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Drug Development and Industrial Pharmacy, 28(6), 655–662 (2002)

RESEARCH PAPER

# Hydrodynamic Flows Around Tablets in Different Pharmacopeial Dissolution Tests

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## ABSTRACT

*We investigated the hydrodynamic flows around tablets during several pharmacopeial dissolution tests: the rotating basket (RB), paddle (PD), flow-through cell (FT), and disintegration (DI) tests. The determination of hydrodynamic flow was based on the dissolution rate of United States Pharmacopeial salicylic acid nondisintegrating calibrators, and showed that, compared with the PD and RB methods, the FT method produced a lower hydrodynamic flow value whereas the DI method produced a higher value. The hydrodynamic flows during the PD and RB tests appeared to be similar at the same rotational speed, although the flow patterns around the tablet differed; with the RB method, homogeneous dissolution occurred from all surfaces of the tablet, while with the PD method, dissolution from the lower surface was slower. The use of a sinker seemed to enhance dissolution from the lower surface. Such differences in hydrodynamic flow could explain the apparently different dissolution behaviors of disintegrating prednisone and nondisintegrating acetaminophen tablets when assessed by the PD and RB methods. These differences in hydrodynamic flow between in vitro tests should be considered when choosing dissolution tests for studying in vitro/in vivo relationships and for quality control purposes.*

***Key Words:*** *Dissolution test; Hydrodynamic flow; Salicylic acid tablet; USP calibrator*

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## INTRODUCTION

The dissolution of drugs from orally administered solid dosage forms in vivo and in vitro is influenced by variations in the natural or simulated gastrointestinal fluids (e.g., pH, surfactants) and physical variables such as hydrodynamic flow (1,2) and mechanical stress (2–5). Although the effects of pH have been well studied, there have been hardly any published investigations on the effects of physical variables, making it difficult to establish or select the most appropriate types of dissolution apparatus and stirring rates for predicting the in vivo performance of oral solid dosage forms. Our previous studies revealed that the dissolution of erodable or crushable tablets was principally influenced by mechanical stress in vivo (3,4) and that hydrodynamic flow in the human gastrointestinal (GI) tract was very low; these features are very similar to those provided by the paddle (PD) test when performed at 10 rpm (1). In order to develop reliable in vitro test systems, information on the hydrodynamic flow and mechanical stress components of various in vitro tests is required; however, there have been few studies in this field to date (5–7). The present study was undertaken to investigate hydrodynamic flows around tablets during widely used pharmacopeial dissolution tests, namely the PD, rotating basket (RB), flow-through cell (FT), and disintegration (DI) tests, in the hope that the results will assist in the choice of appropriate types of dissolution apparatus and stirring rates. The hydrodynamic flows were determined using United States Pharmacopeial (USP) salicylic acid tablets of the nondisintegrating calibrator type, since with these tablets the dissolution rate changes depending on the hydrodynamic flow around the tablet and is not influenced by mechanical stress, meaning that the dissolution rate can be used as an indicator of hydrodynamic flow.

## MATERIALS AND METHODS

### Materials

Salicylic acid tablets (USP dissolution calibrator of the nondisintegrating type, 300 mg; Lot N) were used to assess hydrodynamic flow. Prednisone tablets (USP disintegrating type calibrator) and an experimental sustained-release acetaminophen tablet which does not disintegrate were employed to investigate the effects of hydrodynamic flow on dissolution.

### Dissolution Tests

Dissolution tests on the salicylic acid tablets were carried out in 900 mL 0.05 M phosphate buffer (pH 7.4) at 37°C using the PD method at 20–200 rpm, the RB method at 50–200 rpm, the FT method at 9–44 cm/min, and the DI method at 10–30 cpm, as described in the Japanese Pharmacopoeia (JP) edition XIII (Fig. 1). For the RB and DI tests, the salicylic acid tablets were placed in two positions: (A) inside the basket and (B) on the bottom of the vessel. For the FT test, the salicylic acid tablets were placed in three positions: (A) on a holder, (B) on top of a layer of glass beads, and (C) within the glass bead layer. The amount of salicylic acid dissolved was measured at 257 nm every 5 min, using an automated sampling system with sampling probes 4 mm in diameter. Three further kinds of salicylic acid tablets, coated with an insoluble synthetic polymer resin so that they released the drug only from the upper, side, or lower surface, respectively, were prepared and their dissolution behavior was determined by the PD and RB methods.

