Studies on Uniformity of the Active Ingredients in Acetaminophen Suppositories Re-solidified after Melting under High Temperature Conditions

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The target of the present pharmaceutical study was the antipyretic analgesic, acetaminophen; its suppository form is usually split when used in pediatric patients. We focused on the active ingredient uniformity in these products, which were re-solidified after melting under high temperature condition. When sections of the cut surfaces of the seven acetaminophen suppository products (SUP-A–G) commercially available in Japan were visualized by polarized microscopy, acetaminophen crystals that were dispersed in the base were identified. The results of the quantitative determination of agent concentration for each cut portion (mg/g) suggested uniform dispersion of these crystals in the base of each product. The agent concentration in each portion of the suppositories that was re-solidified after melting at high temperatures was measured. Segregation of the active ingredient was observed in four products at a temperature of 40°C for 1 h, while active ingredient uniformity was maintained in the other three products (SUP-C, SUP-F and SUP-G). The latter three products also showed high viscosity at 40°C. At 50°C for 4 h, only the uniformity of the active ingredient in SUP-C was maintained. These results suggest that the uniformity of the active ingredient is lost in some acetaminophen suppositories that were re-solidified after melting under high temperature conditions. The degree of loss varies depending on the product.

Key words suppository; acetaminophen; uniformity; re-solidification; rheology; hard fat

Rectal suppositories (suppository), due to their local and systemic effects, are suitable for pediatric patients who cannot take drugs orally and for patients who cannot swallow. Additionally, suppositories have an advantage in that they can be used to possibly avoid aggravating gastrointestinal disorders and to circumvent the hepatic first-pass effect. In pediatric areas of Japan, suppositories are split when used (such as into 2/3 or 1/2 before use), depending on the weight of the patient. In these cases, it is essential that the active ingredient is dissolved or dispersed uniformly in its base. Oleaginous bases (e.g. hard fat) melt at nearly body temperature after insertion into the anus, and thus release the active ingredient into the rectal cavity. The instructions on the outer casing of the acetaminophen suppositories actually encourage patients to store them at 30°C or less. However, since suppositories can occasionally be stored at temperature greater than body temperature during the summer in user’s home, there is a possibility of pharmaceutical change due to melting. Even if the atmospheric temperature is not so high, for example, when a suppository has been left inside a car, melting of base can still occur because the internal temperature of the car is likely to rise. It has been reported the active ingredient acetaminophen, an antipyretic analgesic, is uniformly dispersed in suppositories sold in Japan. If the base is re-solidified after melting in a state such that the uniformity of the agent is lost, the split ratio of the active ingredient in the suppository is considered no longer accurate, even if the suppository is split as directed by the doctor. As a result, the occurrence of side effects due to an overdose, or worsening of symptoms due to under administration is concerned. Despite this concern, however, there have been no reports on the melting of a suppository base at high temperatures, and its effects on the drug’s active ingredient uniformity point of view of pharmaceutical sciences. For the steroidal ointment products, we have evaluated the distribution of the main agent and additives in steroidal ointment products by the polarization microscope or micro infrared spectroscopy. In the present study, we investigated active ingredient uniformity and pharmaceutical properties in acetaminophen suppositories, which was influenced under high temperature.

