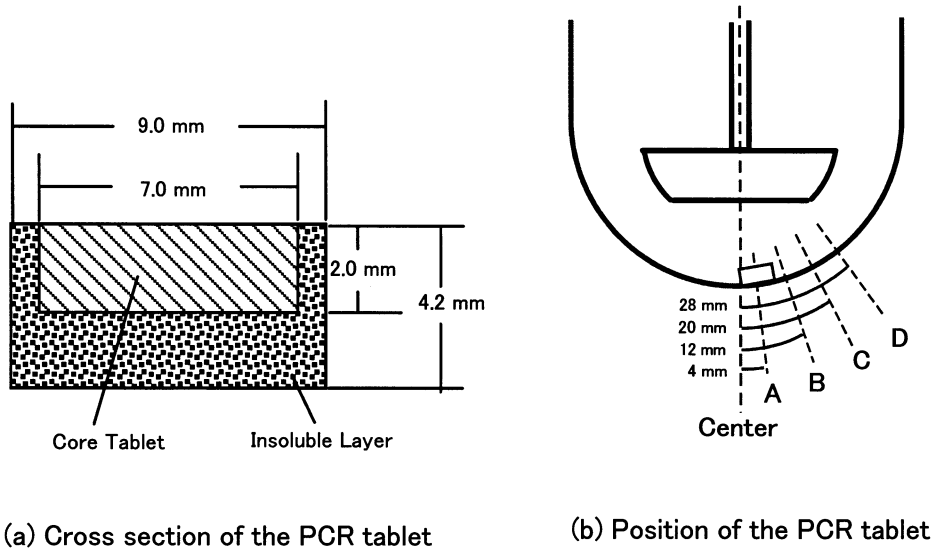

Fig. 1. Cross section and position of the PCR tablet.

force was 9.8 kN/punch. The solubility of benzoic acid is 3.3 mg/ml in water (JP XIII) and is high enough to maintain the test media under sink conditions because the concentration of benzoic acid after whole core tablet dissolution is 0.11 mg/ml.

2.3. Measurement of the dissolution rate (paddle method)

The PCR tablets were used to study the relationship between the tablet position in the vessel and the dissolution rate. The PCR tablets were fixed to the bottom of the dissolution vessel in the center or at one of the positions A, B, C, and D with double-stick tape (Fig. 1b). The positions A, B, C and D were 4, 12, 20 and 28 mm away from the center along the hemispherical vessel bottom. The dissolution rates were measured at each paddle rotation speed of 25, 50, 75, 100, 125 or 150 rpm. The dissolution test medium was water at 37 °C. The dissolution fluids were assayed at 0, 10, 20, 30, 40, 50 and 60 min. Benzoic acid was detected spectrophotometrically (Shimadzu UV-160A) at 227 nm.

2.4. Fluid resistance measurement set up (paddle method)

The dissolution test method 2 (paddle rotation method) was carried out in accordance with Japanese Pharmacopoeia (1996) (JP) XIII except for a change in the set up of the sensor (Fig. 2). A dissolution test bath (NTR-VS3, Toyama Sangyo, Japan) was used to measure the fluid resistance in the dissolution vessel. A square, brass baffle plate (8×8 mm^2, thickness 0.2 mm) was fixed to the end of a stainless steel rod (diameter, 1.2 mm). The

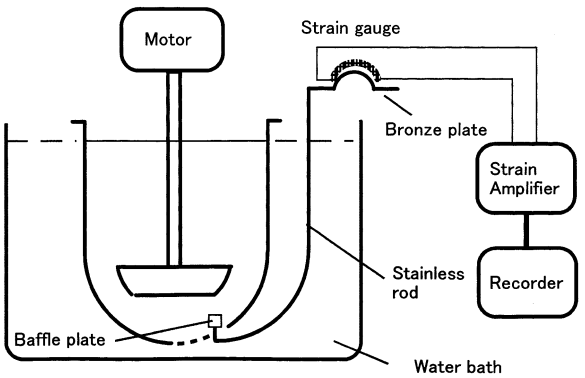

Fig. 2. Scheme of the dissolution test apparatus and fluid resistance measuring device.

other end of the rod was fixed to a convex bronze plate. A strain gauge (KFG-2-120-C1-11 L3M2R, KYOWA, Japan) was fixed to the bronze plate with adhesive (Aron alpha A, Toa Gosei, Japan) and connected to the strain amplifier (6M82, SAN-EI, Japan). The baffle, the rod and the convex bronze plate formed the baffle sensor. A rectangular slit (opening size: 1×4 cm^2) was made at the bottom of the dissolution vessel, and the baffle plate was inserted into the vessel. The baffle plate was set perpendicularly to the paddle rotation direction. The dissolution fluid depth in the vessel with the slit was adjusted by changing the water level of the dissolution bath since the vessel water and the bath water were connected through the slit.