Dissolution tests were carried out on the acetaminophen sustained-release tablets using the RB and PD methods at 50–100 rpm, and on the prednisone tablets using the PD method at 50 rpm. Deaerated water (900 mL) was used as the vehicle. The amounts of prednisone and acetaminophen dissolved were measured at 242 and 280 nm, respectively.

### Dissolution Rate Constants ($K_d$) for the Salicylic Acid Tablets

Dissolution can be expressed as shown in Eq. (1), according to Fick's diffusion theory (8):

$$\frac{dc}{dt} = \frac{DS(C_s - C)}{vh} \quad (1)$$

where $dc/dt$ is the dissolution rate of the drug, $D$ is the diffusion coefficient, $h$ is the diffusion layer thickness, $v$ is the volume of the dissolution medium, $S$ is the surface area, $C_s$ is the solubility, and $C$ is the drug concentration in the medium. Under sink conditions ($C_s \gg C$), the concentration gradient would

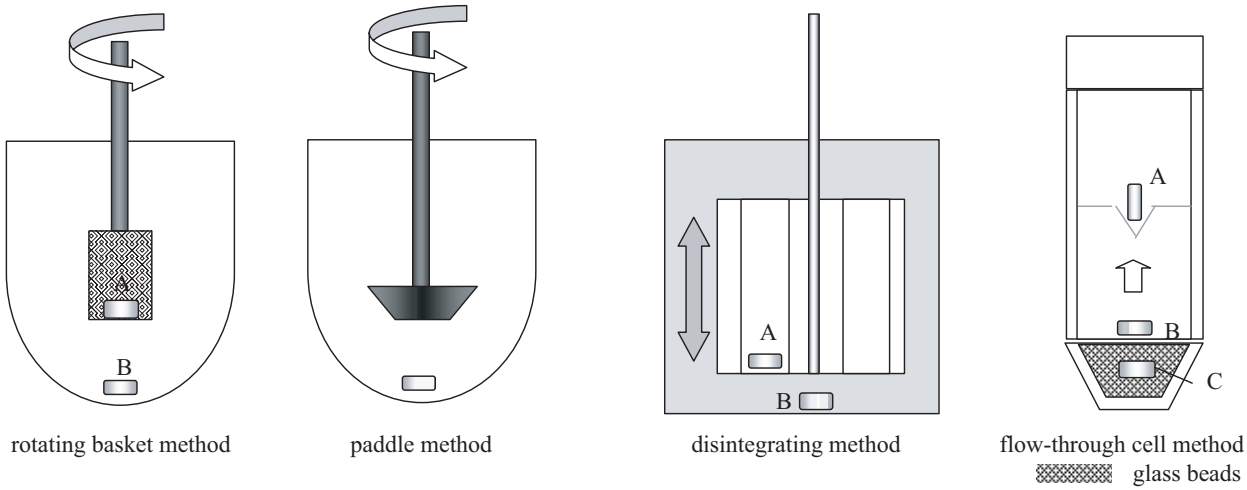


**Figure 1.** Dissolution test methods used during the study: the rotating basket method [the tablet was placed either inside the basket (A) or on the bottom of the vessel (B)]; the paddle method; the disintegration method [the tablet was placed either inside the basket (A) or on the bottom of the vessel (B)]; and the flow-through cell method [the tablet was placed on a holder (A), on top of a layer of glass beads (B), or within the glass bead layer (C)].