Experimental

Materials The 200mg innovator acetaminophen suppository products Alpininy Suppositories (lot. 30106, SUP-A), Anhiba® (lot. 22082YQ1, SUP-B) and Calonal® Supp. (lot. 3286K, SUP-C) were obtained from Hisamitsu Pharmaceutical Co., Inc. (Tokyo, Japan), Abbott JAPAN Co., Ltd. (Tokyo, Japan), and Showa Yakuhin Kako Co., Ltd. (Tokyo, Japan), respectively. The 200mg generic acetaminophen suppository products Paraceta® Supp. (lot. 004701, SUP-D), Acetoaminophen Suppositories 200mg for Pediatric [Tanabe] (lot. U009, SUP-E), Aphiogon Supp. (lot. 908021, SUP-F) and Acetaminophen Supp. for Pediatrics [TYK] (lot. W0311, SUP-G) were obtained from Nippon Shinyaku Co., Ltd. (Tokyo, Japan).
Japan), Choseido Pharmaceutical Co., Ltd. (Tokyo, Japan), Nissin Pharmaceutical. (Yamagata, Japan) and Taisho Pharm. Ind., Ltd. (Tokyo, Japan), respectively. VOSCO® H-15 (H-15) and VOSCO® E-75 (E-75), the hard fats, were obtained from Maruishi Pharmaceutical Co., Ltd. (Osaka, Japan). The acetaminophen and all other reagents used were of reagent-grade obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan).

A Study of Active Ingredient Uniformity in Suppositories

To evaluate active ingredient uniformity of the suppositories in the present study, we defined each part of the suppository as shown in Fig. 1. We labeled the side to be inserted into anus the “tip side,” and the other side, “tail side.”

The suppository is divided into four parts from its tip side. Each portion and cut surface is defined as P1–P4 and S1–S3, respectively. The length of each portion was approximately 5 mm.

Acetaminophen suppositories (three innovator products and four generic products, Table 1) were placed in a thermostatic container (1.35 mL \( \times \) 40 mm) set to permeation mode at 500 \( \mu \text{m} \) magnification. Each portion slice (S1–S3) was put on a microscope slide with a cover slip to observe the dispersion of the acetaminophen crystals.

Preparation of the Model Acetaminophen Suppository Product (200 mg)

The hard fat (18.0 g) was mixed at several different ratios of H-15:E-75, and melted in a thermostatic bath at 50°C. Acetaminophen powder (3.0 g) was added slowly to the melted hard fat, while stirring well with a magnetic stirrer. The stirring was continued at 38–40°C until the hard fat that acetaminophen was dispersed in filled the plastic suppository container (1.35 mL × 15 containers, Maruishi Pharmaceutical Co., Ltd. Osaka, Japan)). Then, they were cooled at room temperature (25°C) with the tip side down. After confirming the solidification, the products were stored at 4°C until used in the dissolution test.

Dissolution Test for the Acetaminophen Suppositories

The dissolution tests were carried out by the PTSW-type rotating dialysis cell method (PTSW-J, Pharma Test, Hamburg, Germany). One hundred milliliters of saline was used as a dissolution medium. The test was performed at a rotary speed of 100 rpm at 37.0±0.5°C or 41.0±0.5°C. An aliquot (10 mL) of the dissolution medium was withdrawn from the vessel using a pipette at appropriate time intervals for 3 h. The same volume (10 mL) of fresh medium was added to the dissolution medium after each sampling.

The agent concentrations in the dissolution at each time point were assayed spectrophotometrically at 242 nm after a 40-fold dilution with saline. The dissolution rates (%) were calculated as a percentage of obtained active ingredient dissolution volume (mg) to the label amount of acetaminophen (200 mg).

Determination of Rheological Characteristics

Flow curves of shear rate against shear stress were obtained using a viscometer (TV-30; Toki Sangyo Co., Ltd., Tokyo, Japan). The temperature of the base plate was 40±0.1°C. The shear rate ranged from 10 to 200 s\(^{-1}\).