The fluid resistance was measured with a paddle rotation speed of 25, 50, 75, 100, 125 or 150 rpm at the positions A, B, C and D. The positions were the same positions as those at which the dissolution rates of the PCR tablets were measured. The fluid resistance at the center was not measured because our sensor responded to one-way flow perpendicular to baffle plate.

2.5. Manufacturing process of the enteric-coated tablet

Enteric-coated tablets were prepared under the following conditions. Convex, plain tablets having a diameter of 7 mm, were produced by a tableting machine (Correct 24, Kikusui, Japan). The tablets were coated with an enteric film by a coating machine (Dria-coater DRC-200, Powrex, Japan) under standard operating conditions. The tablets were composed of 150 mg of excipients (lactose, low-substituted hydroxypropylcellulose, microcrystalline cellulose and magnesium stearate) and enteric film constituents. The constituents of the enteric film solution were 70 g of Eudragit S100, 35 g of talc, 7 g of polyethyleneglycol 6000, 700 g of ethanol and 188 g of purified water. The amounts of enteric film were 16, 22 or 28 mg per tablet (tablet weight 166, 172 or 178 mg).

2.6. Disintegration tests of the enteric-coated tablet

The impulsive force of tablets colliding against the wire gauze of the basket-rack was measured using the enteric-coated tablet as a model formulation. The disintegration test was carried out in JP first fluid (pH 1.2) using a normal basket-rack. The reference test was carried out by fixing the tablet on the wire gauze at the bottom of the basket-rack assembly using a polyethylene net (mesh opening size, 2 mm) to prevent the collision of the tablet and the wire gauze. This test was carried out without disks. The disintegration time of the enteric-coated tablet was defined as the time until the enteric film coating was ruptured and the contents of the tablet were released.

2.7. Impulsive force measurement set up

The disintegration test was carried out in accordance with JP XIII. The disintegration test was carried out in water at 37 °C using a disintegration test machine (T-4HS, Toyama, Japan). The cyclic movement of the basket-rack and disk was recorded by a video camera (Handycam CCD-TRV91, Sony, Japan). The positions of the bottom of the basket-rack assembly and the bottom of the auxiliary disk were recorded at 30 frames/s.

The disintegration test apparatus was used with some modifications. A strain gauge transducer (LTS-1KA, Kyowa, Japan) was fixed to the central shaft of the basket-rack (Fig. 3a). The tip of the L-shaped rod sensor was set at 2 mm above the bottom of the basket-rack through the wire gauze. The impulsive force, generated by the collision of the disk with the tip of the sensor, was converted to an electrical signal by the strain gauge transducer, and then recorded with a recorder (Analyzing Recorder 3655E, Yokogawa, Japan) through the dynamic strain amplifier (DMP-612B, Kyowa, Japan). Then the effect of the volume of immersion fluid and the frequency of the basket-rack movement on the impulsive force was studied.

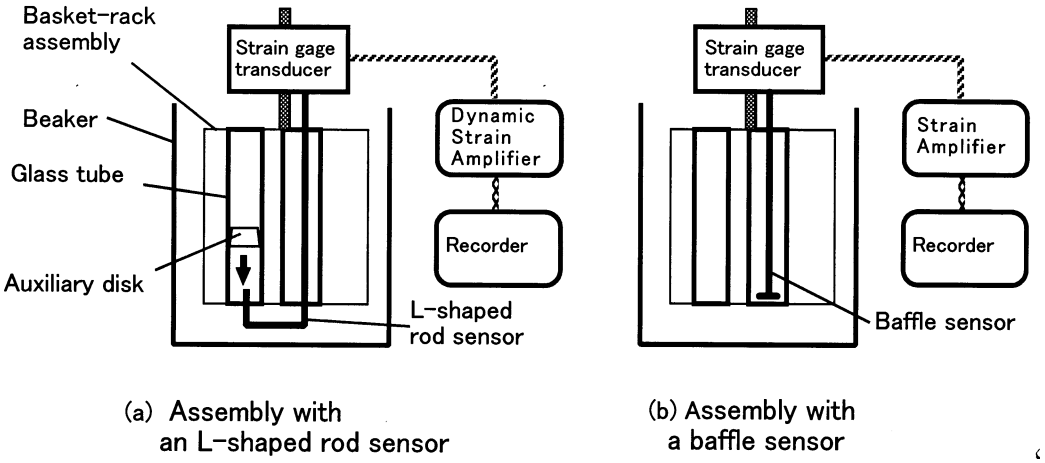

Fig. 3. Basket-rack assembly for the measurement of impulsive force and fluid resistance.