be reduced to $C_s/h$. The $D$ and $C_s$ are constant parameters for each drug. When $v$ and $h$ are held constant under fixed conditions, the dissolution rate will follow zero-order kinetics if $S$ is not changed, as shown in Eq. (2):

$$\frac{dc}{dt} = \frac{DSC_s}{vh} = K_d \tag{2}$$

Eq. (2) also indicates that $K_d$ will vary depending on $h$ when the degree of agitation is changed, meaning that $K_d$ can be used as an indicator of the hydrodynamic flow around solid drug dosage forms during dissolution tests. Salicylic acid tablets of the nondisintegrating type can be expected to show zero-order dissolution in the initial stages, since $S$ remains almost constant. In this study, all flow rates are expressed as mean values and diffusion layer thicknesses are averaged over the whole surface of the tablet. Complete homogeneity of the bulk solution is also assumed. Figure 2 shows the dissolution profiles of nondisintegrating salicylic acid tablets as assessed by the PD method at 50–150 rpm. These indicate that dissolution followed almost zero-order kinetics until the time at which 50% of the drug had been dissolved. Zero-order dissolution was also observed with the RB, FT, and DI methods. The rate constant $K_d$ was determined from dissolution profiles measured between zero and 30 min.

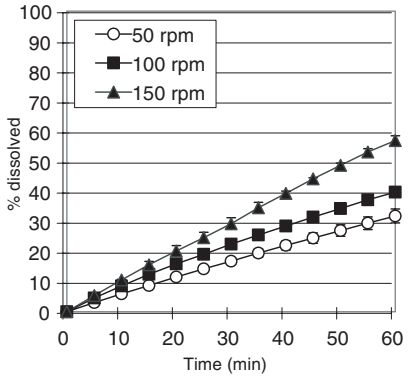


**Figure 2.** Dissolution profiles for nondisintegrating salicylic acid tablets as measured by the paddle method at 50–150 rpm. The vertical lines indicate the standard deviation (SD).

## RESULTS

### Dissolution Rate Constants for the Salicylic Acid Tablets as Measured by Different Methods

Figure 3 shows the $K_d$ values for nondisintegrating salicylic acid tablets as measured by the PD and RB methods; these increased as the rotational speed increased. The $K_d$ values obtained using the RB method with the tablets in the basket were close to

those obtained using the PD method without a sinker at each speed, indicating that these methods produce similar hydrodynamic flows around the tablet. The $K_d$ for the PD method increased when a sinker was used. With the RB method, the $K_d$ was significantly lower when the tablet was placed on the bottom of the vessel than when it was placed in the basket, as shown in Table 1. This indicates that the intensity of agitation is lower at the bottom of the vessel than inside the basket.

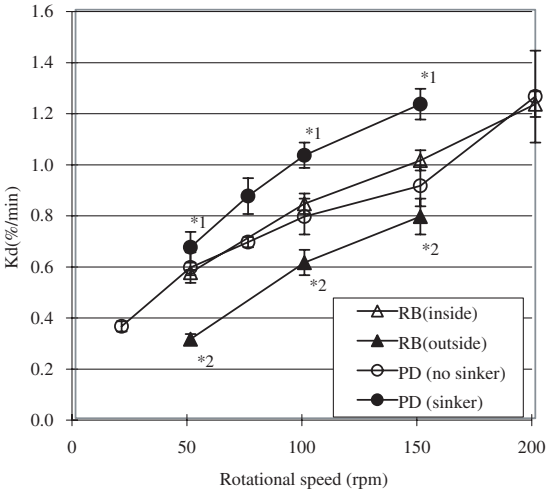


**Figure 3.** The $K_d$ values for nondisintegrating salicylic acid tablets as measured by the PD method with or without a sinker and by the RB method at 0–200 rpm. The vertical lines indicate the SD. *1 $P < .05$; significantly different from PD (no sinker). *2 $P < .05$; significantly different from RB (inside). Individual data of $K_d$ (rotational speed 50, 100, and 150 rpm) were analyzed using Scheffe test following one-way analysis of variance (ANOVA).

