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Note

Reciprocating dialysis tube method: Periodic tapping improved in vitro release/dissolution testing of suppositories

Soichi Itoh [a,*], Naomi Teraoka [a], Toshio Matsuda [a], Kousuke Okamoto [a], Tatsuya Takagi [a], Charles Oo [b], H. Danny Kao [c]

[a] *Graduate School of Pharmaceutical Sciences, Osaka University, Japan*
[b] *Daiichi Asubio Pharmaceuticals, Rochelle Park, USA*
[c] *Endo Pharmaceuticals, Westbury, USA*

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Abstract

The reciprocating dialysis tube (RDT) method can be used for in vitro release/dissolution testing of suppositories and has been reported to show good in vitro and in vivo correlation. However, for suppositories with viscous excipients, the result remains variable and generally under-predicts in vivo absorption. The purpose of this study was to assess whether periodic tapping of the closure of the RDT could improve in vitro release testing of suppositories. Two commercially available acetaminophen suppositories (A and B) that showed characteristic release behavior under normal rectal temperatures (37 and 38 °C) were chosen as test suppositories. In the absence of tapping, suppository A showed different release profiles at 37 and 38 °C, but the difference disappeared with periodic tapping. This finding was consistent with minimum temperature effect in the rectal absorption of suppository A in rabbits. Suppository B showed distinct release profiles at 37 and 38 °C irrespective of tapping, and the rectal absorption of suppository B in rabbits was affected by temperature. The test variability (CV% and ranges of release values) was substantially reduced in the presence of tapping. In conclusion, the addition of periodic tapping to RDT method developed in this study could improve in vitro release testing of suppositories.

Keywords: In vitro and in vivo correlation; IVIVC; In vitro release; Dissolution test; Dialysis membrane; Suppository; Acetaminophen

1. Introduction

In vitro release/dissolution tests are widely recognized as a quality control procedure to assure lot-to-lot uniformity for pharmaceutical dosage forms as well as a predicative tool for in vivo absorption. In spite of their importance, compendial tests are mainly limited to solid oral dosage forms. For other dosage forms such as suppositories, numerous methods have been published for testing in vitro release, but such testing remains a challenge in terms of their variability and predictability [1,2]. A recent guideline [1] stated that no single test method will be suitable for all suppository formulations. The recommendation is to begin with the basket or paddle method in the case of hydrophilic suppositories and with the modified flow-through cell in the case of lipophilic formulations [1]. Therefore, a more robust in vitro release/dissolution test for suppositories is needed, which may obviate the need to employ different techniques on a case-by-case basis.

Dialysis membrane has been used for in vitro release testing of suppositories. Lootvoet et al. [3] reported that the dialysis rotating cell method (Pharmatest®) showed better in vitro and in vivo correlation than the flow-through method (Dissotest®) [2] using three commercially available indomethacin suppositories. In our previous studies [4–6], the reciprocating dialysis tube method showed the highest correlation between in vitro release and in vivo absorption in rabbits for seven commercially available indomethacin suppositories (two water-soluble, three oleaginous base

* Corresponding author. Present address: Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan. Tel.: +81 6 6879 8168.
E-mail address: soichi@phs.osaka-u.ac.jp (S. Itoh).

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and two rectal capsules), while a lower correlation was obtained using other apparatus such as the TMS-103 suppository dissolution apparatus (Toyama Sangyo Co., Ltd., Osaka, Japan), rotating dialysis cell, and dialysis tube. Both the TMS-103 apparatus and rotating dialysis cell methods use membranes with $\geqslant 0.45$ μm pore size, which are much larger than those of dialysis membranes. Aoyagi et al. [7] reported higher in vitro release and in vivo bioavailability in rabbits and pigs using the dialysis tube method for three oleaginous indomethacin suppositories than by using the TMS-103 apparatus. However, they cautioned that the presence of a small quantity of fluid in the dialysis tube would result in substantially delayed drug release and consequently low reproducibility. In short, a conventional dialysis tube method, in which a dialysis tube is immersed in dissolution vessel with a hemispherical bottom (USP Dissolution Test Apparatus I), has several drawbacks: (a) difficulty in controlling aqueous fluid volume in the dialysis tube, (b) heterogeneous agitation of dissolution medium, (c) off-center position and/or swaying of the dialysis tube and agitator in the reservoir resulting in non-uniform distribution of drug concentration in the medium and (d) slower release rates compared to in vivo absorption. These problems could largely be alleviated by installing a reciprocating dialysis tube to the disintegration apparatus, but the problem of reproducibility and slower release still remains to be overcome.