2.8. Fluid resistance measurement set up (disintegration test)

A strain gauge transducer (LTS-1KA, Kyowa, Japan) was fixed to the central shaft of the basket-rack assembly (Fig. 3b). The baffle plate (8×8 mm^2) was perpendicularly soldered onto the lower tip of the rod sensor. Fluid resistance, which was generated by the vertical movement of the baffle plate, was measured. The distance between the baffle plate and the wire gauze of the basket-rack was 2 mm. The fluid resistance was converted to electrical signals by the strain gauge transducer, and then recorded on a recorder (Analyzing Recorder 3655E, Yokogawa, Japan) through a strain amplifier (6M82, San-ei, Japan). The test was also carried out without both the disk and tablet. The fluid resistance was measured by changing the frequency of the basket-rack movement from 15 to 30, 45 and 60 cycles per min (cpm).

2.9. Dissolution rate of the PCR tablet in the disintegration test

The dissolution rate was measured using the PCR tablet (Fig. 1a). The test was carried out by changing the frequency of the up and down basket-rack cycles (15, 30, 45 and 60 cpm). The tablet was fixed on the wall of the glass cylinder so that the uncovered surface of the tablet was exposed to the test medium. The test medium was water at 37 °C. The test fluids were assayed at 0, 10, 20, 30, 40, 50 and 60 min. Benzoic acid was detected spectrophotometrically (Shimadzu UV-160A) at 227 nm.

2.10. Statistical analysis

Unpaired t-test was used to test the significance of difference. P-values less than 0.05 was accepted as statistically significant. All data analyses were done using the analytical function of Microsoft® Excel 2000.

3. Results and discussion

3.1. Measurement of the dissolution rate

The dissolution profiles of the PCR tablets at position D are shown in Fig. 4. The drug release from the PCR tablets followed the zero-order kinetics at each speed of the paddle rotation. Benzoic acid in the core tablet was dissolved only from the uncovered side of the PCR tablet. As the dissolution proceeded, the uncovered surface of the core tablet was gradually dissolved without a

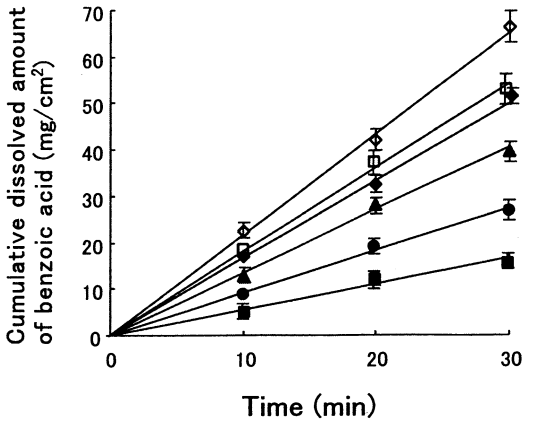

Fig. 4. Dissolution profiles of the PCR tablets in the paddle method at position D. Paddle rotation speed: (■) 25 rpm, (●) 50 rpm, (▲) 75 rpm, (◆) 100 rpm, (□) 125 rpm, (◇) 150 rpm. Error bars represent S.D., $n = 3$. The lines are linear regression lines. Correlation coefficients for the paddle rotation speeds of 25, 50, 75, 100 and 125 rpm were 0.997, 0.997, 0.998, 0.997, 0.998 and 0.998, respectively.

change in the surface area. Table 1 shows the relationship between the position of the PCR tablet and the dissolution rate of benzoic acid. The dissolution rate increased as the paddle rotation speed increased and the dissolution rate also increased as the distance between the vessel center and the tablet position increased.

3.2. Measurement of the fluid resistance in the paddle method

As the rotation speed increased from 25 to 150 rpm, the fluid resistance increased at every position A, B, C and D (Table 2). The fluid resistance also increased as the distance from the center of the vessel increased.