Evaluation of Precipitation Properties of Acetaminophen

The model products for the precipitation test were created thus. The hard fats which were melted in a thermostatic bath at about 50°C were filled to the horizontal line of

Table 1. Pharmaceutical Information of Acetaminophen (200 mg) Suppository Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Pharmaceutical ingredients</th>
<th>Length of product (mm)</th>
<th>Weight of product (g)</th>
<th>LA/M((^{a})) (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Innovator</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUP-A</td>
<td>Hard fat</td>
<td>23.3</td>
<td>1.2</td>
<td>166.7</td>
</tr>
<tr>
<td>SUP-B</td>
<td>Hard fat</td>
<td>25.5</td>
<td>1.3</td>
<td>153.8</td>
</tr>
<tr>
<td>SUP-C</td>
<td>Hard fat</td>
<td>24.4</td>
<td>1.15</td>
<td>173.9</td>
</tr>
<tr>
<td><strong>Generic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUP-D</td>
<td>Hard fat</td>
<td>25.5</td>
<td>1.3</td>
<td>153.8</td>
</tr>
<tr>
<td>SUP-E</td>
<td>Hard fat</td>
<td>25.1</td>
<td>1.3</td>
<td>153.8</td>
</tr>
<tr>
<td>SUP-F</td>
<td>Hard fat</td>
<td>25.5</td>
<td>1.2</td>
<td>166.7</td>
</tr>
<tr>
<td>MCT(^{b})</td>
<td>Silicic anhydride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUP-G</td>
<td>Hard fat</td>
<td>26.1</td>
<td>1.2</td>
<td>166.7</td>
</tr>
<tr>
<td>MCT(^{b})</td>
<td>Silicic anhydride</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) LA/M, Label amount of acetaminophen (200 mg) per mass of product (g). \(^{b}\) Medium-chain triglyceride.
the aforementioned plastic suppository containers (3 cm from the tip, Fig. S1ab), and cooled at room temperature (25°C). After confirming the solidification of the base, acetaminophen powder (20 mg) was added uniformly to the base surface (Fig. S1c). Then additional melted base was added to the top of the tail side (Fig. S1d), and cooled at room temperature (25°C) with the tip side down. After confirming the solidification, the products were stored at 4°C until used in the following experiments.

The model products were placed in a thermostatic bath with tip side down and left under high temperature conditions (40°C) for 3 h (Fig. S1e). The precipitated amount of the active ingredient (mg) at a site 1 cm from the tip was assayed spectrophotometrically at 250 nm after a 40-fold dilution by 99.5% ethanol (Fig. S1f).

**Statistical Analysis** In the evaluation of the uniformity of acetaminophen for commercial suppositories, the significance of the difference between theoretical and measured acetaminophen concentration of each portion of commercial suppository products was determined using the one sample t-test. In the evaluation of affects on the uniformity by heating, significance of the difference of acetaminophen concentration between intact and re-solidified products was determined using the unpaired t-test. In the precipitation test, the significance of the difference among the means of more than three groups was determined using a one-way ANOVA test followed by a modified Fisher’s least-squares difference method.

A p value of less than 0.05 was considered to be statistically significant.

**Results**

**Uniformity of the Active Pharmaceutical Ingredient of Acetaminophen Suppository Products** First, the theoretical concentration of the active ingredient was determined in the acetaminophen suppositories to evaluate active ingredient uniformity in following experiments. The values were obtained by dividing the label amount of acetaminophen (200 mg) by the mass of products (g) (LA/M; Table 1). No significantly differences were observed between LA/M values and the acetaminophen concentration in each portion of all suppository products.

In the evaluation of affects on the uniformity by heating, significance of the difference of acetaminophen concentration between intact and re-solidified products was determined using the unpaired t-test. In the precipitation test, the significance of the difference among the means of more than three groups was determined using a one-way ANOVA test followed by a modified Fisher’s least-squares difference method.

A p value of less than 0.05 was considered to be statistically significant.

![Graphs](image-url)

**Fig. 2. The Concentration of Acetaminophen in Each Portion of the Suppository Products**

(a) SUP-A, (b) SUP-B, (c) SUP-D and (d) SUP-E. □, intact; ■, exposed at 40°C for 1 h. Each bar indicates the mean±S.D. (n=3). The dashed-line indicates label amount per mass of product (mg/g). *p<0.05, **p<0.01, significantly difference vs. intact (unpaired t-test).
products (one sample t-test, Table 1, Figs. 2, 3).