Table 2 shows the $K_d$ values for the FT method, which differed depending on the position of the tablet (Fig. 1). Cammarn also reported that the orientation of the tablet within the cell has an effect on the dissolution rate with the FT method (7). The $K_d$ was highest when the tablet was placed within the bead layer. However, in this case, the high $K_d$ does not automatically indicate high hydrodynamic flow, since the tablet surface buried in the bead layer became eroded, which must have resulted in increased dissolution. This erosion was probably caused by turbulent flow around the tablet and the pressure of the beads on its surface. When the tablet was placed on a holder or on top of the bead layer, as is usually the case, the $K_d$ at 5 cm/min (19 mL/min), a normal flow rate, was lower than that for the PD method at 50 rpm. This indicates that the FT method produces a low hydrodynamic flow, which was especially apparent when the tablet holder was used; even at 44 cm/min (50 mL/min), the maximum flow of the apparatus, the $K_d$ value was approximately 80% that obtained using the PD method at 50 rpm.

Table 3 shows the $K_d$ values for the DI method. At 30 cpm, the officially recommended cycling rate, the $K_d$ was remarkably high, being close to the

***Table 1***

*$K_d$ of Salicylic Acid Tablets by RB and PD Methods*[a]

| Rotational Speed (rpm) | $K_d$ (%/min) | | | |
|---|---|---|---|---|
| | RB | | PD | |
| | Inside[b] | Outside[c] | No Sinker | Sinker |
| 20 | | | 0.36±0.02 | |
| 50 | 0.57±0.01 | 0.31±0.02 | 0.59±0.06[d] | 0.67±0.06 |
| 75 | | | 0.69±0.02 | 0.87±0.07 |
| 100 | 0.84±0.04 | 0.61±0.05 | 0.79±0.07 | 1.03±0.05 |
| 150 | 1.01±0.04 | 0.79±0.07 | 0.91±0.08 | 1.23±0.06 |
| 200 | 1.23±0.05 | | 1.26±0.18 | |

[a]Data are presented as mean±SD for each group ($n = 6$).
[b]Tablets were placed in the basket.
[c]Tablets were placed on the bottom of the vessel.
[d]$n = 20$.

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***Table 2***

$K_d$ *of Salicylic Acid Tablets by FT Method*[a]

| Liquid Velocity (cm/min) | $K_d$ (%/min) | | |
|---|---|---|---|
| | Holder | On Bead | In Bead |
| 5[b] | 0.15±0.06 | 0.29±0.02 | 0.70±0.07 |
| 9[c] | 0.22±0.02 | | |
| 18[c] | 0.32±0.02 | | |
| 44[c] | 0.45±0.02 | | |

[a]Data are presented as mean±SD for each group ($n = 3$).
[b]Using large cell (22 mm diameter).
[c]Using small cell (12 mm diameter).

***Table 3***

$K_d$ *of Salicylic Acid Tablets by DI Method*[a]

| Stroke (cpm) | $K_d$ (%/min) | |
|---|---|---|
| | No Disk | Disk |
| 10 | 0.67±0.04[b] | |
| 20 | 1.02±0.01[b] | |
| 30 | 1.23±0.04[b] | 1.27±0.04[b] |
| 30 | 0.55±0.02[c] | |

[a]Data are presented as mean±SD for each group ($n = 6$).
[b]Tablets were placed in the tube.
[c]Tablets were placed on the bottom of the beaker.

value obtained with the PD method at 200 rpm. The use of plastic disks did not significantly affect dissolution. When the tablet was placed on the bottom of the beaker, the $K_d$ value was less than half of that obtained when it was placed in the tube (Table 3).