Fluid resistance is generally called the drag in the field of hydrodynamics. The equation expressing the relationship between drag and fluid velocity was first derived by Newton and is described as $\text{Drag} = C_D A \rho U^2/2$, where C_D is the drag coefficient, A is the projected surface area of the object, ρ is the fluid density, and U is the fluid velocity (Yamanaka, 1998; Lovvorn et al., 2001). From this equation, we can see that the fluid resistance (drag) is proportional to the square of the fluid velocity. In a graph plotting, the square of the rotation speed against fluid resistance, straight lines that fit the data of each position were obtained (Fig. 5). Therefore, the fluid velocity around the baffle plate can be considered to be proportional to the paddle rotation speed. The flow velocities around the baffle plate were back calculated by plotting the measured fluid resistance, $C_D = 1.12$ (Yamanaka, 1998), $A = 0.000064$ m^2, $\rho = 993$ kg/m^3 at 37 °C, into the equation (Table 3).

Table 1
Relationship between paddle rotation speed and dissolution rate of benzoic acid from PCR tablets at each tablet position

Paddle rotation speed (rpm)	Dissolution rate (mg/cm^2/h)				
	Tablet position				
	Center 0 mm[a]	A 4 mm[a]	B 12 mm[a]	C 20 mm[a]	D 28 mm[a]
25	22.1 (1.8)	22.6 (2.4)	30.0 (1.7)**	30.8 (1.7)**	33.4 (1.2)**
50	35.8 (2.4)	39.5 (3.1)	52.6 (2.3)***	46.3 (3.5)*	55.3 (2.9)***
75	43.2 (1.6)	51.1 (2.7)*	73.2 (2.8)***	69.7 (1.1)***	81.6 (2.9)***
100	52.1 (2.6)	66.8 (3.0)**	89.7 (4.6)**	83.7 (3.3)***	103.7 (1.5)***
125	57.9 (2.6)	63.2 (1.7)	93.2 (4.6)**	96.8 (2.8)***	105.8 (5.2)***
150	70.5 (3.0)	68.7 (3.3)	120.0 (5.0)***	120.5 (4.1)***	130.3 (2.9)***

$n = 3$, (S.D.). Dissolution rates at position A, B, C and D were compared to the rate at the center at each rotation speed.
[a] Distance from the center of the vessel bottom.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

Table 2
Relationship between paddle rotation speed and fluid resistance at each position

Paddle rotation speed (rpm)	Fluid resistance[a] ($\times 10^{-3}$ N)			
	Position			
	A 4 mm[b]	B 12 mm[b]	C 20 mm[b]	D 28 mm[b]
25	n.d.	n.d.	0.03	0.04
50	0.03	0.06	0.24	0.35
75	0.25	0.51	0.56	0.80
100	0.30	0.68	1.12	1.52
125	0.59	1.13	1.84	2.41
150	0.86	1.86	2.57	3.53

n.d.: not detected.
[a] Fluid resistance on the baffle plate (8×8 mm^2). The data represent means of values measured continuously for 30 s.
[b] Distance from the center of the vessel bottom.

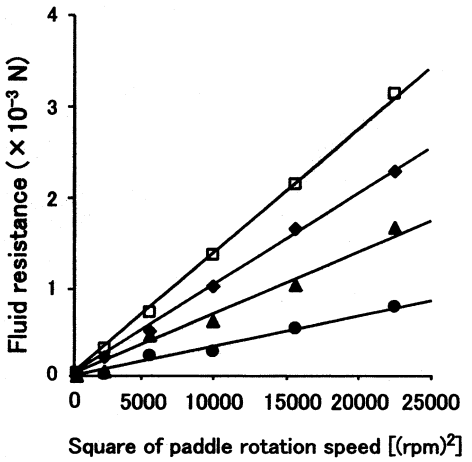

Fig. 5. Relationship between the square of the paddle rotation speed and the fluid resistance. (●) Position A; (▲) Position B; (◆) Position C; (□) Position D. The lines were fitted to the data values of each position. Correlation coefficients for position A, B, C and D were 0.992, 0.992, 0.994 and 0.999, respectively. The data results of fluid resistance were obtained from a single measurement (Table 2).