The aim of this study was to assess the effect of periodic tapping of the closure (which closes the lower end of the dialysis tube) of the reciprocating dialysis tube on the reproducibility and predictability of the in vitro release of suppositories. In the study, two commercially available acetaminophen suppositories, which had characteristic release profiles reported by our group [6], were chosen as test suppositories. Our long-term goal is to develop a robust in vitro release test for suppositories that could predict the in vivo bioavailability in humans.

2. Materials and methods

2.1. Materials

Two commercially available acetaminophen suppositories with oleaginous base (suppositories A and B) were purchased [6]. Each suppository contained 100 mg of acetaminophen. The dialysis tube (membrane size 27) was purchased from Viskase Sales (IL, USA). The molecular weight cut-off of the dialysis membrane is 12,000–14,000 Da. Acetaminophen standard and all other reagents were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan).

2.2. Reciprocating dialysis tube (RDT) method

The reciprocating dialysis tube method developed by our group for testing the in vitro release of suppository is shown in Fig. 1. The apparatus consists of a stainless steel

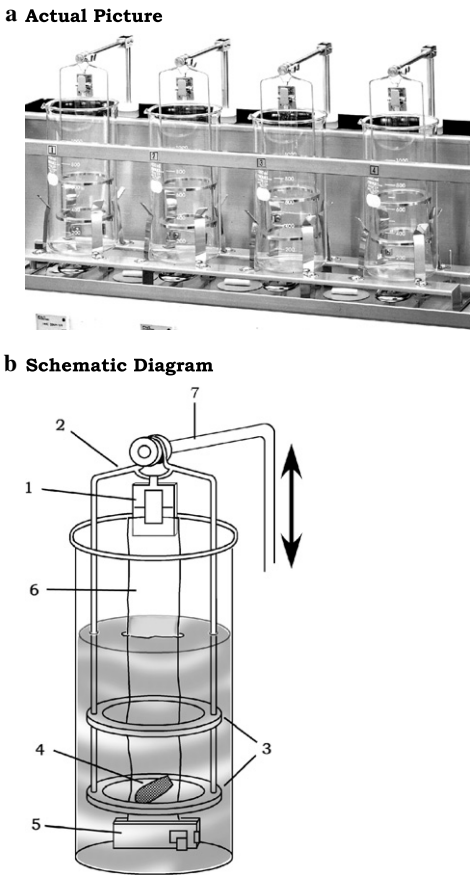

Fig. 1. Actual picture (a) and schematic diagram (b) of the reciprocating dialysis tube method for the in vitro release/dissolution test for suppositories. 1: clip, 2: agitator, 3: ring, 4: suppository, 5: closure, 6: dialysis tube and 7: arm of disintegration apparatus.

agitator, a clip that suspends a dialysis tube from an arm of a disintegration apparatus, a plastic closure (Spectra/Por® No. 132736, Spectrum Laboratories, Inc., CA, USA) attached to a weight (5 g) which closes the lower end of the dialysis tube, a 1 L beaker (20 cm of height, 9.2 cm of internal diameter), and a disintegration apparatus HZ-41D specially modified to fit the dissolution chamber (Miyamoto Riken Ind. Co., Ltd., Osaka, Japan; www.miyamotoriken.co.jp). The agitator is hung by the arm of a disintegration apparatus and moves up and down. The attached weight and a closure do not touch the bottom of the reservoir during the experiment. The dialysis tube is suspended in a beaker containing 1 L of 50 mM phosphate buffer (pH 7.0) at 37.0 ± 0.1 or 38.0 ± 0.1 °C. The top of the disintegration apparatus is equipped with a plastic cover to reduce evaporation of the dissolution medium. The arm of the disintegration apparatus moves up and down automatically at a constant speed (40 rpm).