## Dissolution Behavior of Salicylic Acid Tablets as Assessed by the Paddle and Rotating Basket Methods

Three kinds of salicylic acid tablets, coated with an insoluble polymer so as to release the drug from the upper, side, or lower surface, respectively, were prepared. No drug dissolved when the tablet was completely coated with the polymer. Table 4 shows the $K_d$ values and relative ratios (%) of the $K_d$ for each surface to the total $K_d$. These data revealed that the drug was almost uniformly dissolved from all surfaces of the tablet when the RB method was used, irrespective of the rotatory speed, as illustrated in Fig. 4. On the other hand, the drug dissolved more slowly from the lower surface when the PD method was used (Fig. 4), and this was particularly marked at the low stirring rate of 50 rpm. At 200 rpm, dissolution from the lower surface was enhanced. This can be ascribed to increased tablet movement due to the vigorous agitation.

***Table 4***

$K_d$ *of Coated Salicylic Acid Tablets Releasing the Drug from Upper, Side, or Lower Surface by RB and PD Methods*[a]

| Rotational Speed (rpm) | Surface | $K_d$ (%/min) | |
|---|---|---|---|
| | | RB | PD |
| 50 | Upper | 0.19±0.02 (30) | 0.24±0.02 (35) |
| | Side | 0.24±0.01 (37) | 0.35±0.01 (52) |
| | Lower | 0.22±0.04 (33) | 0.08±0.01 (12) |
| 100 | Upper | 0.26±0.04 (31) | 0.32±0.03 (38) |
| | Side | 0.29±0.08 (34) | 0.44±0.02 (52) |
| | Lower | 0.29±0.04 (35) | 0.09±0.04 (11) |
| 200 | Upper | 0.39±0.05 (31) | 0.39±0.04 (33) |
| | Side | 0.43±0.05 (35) | 0.48±0.06 (41) |
| | Lower | 0.42±0.05 (34) | 0.30±0.07 (26) |

[a]Data are presented as mean±SD for each group ($n = 3$). The figures in parentheses show the relative ratio (%) in dissolution from each surface to the entire surface area.

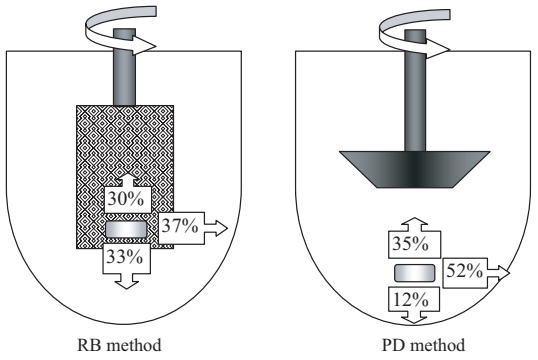


**Figure 4.** The relative ratios of dissolution from each tablet surface to the total dissolution obtained for polymer-coated salicylic acid tablets using the RB and PD methods at 50 rpm.

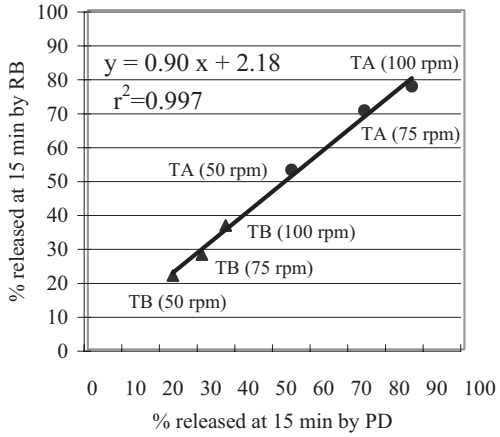


**Figure 5.** Comparison of dissolution rates for acetaminophen tablets of the nondisintegrating type assessed by the RB and PD methods. Here TA and TB indicate tablet types A and B, respectively. The figures in parentheses show the rotatory speeds.