From the relationship between the paddle rotation speed and the dissolution rate (Table 1) and the relationship between the paddle rotation speed and the fluid velocity (Table 3), another relationship can be derived between the fluid velocity and the dissolution rate (Fig. 6). Fig. 6 shows that the dissolution rate of the PCR tablet is proportional to the fluid velocity around the baffle plate. The linear regression line intercepts the Y-axis. As there is an upward flow could just beneath the paddle shaft (Bocanegra et al., 1990), a small amount of the drug could be dissolved by this flow. Fig. 6 also shows that the dissolution rate from the PCR tablet depends on the fluid velocity at the position where the tablet stays during the dissolution test.

Based on the measurements with the PCR tablet and the fluid resistance sensor, it was shown that there is a considerable tablet position-dependent difference in agitation force intensity at the dissolution vessel bottom. This could be one of the reasons for the intra batch variation in the paddle method of solid dosage forms, such as film-coated tablets and hydrogel-type sustained-release tablets. They often adhere irregularly to the vessel bottom. Moreover, we sometimes observe cone-shaped sediments formed from granules resulting from the disintegration of the tablet together with a large decrease in the dissolution rate. The extremely weak agitation force just under the paddle shaft explains the formation of these sediments.

3.3. Measurement of the impulsive force in the disintegration test

The position of the auxiliary disk and basket-rack from the bottom of the test beaker over time

Table 3
Relationship between paddle rotation speed and fluid velocity at each position

Paddle rotation speed (rpm)	Fluid velocity[a] (m/s)			
	Position			
	A 4 mm[b]	B 12 mm[b]	C 20 mm[b]	D 28 mm[b]
25	–	–	0.030	0.035
50	0.027	0.040	0.081	0.098
75	0.084	0.119	0.125	0.150
100	0.092	0.138	0.177	0.206
125	0.128	0.178	0.227	0.259
150	0.155	0.228	0.268	0.314

[a] The fluid velocity was back calculated using the fluid resistance equation.
[b] Distance from the center of the vessel bottom.

is shown in Fig. 7. The disk stayed near the surface of the water most of the time and the disk collided with the bottom of the basket-rack at its highest point in the up-and-down cycle.

The wave pattern of the impulsive force in Fig. 8a reveals that a sharp impulsive force is produced when the disk comes into contact with the sensor rod. The peak height represents the strength of the impulsive force. The impulsive force of the disk in 900 ml of water was about 0.31 N (32 g weight) (Table 4). As suggested in the Japanese Pharmacopoeia, the volume of test water was regulated to about 900 ml. There was no significant difference in the impulsive force from 850 to 1000 ml. Therefore, the effect of water volume on the impulsive force was not recognized around the water volume of 900 ml.

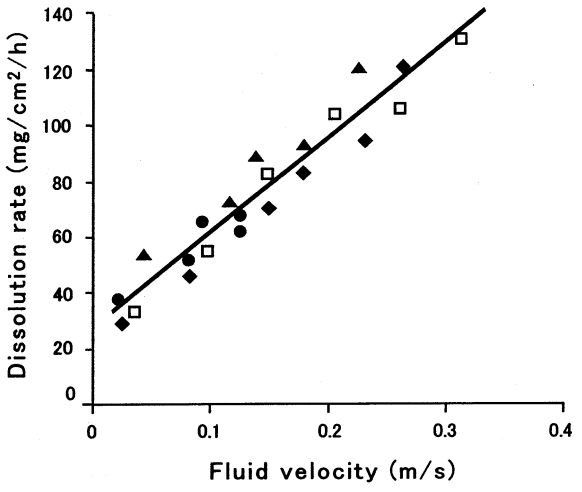

Fig. 6. Relationship between the fluid velocity and the dissolution rate of benzoic acid from the PCR tablets. (●) Position A; (▲) Position B; (◆) Position C; (□) Position D. The line is a linear regression line. $r = 0.960$ ($P < 0.01$). The data of the dissolution rate are represented as the mean of three measurements carried out at each position and each paddle rotation speed (Table 1). The error bars were omitted.

An increase in the cycle frequency did not proportionately increase the impulsive force (Table 4). This can be understood in the following way. The impulsive force depends on the ascending speed of the basket-rack, which is fastest at mid-point of the ascending movement. An increase in cycle frequency increased the ascending speed of the basket-rack. This also changed the up–down movement of the disk and shifted the perpendicular position of the collision between the disk and basket-rack. Therefore, the impulsive force of the collision is not directly proportional to the cycle frequency.