Prior to in vitro release testing, residual fluid in the dialysis tube was removed manually by pulling the dialysis tube through a film squeegee (King®, Asanuma & Co., Japan) that pinched the dialysis tube. The dialysis tube (length 17 cm) was soaked in purified water and was rinsed before being used. After one end of the dialysis tube was closed

with a closure, the suppository was inserted into the dialysis tube from the other end. The suppository was placed at the lowest position in the tube. The tube was then suspended from the arm of the disintegration apparatus. To maintain the same volume, 1 mL of fresh buffer was added following each sampling (1 mL). Before measurement, the 1 mL sample was diluted with 4 mL of fresh buffer. The concentration of acetaminophen was determined spectrophotometrically at 243 nm (V530 spectrophotometer, JASCO Co., Tokyo, Japan). The analytical method was validated (0.87% of inter-assay CV, 0.61% of intra-assay CV at 20 μg/mL). The detection limit was 0.3 μg/mL. Prior to dissolution test, both suppositories A and B were assayed for acetaminophen by an HPLC method and the results were comparable to those of the spectral measurement. The temperature control unit of the disintegration apparatus was reset after each test with a precision grade immersion thermometer. In order to evaluate intersubject variability, a total of six operators were recruited to perform the test, and each operator repeated four samples at each time point. Each operator was instructed to follow the procedures consistently in the manner of squeezing the dialysis tube and setting up a suppository in the tube.

To standardize a test procedure, a number of assessments were completed prior to in vitro release tests. A cover was shown to be effective to decrease the evaporation of the dissolution medium with the use of a cover, 0.3% of the medium was lost over 24 h, while the loss was 10% in the absence of a cover (release medium, 37 °C; room temperature, 24 °C; relative humidity, 50%; unpublished data). The residual fluid volume in the dialysis tube was reduced effectively by the use of a squeegee; the weight of the membrane before and after pulling through the squeegee was 40 ± 19 and 9 ± 5 mg, respectively [5]. Afterwards, the dialysis tube containing suppository could be hung from the arm of the disintegration apparatus for up to 9 min without affecting the release pattern (0, 3, 6, and 9 min intervals were studied; unpublished data). Sink condition during testing was demonstrated for suppositories A and B: samples were withdrawn simultaneously from nine locations in the reservoir, and no difference in drug concentrations was observed (unpublished data). No difference in release profiles was observed with various weights (5, 10, 20, and 50 g) attached to the plastic closure.

2.3. Reciprocating dialysis tube method, with tapping (RDT/TAP)

The same apparatus (Fig. 1) was used except that the plastic closure attached to a 5 g weight was replaced with a stainless steel closure (50 g). The closure touched the bottom of the reservoir at the lowest point of the reciprocating movement, which resulted in periodic tapping (40 rpm) on the closure. The tension of the stretched dialysis tube was released when the closure touched the bottom of the reservoir, but the tension increased when the tube was lifted up.

2.4. Data analysis

To compare variability, mean and standard deviation of the release values from six operators and their four repeats were evaluated. Variance ratios were computed by dividing the variance of the original method (RDT) by the variance of the method with periodic tapping (RDT/TAP). Bonferroni F-test ($p = 0.05$) was used to assess for significant difference between the variance ratios of the two methods.

3. Results and discussion

It is necessary for suppositories to show consistent release characteristics under temperature range of the rectum. Lipophilic suppositories that release drugs after melting in the rectal cavity are significantly affected by rectal temperature, which is reported as typically 36 and 37.5 °C [1], while higher temperature can be encountered in patients with fever. To simulate in vivo conditions, the temperature in the medium cell was set at 37.0 and 38.0 °C for this study.

The release of suppository A at 37.0 and 38.0 °C by the RDT method (with or without periodic tapping) is shown in Fig. 2 and Table 1. The rate of release of acetaminophen from suppository was rapid for all the profiles and more than 90% was released within 60 min. The release is dependent on temperature and periodic tapping. In the original RDT method, the release at 38.0 °C was faster than that at 37.0 °C, but the addition of tapping enhanced the release and diminished the difference in release between them. In our previous study in rabbits [6] where the rectal temperatures varied from 37.1 to 38.8 °C, the effect of temperature on the absorption of suppository A was negligible, which was consistent with the release reported here under tapping condition. In addition, the time to maximum concentration in plasma (T_{max}) for acetaminophen was 20 min, again more consistent with the release profiles (time to plateau was about 20 min) for the method with tapping at 37.0 and 38.0 °C than for the original method without tapping (time to plateau was about 60 min; Fig. 2). Therefore, the

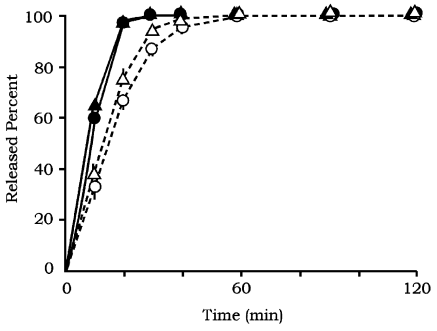

Fig. 2. Effect of periodic tapping on the release profiles of suppository A: (○) without tapping at 37.0 °C; (●) with tapping at 37.0 °C; (△) without tapping at 38.0 °C; (▲) with tapping at 38.0 °C. Symbols represent mean ± SD ($n = 24$).

