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# Examination of factors that delay the elution of acetaminophen from over-the-counter drugs

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The information on the stability of medications is important to secure their quality. There is, however, little information about the stability of medications which assume to be kept by patients and customers. We previously showed that a delay in drug release occurs in some over-the-counter (OTC) drugs following storage in a high temperature, high humidity environment. In this study we prepared model tablet formulations containing an active ingredient and excipients to investigate the cause of this delayed release. The results reveal that delayed release occurs in preparations compounded with acetaminophen (AA) as the active ingredient and erythritol (ET) and crospovidone (CP) as excipients. In addition, ET deliquesces in a high humidity environment, then incorporates other particles during room temperature storage to form an aggregate. SEM observations and micropore distribution measurements conducted on OTC tablets that exhibit delayed release revealed that the number of intraparticle pores decreased after storage under high temperature, high humidity conditions. Thus, the delayed release by these pharmaceutical product formulations may be due to a change in the micropore structure both on the surface and within the particles, thereby decreasing the solvent infiltration pathways leading to the interior of the preparation.

## 1. Introduction

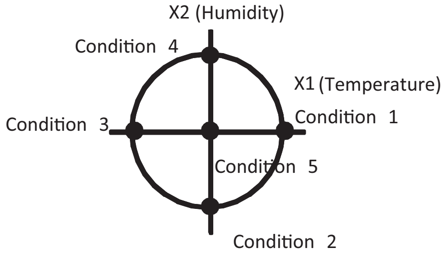
Over-the-counter (OTC) drugs are convenient medications since they can be purchased from pharmacies and retail stores at the discretion of patients and customers. A seller registration system was introduced in Japan in June 2009 through a revision in the Pharmaceutical Affairs Act, thus enabling customers to purchase most OTC drugs without going through a pharmacist.

One study reported that 50 of 281 patients (17.8%) responded that they did not read the package insert after purchasing an OTC drug (Shimizu et al. 2005). Moreover, 58.1% of the patients responded that they understood the “Precautions for Storage and Handling” printed on the package insert or the exterior package “very well or well”. In response to the question concerning which parts of the package insert the patients had read, 143 reported reading the “Dosage and Administration”, 140 reported reading the “Indications”, and 94 reported reading the “Precautions for Use”, but only 8 reported reading the “Storage Conditions”. Therefore, it appears that few patients pay attention to the storage conditions after purchasing OTC drugs. Furthermore, we can assume that most purchasers interpret the expiration date in the same manner as the “best if used by” designation for food products, and believe that no problems will result from taking a medication before an expiration date, regardless of its state or appearance (Shimizu et al. 2005).

Relatively few OTC drugs (tablets) in Japan are packaged in push-through packages (PTP); rather, most are packaged in resealable glass or plastic bottles (Kodama 2008). Moreover, most orally disintegrating tablets can be provided as single dose preparations as uncoated tablets (Sagawa 2008). Many people, however, have no misgivings about storing an uncoated drug tablet in a pill box, and it has been pointed out that patients have a low level of awareness about drug product quality. It has therefore been proposed that information on how to maintain the quality of opened drug products be provided to patients (Nishioka 2003).

The Ministry of Health, Labour and Welfare (MHLW) in Japan has suggested the need for active intervention by pharmacists to promote the proper use and storage of OTC drugs (MHLW 2002). Unlike prescription drugs, however, there have been few reports of test data relating to the stability of OTC drugs. Moreover, unlike prescription drugs that contain a new active ingredient, after the stability tests required for the new drug application have been completed, providing data from stress tests and accelerated aging tests of OTC drugs that contain a previously approved active ingredient is left up to the applicant (Japan Pharmacists Education Center, 2008). Because data concerning the properties of OTC drug product formulations are scarce, and little information is provided to pharmacists by drug manufacturers, collecting data in a straightforward manner as in the case of prescription drugs has proven extremely difficult. Therefore, we believe that revealing the properties of OTC drug products and compiling data on their quality can be very helpful for the proper use of OTC drugs.

OTC drugs containing acetaminophen (AA) can be sold in Japan by a registered seller other than a pharmacist as a Class 2 pharmaceutical product. AA is approved for indications of pain such as headache and menstrual pain, as an antipyresis to relieve




| Condition | X1 | X2 | °C | RH (%) |
|---|---|---|---|---|
| 1 | $\sqrt{2}$ | 0 | 80.0 | 68.0 |
| 2 | 0 | $-\sqrt{2}$ | 50.0 | 40.0 |
| 3 | $-\sqrt{2}$ | 0 | 20.0 | 68.0 |
| 4 | 0 | $\sqrt{2}$ | 50.0 | 95.0 |
| 5 | 0 | 0 | 50.0 | 68.0 |