The impulsive force caused by the collision between the enteric-coated tablet and the wire gauze of a basket-rack is shown in Table 4. The force by the tablet alone was 0.19 N and that by the tablet with the disk was 0.16 N. These forces were smaller than the force of the disk alone (0.31 N).

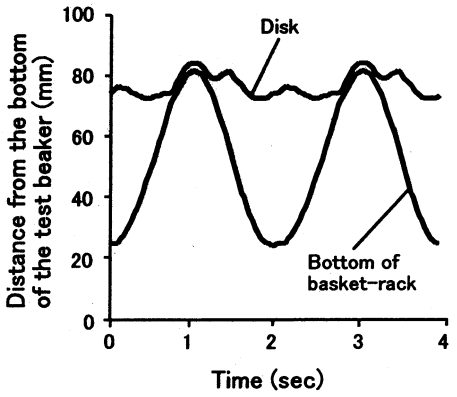

Fig. 7. Movement of the disk in the disintegration test. The position of the disk and the bottom of the basket-rack were plotted on the basis a video camera recording. This figure is a typical case in which the data values were obtained at a cycle frequency of 30 cpm and water volume of 900 ml.

3.4. Relationship between the fluid resistance and the dissolution rate in the disintegration test

The wave pattern of fluid resistance is shown in Fig. 8b. The maximum fluid resistance and dissolution rate of PCR tablets at various cycle frequencies of the basket-rack is shown in Table 5. Both the fluid resistance and dissolution rate of the PCR tablet increased with increasing cycle frequency of the basket-rack.

With a basket-rack movement of 30 cpm, the release rate of benzoic acid from the PCR tablet was 59.7 mg/cm^2/h. This dissolution rate was comparable to the dissolution rate in the paddle method at 4 mm away from the center at 125 rpm. The dissolution rate was 63.2 mg/cm^2/h. Although the dissolution rates of the PCR tablets were similar, the fluid resistance in the paddle method was smaller than that in the disintegration test. The tablet was given 0.59×10^{-3} N/(64 mm^2) of fluid resistance in the paddle method at 4 mm away from the center at 125 rpm. Meanwhile, the tablet was given a 1.66×10^{-3} N/(64 mm^2) of maximum fluid resistance at 30 cpm in the disintegration test. The fluid resistance in the disintegration test was larger than that in the paddle method under similar dissolution rate conditions. This was because the maximum force was applied to the tablet only when the basket-rack had the fastest movement in the cycle, which was a mid-way during the ascent or descent (Fig. 8b).

3.5. Disintegration test of the enteric-coated tablet

The effect of the impulsive force on tablet disintegration was evaluated with an enteric-coated tablet (Table 6). The enteric-coated tablet was non-adhesive and insoluble in JP first fluid.

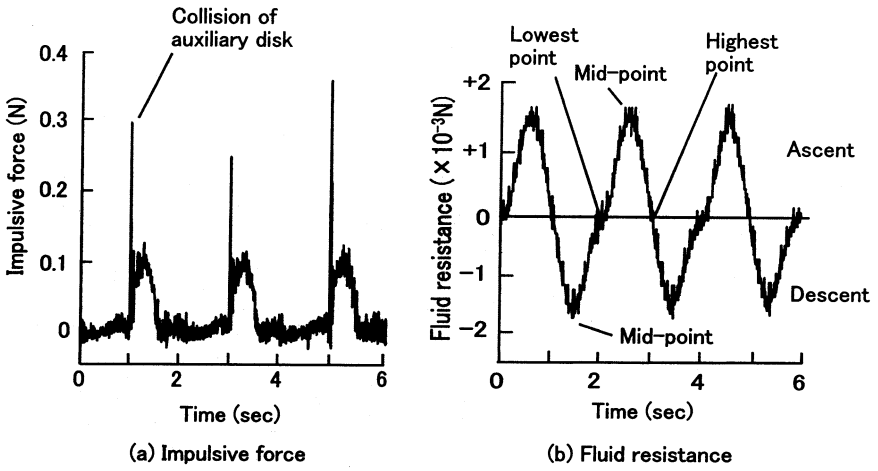

Fig. 8. Impulsive force by the disk and fluid resistance in the disintegration test apparatus. These figures represent typical cases in which the data values were obtained at a cycle frequency of 30 cpm and water volume of 900 ml.