In SUP-A, SUP-B, SUP-D and SUP-E, that had been re-solidified after melting at 40°C/1 h, acetaminophen concentrations of the portion near the tip and tail side were observed to be higher and lower respectively, when compared with each portion of intact suppositories (Fig. 2). However, in SUP-C, SUP-F and SUP-G as shown in Fig. 3, the concentrations in each portion of re-solidified products was not different from that of intact products (Table 1, Figs. 2, 3). In only P4 of SUP-C, the concentration of acetaminophen in re-solidified products was slightly lower than that in intact products (Fig. 3(a)). Although it is statistically significant, we considered that the uniformity is maintained in this condition. These three products were thus studied further under melting conditions of 50°C/4 h. Segregation was observed in SUP-F and SUP-G, but not in SUP-C (Fig. 3). In the SUP-C, the concentration of acetaminophen of each portion was not significantly different from that of intact products, indicating the preservation of active ingredient uniformity (Fig. 3(a)).

**Polarization Microscopy and PXRD** In each cut surface section (S1–S3) of all intact acetaminophen suppository products, it was observed that acetaminophen crystals with the size of approximately 20–50 µm were dispersed in the oleaginous base from the polarization microscope (PMS) (Fig. 4(a), SUP-A only indicated). By PXRD, a diffraction peak attributable to acetaminophen was observed in each section (Fig. 4(a)). The PMS image showed decreased acetaminophen crystals in the S3-section (Fig. 1) of SUP-A at 40°C/1 h (Fig. 4(b)). At 50°C/4 h, the crystals in S3 disappeared completely, as did the diffraction peak in the PXRD (Fig. 4(c)). In SUP-C, the crystals were visualized in each cut section (S1–S3) and a diffraction peak attributable to acetaminophen was observed.

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**Fig. 3. The Concentration of Acetaminophen in Each Portion of the Suppository Products**

(a) SUP-C, (b) SUP-F and (c) SUP-G. □ intact; ■ exposed at 40°C for 1 h; ▲ exposed at 50°C for 4 h. Each bar indicates the mean±S.D. (n=3). The dashed line indicates label amount per mass of product (mg/g). *p<0.05, **p<0.01, significantly different vs. intact (unpaired t-test).
under the same conditions of 50°C/4h. These results show the good correlation with the results of the quantitative determination described above (Fig. 4(d)).

Evaluation of Precipitation Property of Acetaminophen

The precipitation test was conducted using the model suppository products with acetaminophen (20mg) localized in tail side (Fig. S1). H-15 and E-75 were mixed in several ratios respectively; 100:0, 80:20, 70:30, 60:40, 50:50. In ratios of up to 30% E-75 (H-15:E-75=70:30), acetaminophen had almost completely precipitated to the tip side (approximately 20mg). The precipitation amount was significantly reduced at ratios of 40% E-75 (H-15:E-75=60:40, approximately 12mg), and more reduced at 50% (H-15:E-75=50:50, less than 1mg) (Fig. 5).

Determination of Rheological Characteristics of Commercial and Model Acetaminophen Suppository Products

Figure 6(a) shows the flow curves for the acetaminophen suppositories. Viscosity values at a shear rate of 200 s$^{-1}$ for SUP-A, SUP-B, SUP-C, SUP-D, SUP-E, SUP-F and SUP-G were 4.17, 4.65, 4.95, 4.21, 4.34, 4.85 and 5.23 mPa·s, respectively.

In the model products made from mixtures of H-15 and E-75, the viscosity values at a shear rate of 200 s$^{-1}$ increased depending on ratio of E-75 (Fig. 6(b)).