### Dissolution Tests for Disintegrating and Nondisintegrating Tablets

The hydrodynamic flow characteristics of the in vitro tests identified during this study may be useful in understanding differences or similarities in the dissolution behaviors of actual pharmaceutical products when determined by different methods. To confirm this possibility, we performed dissolution tests using a disintegrating tablet (USP prednisone calibrator) and two nondisintegrating ones (sustained-release tablets of acetaminophen, designated A and B). As shown in Fig. 5, the two acetaminophen tablets had almost equivalent dissolution characteristics when tested using the PD and RB methods at the same rotational speed, as would be expected from the similar hydrodynamic flows of these tests (Fig. 3). On the other hand, the disintegrating prednisone tablet exhibited much slower dissolution during the RB test than during the PD test (Fig. 6). When using the RB method, the tablet rapidly disintegrated into small particles which passed through the wire mesh of the basket and piled up on the bottom of the vessel. The drug then dissolved from the pile, and this is probably the major reason for the slow dissolution, since the hydrodynamic flow at the bottom of the vessel is lower with the RB than with the PD method (Table 1).

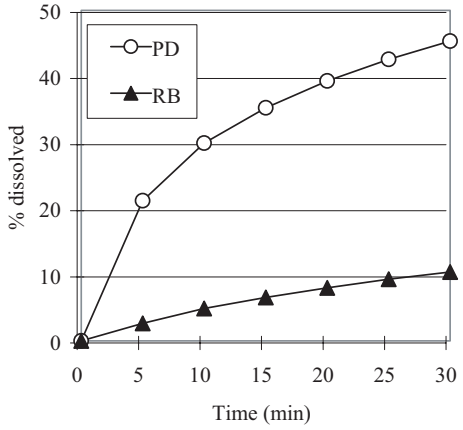


**Figure 6.** Dissolution profile for disintegrating prednisone tablet as assessed by the PD and RB methods at 50 rpm.

## DISCUSSION

In order to predict the most reliable in vitro dissolution systems, in vitro and in vivo assessments of hydrodynamic flow and mechanical stress, both of which affect dissolution, must be undertaken. Our previous studies revealed that there is great interindividual variability in mechanical stress in the GI tract (3,4), and that the hydrodynamic flow in the human GI tract is unexpectedly low; these features are very similar to those obtained with the PD method at 10 rpm (1). In order to choose or develop the most appropriate dissolution systems for mimicking the in vivo situation, the hydrodynamic flow and mechanical stress characteristics of in vitro

tests must be determined. However, direct measurement of hydrodynamic flow, especially turbulent flow occurring in a round vessel, is technically difficult and it is not easy to relate the hydrodynamic flow to the actual dissolution rates of drug products. Therefore, in this study, hydrodynamic flows were measured indirectly using a nondisintegrating tablet with flow rate-dependent dissolution (6).

Our results revealed that hydrodynamic flow varies with the apparatus, the rotational speed used, and the location of the tablet in the vessel. The widely used PD and RB methods appeared to produce similar hydrodynamic flows around the tablet when the same rotational speed was used and the tablet was placed in the basket; however, there were some differences in the details of the flow patterns: with the RB method, homogeneous hydrodynamic flow occurred all around the tablet, while with the PD method, the flow around the upper surface of the tablet was higher than that around the lower and side surfaces (Table 4). The use of sinkers accelerated dissolution during the PD test, while increasing the stirring rate promoted dissolution from the lower surface of the tablet. This indicates that only a limited area of the lower surface of the tablet was available for dissolution without the sinker at low stirring rates, and/or the hydrodynamic flow around the lower surface of the tablet was poor. With the RB method, the hydrodynamic flow at the bottom of the vessel was significantly lower than that in the basket. This difference will significantly affect the dissolution behaviors of drug products, depending on whether they are retained in the basket or not during dissolution, as exemplified by the dissolution tests for acetaminophen and prednisone tablets (Figs. 5 and 6).