Table 4
Effect of the test conditions on the impulsive force by the disk or the tablet

Volume (ml)	Impulsive force by disk (N)
(A) *Effect of water volume*[a]	
800	0.16 (0.03)*
850	0.27 (0.03)
900	0.31 (0.05)
950	0.20 (0.05)
1000	0.38 (0.06)
Cycle frequency (cpm)	Impulsive force by disk (N)
(B) *Effect of cycle frequency*[b]	
15	0.25 (0.04)
30	0.31 (0.05)
45	0.20 (0.03)**
60	0.27 (0.04)
Conditions	Impulsive force by tablet (N)
(C) *Collision of tablet*[c]	
Disk alone	0.31 (0.05)
Tablet alone	0.19 (0.03)**
Tablet with disk	0.16 (0.03)**

$n = 6$, (S.D.). Impulsive force under each condition was compared to the force of the disk under the condition of (A) water volume of 900 ml, (B) cycle frequency of 30 cpm, or (C) disk alone.

[a] Impulsive force by the disk. Cycle frequency was 30 cpm.

[b] Impulsive force by the disk. Volume of water was 900 ml.

[c] An enteric-coated tablet was used. Cycle frequency was 30 cpm and the volume of water was 900 ml.

* $P < 0.05$.

** $P < 0.01$.

Table 5
Fluid resistance and dissolution rate of the PCR tablet in the disintegration test

Cycle frequency (cpm)	Fluid resistance ($\times 10^{-3}$ N)[a]	Dissolution rate (mg/cm^2/h)[b]
15	1.38 (0.07)*	38.7 (2.3)**
30	1.66 (0.15)	59.7 (3.4)
45	2.53 (0.25)**	80.8 (3.1)*
60	4.42 (0.24)**	88.3 (4.1)**

The data of fluid resistance and dissolution rate at cycle frequencies of 15, 45, and 60 were compared to those at a cycle frequency of 30 cpm. Symbols represent $*P < 0.01$, $**P < 0.001$.

[a] Maximum fluid resistance on the baffle plate (8×8 mm^2). The data were means of six continuous peaks measured during the ascent of the basket-rack. $n = 6$, (S.D.).

[b] The dissolution rate of the PCR tablet. $n = 3$, (S.D.).

The impulsive force of the tablet after collision with the wire gauze of the basket-rack was 0.19 N (Table 4). The force was weaker than the collision force of the disk (0.31 N). However, it was strong enough to accelerate the disintegration rate of the tablet itself since the fixed reference tablets did not disintegrate for 2 h. The fixed tablets received only 1.66×10^{-3} N/(64 mm^2) of maximum fluid resistance (Table 5). However, this force was not enough to disrupt and remove the enteric film from the tablets.

In the disintegration test, tablets were subjected to two different forces, an impulsive force and fluid resistance. In our study, these two forces were evaluated quantitatively to explore the possibility of using the disintegration test apparatus as an in vivo dissolution simulator. The impulsive force applied in the disintegration test was in the range of 0.16–0.38 N (Table 4). In contrast, the mechanical destructive force produced in the human stomach was reported to be 1.5 N (Kamba et al., 2000). Since the frequency and period of stress are different between those two forces, it is difficult to compare both forces directly. However, it would be reasonable to conclude that the impulsive force applied in the disintegration test is much smaller than that in the human stomach. Therefore, the impulsive force is thought not to be strong enough to emulate the human GI mechanical stress.

4. Conclusion

There was a considerable tablet position-dependent difference in the agitation force intensity at the dissolution vessel bottom in the paddle method. This could be one of the reasons for the intra batch variation in the dissolution rates of the solid oral dosage forms.

Tablets were subjected to impulsive forces and fluid resistance in the disintegration test. These forces affected the disintegration rate of the tablet, however, they were much weaker than the mechanical destructive force produced physiologically in the GI tract. Therefore, it would be difficult to simulate the in vivo conditions with the disintegration test apparatus.

Table 6
Effect of impulsive force in the disintegration test

Amount of enteric film coating (mg)	Disintegration time (min)			
	0	16	22	28
Disintegration test conditions				
With disk	< 1	48 (14)	90 (13)	> 120
Without disk	< 1	82 (12)	> 120	> 120
Reference test[a]	< 1	> 120	> 120	> 120

$n = 3$, (S.D.). Test conditions: cycle frequency was 30 cpm and the volume of JP1 was 900 ml.
[a] The tablet was fixed on the wire gauze and the test was performed without the disk.

Acknowledgements

This study was supported by the Japan Health Sciences Foundation.

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