Table 1
Cumulative percent (±SD) of acetaminophen released from suppository A and suppository B at 37.0 and 38.0 °C by using the original RDT method, and the reciprocating dialysis tube method with the addition of periodic tapping (RDT/TAP)

Time (min]	Analyst's number[a]						Mean[b]	Δ[c]
	1	2	3	4	5	6		
RDT method, Suppository A, 37.0 °C								
10	38.8 ± 4.0	34.3 ± 2.8	30.9 ± 4.8	31.8 ± 3.6	26.1 ± 1.0	34.4 ± 3.7	32.7 ± 4.9	19.0
20	69.0 ± 5.8	68.5 ± 5.2	67.1 ± 2.4	66.9 ± 3.9	62.5 ± 2.2	68.1 ± 3.0	67.0 ± 4.1	15.1
40	93.2 ± 2.7	97.1 ± 3.2	95.6 ± 2.6	95.2 ± 1.9	95.5 ± 1.4	94.3 ± 1.8	95.2 ± 2.4	8.7
RDT/TAP method, Suppository A, 37.0 °C								
10	58.1 ± 2.1	58.8 ± 1.8	57.3 ± 1.2	57.6 ± 1.2	58.4 ± 2.0	57.6 ± 1.3	58.0 ± 1.5	4.5
20	97.8 ± 2.2	97.4 ± 1.8	97.0 ± 2.3	96.0 ± 0.3	97.7 ± 2.4	97.7 ± 2.3	97.3 ± 1.9	5.1
RDT method, Suppository A, 38.0 °C								
10	36.1 ± 3.3	40.0 ± 2.6	39.8 ± 7.1	40.0 ± 1.0	38.0 ± 2.8	37.1 ± 5.5	38.4 ± 3.9	14.0
20	73.8 ± 3.1	76.4 ± 2.2	77.9 ± 7.6	78.2 ± 1.2	75.1 ± 4.5	73.4 ± 3.2	75.7 ± 4.0	15.0
40	101.2 ± 2.1	98.0 ± 1.3	98.3 ± 0.3	98.3 ± 1.2	98.9 ± 0.9	99.0 ± 2.9	99.0 ± 1.8	6.5
RDT/TAP method, Suppository A, 38.0 °C								
10	64.5 ± 0.9	61.6 ± 3.9	63.8 ± 0.9	60.5 ± 3.8	62.8 ± 2.6	61.8 ± 1.8	62.5 ± 2.7	9.0
20	99.0 ± 1.8	99.0 ± 1.2	100.0 ± 1.5	98.2 ± 1.9	98.9 ± 2.4	99.5 ± 0.6	99.1 ± 1.6	5.3
RDT method, Suppository B, 37.0 °C								
10	35.0 ± 3.9	31.8 ± 3.4	26.2 ± 4.6	36.5 ± 3.0	36.8 ± 4.7	33.6 ± 6.0	33.3 ± 5.3	22.2
20	50.2 ± 4.0	44.1 ± 6.5	33.7 ± 5.0	53.3 ± 8.4	53.2 ± 10.4	45.3 ± 9.0	46.6 ± 9.6	39.8
40	55.5 ± 4.3	48.8 ± 7.1	37.7 ± 5.1	60.0 ± 9.0	59.3 ± 11.7	49.6 ± 9.6	51.8 ± 10.7	44.1
60	58.9 ± 4.5	51.4 ± 7.3	40.8 ± 5.0	62.8 ± 9.3	63.6 ± 11.1	52.7 ± 9.5	55.1 ± 10.8	44.2
RDT/TAP method, Suppository B, 37.0 °C								
10	32.8 ± 8.3	34.6 ± 2.0	31.6 ± 1.2	31.4 ± 4.8	31.3 ± 1.0	36.3 ± 5.7	33.0 ± 4.4	16.0
20	39.1 ± 9.1	41.3 ± 2.5	38.5 ± 1.1	36.9 ± 5.2	38.4 ± 1.1	43.6 ± 5.6	39.6 ± 4.8	18.0
40	45.4 ± 9.2	47.5 ± 2.2	44.6 ± 1.1	42.6 ± 5.1	45.3 ± 1.0	49.5 ± 5.8	45.8 ± 4.8	18.3
60	50.0 ± 8.8	52.2 ± 3.2	50.0 ± 1.5	47.4 ± 5.2	50.3 ± 1.1	54.4 ± 5.4	50.7 ± 4.7	17.5
RDT method, Suppository B, 38.0 °C								
10	48.2 ± 4.0	45.6 ± 5.9	45.0 ± 2.9	43.2 ± 1.1	45.3 ± 1.6	50.2 ± 5.7	46.3 ± 4.2	13.1
20	85.3 ± 1.8	86.3 ± 5.3	82.1 ± 2.6	79.9 ± 2.7	84.6 ± 4.1	87.6 ± 4.9	84.3 ± 4.1	15.8
40	98.3 ± 1.6	100.3 ± 2.1	100.2 ± 2.6	98.5 ± 1.9	100.3 ± 1.9	100.1 ± 3.1	99.6 ± 2.1	6.2
RDT/TAP method, Suppository B, 38.0 °C								
10	62.7 ± 4.4	60.9 ± 5.1	60.1 ± 1.1	62.0 ± 4.6	61.2 ± 5.2	61.0 ± 2.3	61.3 ± 3.5	11.8
20	94.4 ± 0.8	93.1 ± 1.2	93.3 ± 2.5	94.6 ± 1.0	94.6 ± 1.1	94.7 ± 0.3	94.1 ± 1.3	5.2
40	98.8 ± 2.4	98.8 ± 1.6	99.4 ± 1.3	99.3 ± 2.2	99.5 ± 2.3	99.7 ± 1.8	99.3 ± 1.7	4.5