The different hydrodynamic characteristics of the in vitro tests observed during the study indicate that attention should always be paid to the hydrodynamic flow characteristics when using dissolution tests for studying in vitro/in vivo relationships or for quality control purposes. From the point of view of modeling the in vivo situation, in vitro tests with similar hydrodynamic flow characteristics to those observed in vivo are required. Since hydrodynamic flow is very low in vivo (1), a dissolution test with a low hydrodynamic flow, such as the FT method, is preferable in this setting. This is supported by a study which showed that a FT test conducted at a low flow rate, 0.8 mL/min, predicted the dissolution of clarithromycin tablets in the stomach more accurately than PD methods (9). On the other hand, for quality control purposes, similarities in hydrodynamic flow between the available in vitro tests should be taken into consideration. Currently, the PD test at 50 rpm and the RB test at 100 rpm are extensively employed by the USP and JP. These tests can be interchanged for products that disintegrate, since they produce similar hydrodynamic flows around the bottom of the vessel (Table 1), where the disintegrated particles collect and the majority of drug dissolution occurs. However, for nondisintegrating products which remain in the basket for a long period of time, the same rotation speeds should be applied to produce similar hydrodynamic flows (Table 1).

From the results of this study, we can conclude that, under usual testing conditions, compared with the PD and RB methods, the FT method produces a lower hydrodynamic flow value whereas the DI test produces a higher value. The RB and PD methods produce similar hydrodynamic flow values when used at the same rotation speed and the tablet is retained in the basket. The differences in the hydrodynamic characteristics of the in vitro methods determined during this study will be useful in allowing greater understanding of the dissolution behaviors likely to be seen with different in vitro tests. Such differences in hydrodynamic flow should always be taken into consideration when choosing a dissolution test for studying in vitro/in vivo relationships and for quality control purposes.

## ACKNOWLEDGMENT

This work was partially supported by a grant from the Ministry of Health, Labour and Welfare of Japan.

## REFERENCES

1. Katori, N.; Aoyagi, N.; Terao, T. Estimation of Agitation Intensity in the GI Tract in Human and Dog Based on In Vitro/In Vivo Correlation. Pharm. Res. **1995**, *12*, 237–243.
2. Sako, K.; Mizumoto, T.; Kajiyama, A.; Ohmura, T. Influence of Physical Factors in Gastrointestinal Tract on Acetaminophen Release from Controlled Release Tablets in Fasted Dogs. Int. J. Pharm. **1996**, *137*, 225–232.

3. Shameem, M.; Katori, N.; Aoyagi, N.; Kojima, S. Oral Solid Controlled Release Dosage Forms: Role of GI-Mechanical Destructive Forces and Colonic Release in Drug Absorption Under Fasted and Fed Conditions in Humans. Pharm. Res. **1995**, *12*, 1049–1054.
4. Katori, N.; Ma, W.; Aoyagi, N.; Kojima, S. Effect of Destructive Forces on Drug Release from Multiple Unit Controlled Release Dosage Forms in Humans. Pharm. Res. **1996**, *13*, 1541–1546.
5. Aoki, S.; Ando, H.; Tatsuishi, K.; Uesugi, K.; Ozawa, H. Determination of the Mechanical Impact Force in the In Vitro Dissolution Test and Evaluation of the Correlation Between In Vivo and In Vitro Release. Int. J. Pharm. **1993**, *95*, 67–75.
6. Ogata, H.; Shibazaki, T.; Inoue, T.; Ejima, A. Comparative Studies on Eight Dissolution Methods Using 21 Commercial Chloramphenicol Tablets and a Nondisintegrating Benzoic Acid Tablet. J. Pharm. Sci. **1979**, *68*, 708–712.
7. Cammarn, S.R.; Sakr, A. Predicting Dissolution via Hydrodynamics: Salicylic Acid Tablets in Flow Through Cell Dissolution. Int. J. Pharm. **2000**, *201*, 199–209.
8. Hamad, M.A. *Dissolution*, *Bioavailability & Bioequivalence*; Mark Printing Company: Easton, PA, 1989; 11–14.
9. Ishii, K.; Katayama, Y.; Itai, S.; Ito, Y.; Hayashi, H. In Vitro Dissolution Tests Corresponding to the In Vivo Dissolution of Clarithromycin Tablets in the Stomach and Intestine. Chem. Pharm. Bull. **1995**, *43*, 1943–1948.