Microscopic Observations of Acetaminophen Suppositories at Elevated Temperatures

The melting behavior of acetaminophen suppositories was observed with a polarized microscope equipped with a hot stage (Fig. 7). In the case of SUP-A at 30°C, as shown in Fig. 7(a), there were both obvious and ambiguous crystal structures, indicated by solid and dashed-line circles respectively. The former and the latter are derived from acetaminophen and hard fat, respectively. Although the acetaminophen crystals were identified clearly, the crystals derived from hard fat disappeared when the temperature was increased to 37 and 40°C, due to melting (within dashed-line circle in Figs. 7(b), (c)). Similar images were also
observed in SUP-C, SUP-B, SUP-D and SUP-E (Fig. S2).
As shown within dashed-line circle in Fig. 8, the ambiguous crystal images derived from hard fat were observed at 37°C for SUP-F and SUP-G, indicating that the hard fat had not completely melted at this temperature (SUP-C is shown for reference).

The Dissolution Test of Commercial Acetaminophen Suppositories
In the seven intact products, the dissolution rate of SUP-A, SUP-B, SUP-C, SUP-D and SUP-E was about 100% in 3 h; the rates at 1 h were also very similar (Table 2, Fig. 9). The dissolution profiles of SUP-F and SUP-G however were distinctly different, as their dissolution rates were both approximately 20% in 3 h (Table 2, Fig. 9).

The Dissolution Test of Model Acetaminophen Suppositories
The dissolution rate of the model suppository made from H-15 was approximately 100% in 3 h (Table 2, Fig. S3). Similar dissolution profiles were obtained in high dose (500 or 800 mg) acetaminophen suppositories (as would be seen in hospitals). The dissolution rate of the model suppository made from E-75 was approximately 20% in 3 h, a profile similar to the profiles of SUP-F and SUP-G (Table 2, Fig. 10). When the dissolution test was conducted at 41°C for these three products, the dissolution rates in each product were improved markedly (approximately 100% in 3 h, Table 2, Fig. 10).

Discussion
The target of this pharmaceutical study was the antipyretic analgesic, acetaminophen, in its suppository form, which is often split for pediatric use. We focused on uniformity of the active ingredient in the re-solidified products after melting under high temperatures. When the cut surfaces of sections of the seven acetaminophen suppositories sold in Japan were visualized by polarized microscopy, acetaminophen crystals could be seen dispersed in the base (Fig. 4(a), SUP-A only indicated). The quantitative results of the active ingredient concentration (mg/g) also indicate that there is uniform dispersion in each of the four portions of the intact products (Fig. 1). These results are consistent with the ones reported by Tayama et al.6)

It is important to measure the concentration of the active ingredient in portions of the suppositories after they are melted under high temperature conditions and re-solidified, to ensure there is little pharmaceutical change. At 40°C/1 h, conditions approximate to leaving the products at room temperature during a summer day, the precipitation of acetaminophen to the tip side was observed qualitatively and quantitatively for SUP-A, SUP-B, SUP-D and SUP-E. This tendency was most pronounced in SUP-A (Figs. 2, 4(a)–(c)). The uniformity of the active ingredient was maintained in SUP-C, SUP-F and SUP-G (Fig. 3). The uniformity of SUP-C was maintained not only at 40°C/1 h but also 50°C/4 h, an even higher temperature
condition (Figs. 3(a), 4(d)). Therefore, it can be concluded that active ingredient uniformity in SUP-C, SUP-F and SUP-G is relatively insensitive to temperature, with SUP-A likely being the most affected. Especially for patients that split the acetaminophen suppository before use, it is recommended that they store the acetaminophen suppositories sensitive to high temperatures in a cold place. Hospitals and pharmacies that stock acetaminophen suppositories need to pay similar attention. In some of the commercial acetaminophen suppositories that re-solidified after melting, the uniformity of the active ingredient was lost, and the degree of loss was observed to vary depending on the product.