[a] Mean ± SD of four repeats collected by each operator.
[b] Mean ± SD of 24 values obtained from six operators. Release values are not listed after ⩾95% release are obtained or after plateau values are achieved.
[c] Difference between the maximum and minimum values ($n = 24$) at each sampling time.

reciprocating dialysis tube with tapping method predicted rectal absorption better than in the original RDT method.

The release of suppository B at 37.0 and 38.0 °C from the RDT method (with or without tapping) is shown in Fig. 3 and in Table 1. In general, the release of acetaminophen from suppository B is dependent on temperature but not periodic tapping. For both methods, the release rates at 37.0 °C were much slower than 38.0 °C, and no substantial difference was observed in the release at 37.0 and at 38.0 °C either with or without periodic tapping. Two profiles at 38.0 °C achieved >90% release by 20–40 min, while about 50% was not released from the remaining two profiles (at 37.0 °C) by 40–60 min. At 37.0 °C, additional time did not increase the release substantially, and the release by 180 min was limited to 60–70% (Fig. 3). For suppository B, the influence of rectal temperature on in vivo absorption was large in our previous study in rabbits [6]. C_{max} and AUC in the hypothermal rabbits (37.1 °C rectal temperature) were 35.0 and 64.4% of the corresponding values in normal rabbits (38.5 °C rectal temperature), consistent with lower release rates for both methods at 37.0 °C.

Inter- and intra-assay variations of the release from the reciprocating dialysis tube with tapping method are lower than those for the original RDT (Table 1). The percent differences between the maximum and minimum values in 24 replicates (Δ%) are shown in Table 1. Table 2 lists the

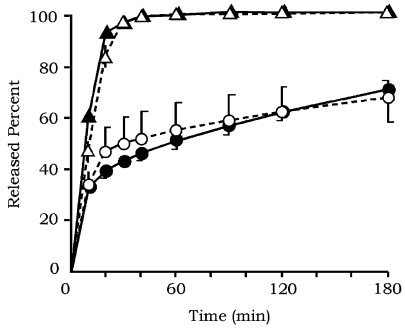

Fig. 3. Effect of periodic tapping on the release profiles of suppository B: (○) without tapping at 37.0 °C; (●) with tapping at 37.0 °C; (△) without tapping at 38.0 °C; (▲) with tapping at 38.0 °C. Symbols represent mean ± D ($n = 24$).

results of *F*-test (Bonferroni) on the variance ratios between the original RDT and the reciprocating dialysis tube with tapping method. The reciprocating dialysis tube with tapping method showed smaller variances in all the cases, some of those were statistically significant ($p < 0.05$; Table 2). No significant difference was reported for the variance ratios for suppository B at 37.0 °C, due to higher variability for the reciprocating dialysis tube method (Table 2; Fig. 3). These analyses indicated that the reciprocating dialysis tube with tapping method provided more reliable result than the reciprocating dialysis tube method.