According to the Stokes’ law, a terminal velocity when the small particles to settle in the fluid depends on the par-

Table 2. Results of the Dissolution Tests of Acetaminophen Suppository Products

<table>
<thead>
<tr>
<th>Test temperature</th>
<th>Products</th>
<th>Dissolution rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 h</td>
</tr>
<tr>
<td>37°C</td>
<td>SUP-A</td>
<td>74.69±6.49</td>
</tr>
<tr>
<td></td>
<td>SUP-B</td>
<td>73.33±1.37</td>
</tr>
<tr>
<td></td>
<td>SUP-C</td>
<td>82.19±4.19</td>
</tr>
<tr>
<td></td>
<td>SUP-D</td>
<td>72.99±9.70</td>
</tr>
<tr>
<td></td>
<td>SUP-E</td>
<td>74.51±7.18</td>
</tr>
<tr>
<td></td>
<td>Model product made from H-15</td>
<td>84.16±9.06</td>
</tr>
<tr>
<td></td>
<td>SUP-F</td>
<td>10.19±1.66</td>
</tr>
<tr>
<td></td>
<td>SUP-G</td>
<td>10.54±3.89</td>
</tr>
<tr>
<td></td>
<td>Model product made from E-75</td>
<td>7.20±1.09</td>
</tr>
<tr>
<td>41°C</td>
<td>SUP-F</td>
<td>71.43±15.10</td>
</tr>
<tr>
<td></td>
<td>SUP-G</td>
<td>67.90±9.87</td>
</tr>
<tr>
<td></td>
<td>Model product made from E-75</td>
<td>67.02±10.24</td>
</tr>
</tbody>
</table>

Each value indicates the mean±S.D. (n=3).
Particle size, particle density, fluid density and fluid viscosity, and there is an inverse relationship between the viscosity of a fluid and terminal velocity. Thus, it is hypothesized that maintaining the viscosity of the suppository base at melting temperatures is one way to maintain the uniformity of the active ingredient. We conducted viscosity measurements of acetaminophen suppositories that were melted at 40°C in order to consider this. SUP-A showed the most prominent active ingredient segregation after melting, and had the lowest viscosity. The uniformity of active ingredient in SUP-C, SUP-F and SUP-G, was maintained at 40°C/1h, and these products had high viscosity (Fig. 6(a)). These results demonstrate that the viscosity of the base preserves active ingredient uniformity after melting at high temperatures. In addition, the base of SUP-F and SUP-G was observed to have not completely melted at 37°C by the hot stage polarized microscope (within dashed-line circle in SUP-F and SUP-G of Fig. 8), and the dissolution properties of the active ingredient for these products were clearly lower than for the other products (Table 2, Fig. 9). The different dissolution profiles of acetaminophen suppository products were reported by studies that used a flow-through cell method. Takatori et al. reported that mixed-base suppositories could regulate drug release by changing the viscosity of their solid fats. Realdon et al. also showed that the dissolution rate of the active ingredient was increased when the viscosity of the melting base was low by studying viscosity and the active ingredient dissolution properties of acetaminophen model suppositories that were made from a mixture of hard fat and Tween-series surfactant. Therefore, it was suggested that SUP-F and SUP-G have indicated high viscosities due to their high melting points (nearly 37°C), which then lead to their low dissolution profiles compared to other products. The high viscosity of SUP-F and SUP-G is considered as the one of factors that maintains the uniformity of the active ingredient when exposed to high temperature conditions (40°C/1h). There is concern that there might be a delay of efficacy with products that have low dissolution profiles. However, bioavailability is influenced not only by
the dissolution properties of the active ingredient but also by the interaction between the suppository and the rectal membrane, or the interaction between the lipophilic excipient of surfactant and the suspended agent particles. Therefore, the poor dissolution properties of SUP-F and SUP-G do not affect agent efficacy, because they contain medium-chain triglycerides (MCT) which have surface activity (Table 1). SUP-C, the only product whose active ingredient uniformity was maintained at 50°C/4h (Fig. 3(a)), was completely melted during polarized microscopic observation at 37°C (Fig. 8), although it continued to have high viscosity at 40°C (Fig. 6(a)). Additionally, a poor dissolution profile was not observed for SUP-C (Fig. 9). These results suggest that the high viscosity of SUP-C is maintained by a different factor than in SUP-F and SUP-G, such as the presence of additives not listed in the accompanying document or the interaction between the base and acetaminophen. In the present study, the investigations were carried out mainly from the perspective of the rheology. It is considered that the other factors are also involved in the settling of the agent crystal as mentioned above.