For testing the in vitro release of drug from suppository base, dialysis membranes (several nm pore sizes) could be better than other membranes with large pore sizes (approximately $\geqslant 0.45$ μm). Membranes with larger pore sizes allow not only drug but also dissolved water-soluble base (which contains drug) to pass through the membrane and could over-predict in vivo absorption. Considering that only a small amount of fluid (and with low buffering capacity) exists in the rectum, dialysis membrane with limited residual fluid could better simulate the rectal condition.

Although the dialysis tube method could show good in vitro and in vivo correlation [7], its inter-laboratory reproducibility was thought to be low [8]. We believed that the low inter-laboratory reproducibility could be attributed to the ill-defined procedures used, e.g. the method of removing fluid from dialysis tube, the position of dialysis tube in the reservoir, the method of closing the tube end, the agitation of the release medium, and the sample position. In addition, the design of the dialysis tube apparatus could be the cause of high variability. The melted oleaginous suppository base often floats as oil drops in the tubing. The wrinkles of dialysis tube formed when the end of tube is closed could trap oil drops which could limit drug release.

The addition of mild pressure changes (whether destructive or spreadable) to the RDT method could simulate the in vivo condition. Sakaniwa et al. [9] monitored the anorectal dynamic pressure change in a volunteer. In their report, a pressure change between 20 and 50 mmH_2O during peristalsis was observed every 40–60 s. During the process of periodic tapping, when the closure is lifted from the bottom of a reservoir, the tension to the dialysis tube increases to a maximum and is then released. Assuming no difference in release rate at different dip speeds (30–50 rpm) and weights of closure (5–50 g), the release and building up of tension of the dialysis tube before and after periodic tapping could be more important than setting at a constant tension. In addition, reciprocating movement allows the melted base to spread in the tube which could increase test reproducibility.

This method can also be useful for suppositories with contents that melt at different temperature. Based on differential scanning calorimetric analysis, suppository A and suppository B showed endothermic curves with peaks at 36.0 and 40.0 °C, respectively, i.e. suppository B contains contents with higher melting point than suppository A. Because the viscosity of suppository A at 37.0 °C is higher than that at 38.0 °C, the difference in release between 37.0 and 38.0 °C was observed in the original RDT method. However, in the reciprocating dialysis tube with tapping method, no difference in release between 37.0 and 38.0 °C was observed in the presence of tapping, which resulted in higher fluidity of the melted suppository in the dialysis tube. The suppository containing the base with higher melting point, like suppository B, could result in higher viscosity at lower temperature. This might be the reason why dissolution rate in both the RDT and the reciprocating dialysis tube with tapping methods was low at 37.0 °C. At 38.0 °C, while a portion of the suppository base did not melt, most of the bases melted and fluidized in the dialysis tube. Improvement of inter- and intra-assay variation was achieved by dispersing the melted base in a dialysis tube through periodic tapping.

In humans, the release of acetaminophen is slower than in rabbits, and T_{max} of acetaminophen in humans could vary from 1.0 to 3.0 h depending on the suppository base [10]. With the delay in acetaminophen release from suppository in humans and its expected dependency on rectal temperature, the ability to discriminate the release profiles of

Table 2
F-test of variance ratios between the original RDT method and the RDT/TAP method

Suppository	Temperature (°C)	Time (min)	Variance (RDT)	Variance (RDT/TAP)	Variance ratio
A	37	10	18.05	0.32	55.95[a]
		20	5.55	0.47	11.78[a]
	38	10	2.83	2.22	1.28
		20	4.16	0.37	11.29[a]
B	37	10	15.63	4.18	3.74
		20	55.15	5.81	9.48
		40	69.97	5.73	12.20
	38	10	6.32	0.83	7.62
		20	8.04	0.52	15.52[a]
		40	0.90	0.14	6.46

[a] $p < 0.05$.

acetaminophen suppository by a more reliable testing method will be critical.

In conclusion, the reciprocating dialysis tube with tapping method increased the reproducibility and predictability of the release of drug from suppository base. Therefore, the reciprocating dialysis with tapping method could represent a simple and robust test for evaluating in vitro release/dissolution for suppositories.

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