The hard fat in the oleaginous base is a mono-, di- and triglyceride mixture of saturated fatty acids having 12 to 18 carbons, generally known as H-15, E-75 and S-55. H-15 is most frequently used, and its melting point is 33.5–35.5°C. E-75 is used when the lower melting point of the drug causes a compounding melt point depression, where the total melting point of the product is lower due to the combination of low melting points of the drug and the base, because the melting point of E-75 is 37–39°C, which is higher than body temperature. Since there was shown to be a relationship between the viscosity of the melted base and the active ingredient uniformity of the re-solidified suppositories, we performed a precipitation test of acetaminophen, using a model products consisting of H-15 and/or E-75, with acetaminophen (20 mg) localized to the tail side (Fig. S2). For a mixed base, the precipitation level of acetaminophen was reduced with an increasing ratio of E-75 (Fig. 5). The viscosity of the base at 40°C is also increased by increasing the ratio of E-75 (Fig. 6(b)), indicating that the viscosity of the base reduces the amount of precipitation. These results suggest that to keep the viscosity of the molten base is leading to the formation of optimal suppository. And these results confirm that active ingredient uniformity is maintained by high viscosity in SUP-C, SUP-F and SUP-G. The dissolution profile of the model product with E-75 was very similar to that of SUP-F and SUP-G (Fig. 10). When the dissolution test was carried out at 41°C for model and commercial acetaminophen suppository products, the rates of the three products were increased, and the profiles were similar to one another (Table 2, Fig. 10).

Some reports have verified the role of additives in controlling sustained active ingredient dissolution from the base, including: solid fats such as the polyglycolcer ester of fatty acids, lecithin, sucrose fatty acid ester, carboxyvinyl polymer, xylloglucan gels, and polyvinyl alcohol hydrogel. However, the only inactive pharmaceutical ingredient in the five products (Table 1; SUP-A, SUP-B, SUP-C, SUP-D and SUP-E) is hard fat. In SUP-F and SUP-G, which have low dissolution profiles, SiO₂ and MCT were added in addition to the hard fat, but only the number of carbon atoms in the fatty acid was less (Table 1). So it is unlikely that the additives described above were used in these products. Iwata et al. examined active ingredient dissolution properties in a model suppository product containing diclofenac sodium, and reported that the dissolution profile was reduced when using a high mixing ratio of hard fat that had a high melting point. Thus, it is suggested that the hard fat used as the base in SUP-F and SUP-G has high melting point (that is, it has similar properties to E-75).

**Conclusion**

We verified the pharmaceutical uniformity of seven commercial acetaminophen suppository products that were re-solidified after melting under high temperature conditions. At 40°C/1h, the uniformity of acetaminophen for four products (SUP-A, SUP-B, SUP-D and SUP-E) was lost, and the degree of loss varied depending on the product.

In the remaining three products (SUP-C, SUP-F and SUP-G), it is suggested that the high viscosity at melting is the one of factors that maintained the uniformity of the active ingredient after exposure to high temperature conditions (40°C/1h).

At 50°C/4h, the only uniformity of the active ingredient of SUP-C was maintained. The dissolution of the active ingredient was also equivalent to other four products (SUP-A, SUP-B, SUP-D and SUP-E). Thus, SUP-C was found to be the least affected by melting under high temperature conditions.

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**Conflict of Interest** The authors declare no conflict of interest.

**Supplementary Materials** The online version of this article contains supplementary materials.

**References**

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