Fig. 1: Design of the composite experiment for evaluating the results of dissolution tests on tablets

chills and fever, and in the field of OB-GYN. Consequently, AA is used by many adults. OTC drugs containing AA are available as conventional tablets, orally disintegrating tablets, and suppositories. The market for oral rapidly disintegrating tablets has expanded sharply because the bitter flavor of AA can be masked by pharmaceutical formulation techniques (Suzuki et al. 2003, 2004). Previously we investigated the relationship between storage conditions and physico-pharmaceutical stability using AA-containing oral preparations that are universally available, and found that release of the drug in orally disintegrating tablets is delayed under some storage conditions (Ota et al. 2010). In this study we verified the reproducibility of the release behavior of OTC drugs, using preparations with different manufacturing lot numbers from our previous report (Ota et al. 2010). In addition, we investigated the properties of pharmaceutical products that were found to have a delay in drug release by preparing model tablet formulations using excipients contained in all the OTC drugs found to have a delayed release. Dissolution tests, pharmaceutical formulation stability tests, and SEM observations were conducted on these formulations.

## 2. Investigations, results and discussion

### *2.1. Stability of currently marketed AA-containing OTC tablets*

We previously reported that AA release is delayed in some OTC drug products stored under high temperature, high humidity conditions (Ota et al. 2010). Therefore, we retested the release behavior of four OTC drugs using different manufacturing lots. In this report we assigned these OTC drugs the designations A, B, C and D, respectively. To investigate formulation storage conditions, we designed a composite experimental matrix (Iwata et al. 1994; Takayama and Nagai 1991) in which temperature (X1, 20 °C to 80 °C) and humidity (X2, 40 % to 95 %) were varied simultaneously (Fig. 1).

We observed a delay in disintegration and drug release in product formulations A and C under Storage Condition 1 (80 °C, 68 %RH). The amount of dissolution of product formulation A after 30 min was 21.6% (Fig. 2). Liquefaction and other conspicuous visible changes occurred when product formulation A was stored under Storage Condition 4 (50 °C, 95 %RH) and when product formulation D was stored under Storage Conditions 1 and 4. Clearly, these storage conditions are unsuitable for

**Table 1: Formulations of the model tablets**

| Formulation | AA (mg) | ET (mg) | CP (mg) | MT (mg) | Total (mg) | Drug content (%) |
|---|---|---|---|---|---|---|
| A | 50 | 100 | | | 150 | 33.3 |
| B | 50 | 100 | 25 | | 175 | 28.6 |
| C | 50 | | 25 | 100 | 175 | 28.6 |
| D | 50 | 250 | | | 300 | 16.7 |
| E | 50 | 250 | 25 | | 325 | 15.4 |
| F | 50 | | 25 | 250 | 325 | 15.4 |

these product formulations. These findings are similar to those in our previous report (Ota et al. 2010). We also conducted a dissolution test of product formulation A after storage under Storage Condition 1 and then further storage at room temperature for 48 h. The amount of dissolution of product formulation A that had been stored for 24 h (Storage Condition 1) plus 48 h (room temperature) was 26.2 % after 30 min in the dissolution medium, similar to the value obtained immediately after 24 h storage under Storage Condition 1. These findings indicate that the physical or chemical changes that cause the delay of release in product formulation A occur during storage.

Storage Condition 1 simulates the temperature in a parked car in the middle the day in the summer (75 °C) (Ohtagaki and Hioki 2008), and is thus a condition encountered in daily life. As noted above, however, because patients have a low level of awareness about drug product quality, it is believed that factors such as changes in packaging, storage conditions, and handling history, which are not normally anticipated in pharmaceutical formulation design, can have a cumulative effect. We are currently conducting an investigation in a clinical setting concerning changes resulting from packaging, such as the widely used single dose package, and changes resulting from short-term storage. However, because a delay in drug release is a problem directly linked to the absorption and pharmacological efficacy of the drug, we concurrently proceeded with detailed investigations into the mechanism underlying this delay.

### *2.2. Investigation of the delayed release mechanism in model tablet formulations*

#### *2.2.1. Effect of pharmaceutical excipients on drug release*

Because the disintegration of the product formulation and drug release are delayed following storage under high temperature, high humidity conditions, we investigated changes in the crystallinity of AA and other constituents of the formulation using powder X-ray diffraction and differential scanning calorimetry. No pronounced changes between intact (not stored) and stored formulations were found (data not shown). When we examined the package inserts of the OTC drugs and investigated the excipients they contained, we found that both erythritol (ET) and crospovidone (CP) were present in the OTC product formulations that exhibited delayed release. Hence, we prepared model tablet formulations containing two or three components including AA, CP and ET in addition to D-mannitol (MT), and compared with sugar alcohol ET (Table 1). We focused our comparison on the dissolution behavior of active ingredient AA. The dissolution profiles of the model tablet formulations are shown in Fig. 3. In the two component systems (AA/ET) of formulations A and D, no delay in drug release either before or after storage under Storage Condition 1 (80 °C, 68 %RH) was observed. On the other hand, in the three component systems (AA/ET/CP) of formulations B and E, significant decreases in dissolution, similar to those of the OTC product formulations, were found: 56.8% dissolution of formulation B and 85.0%

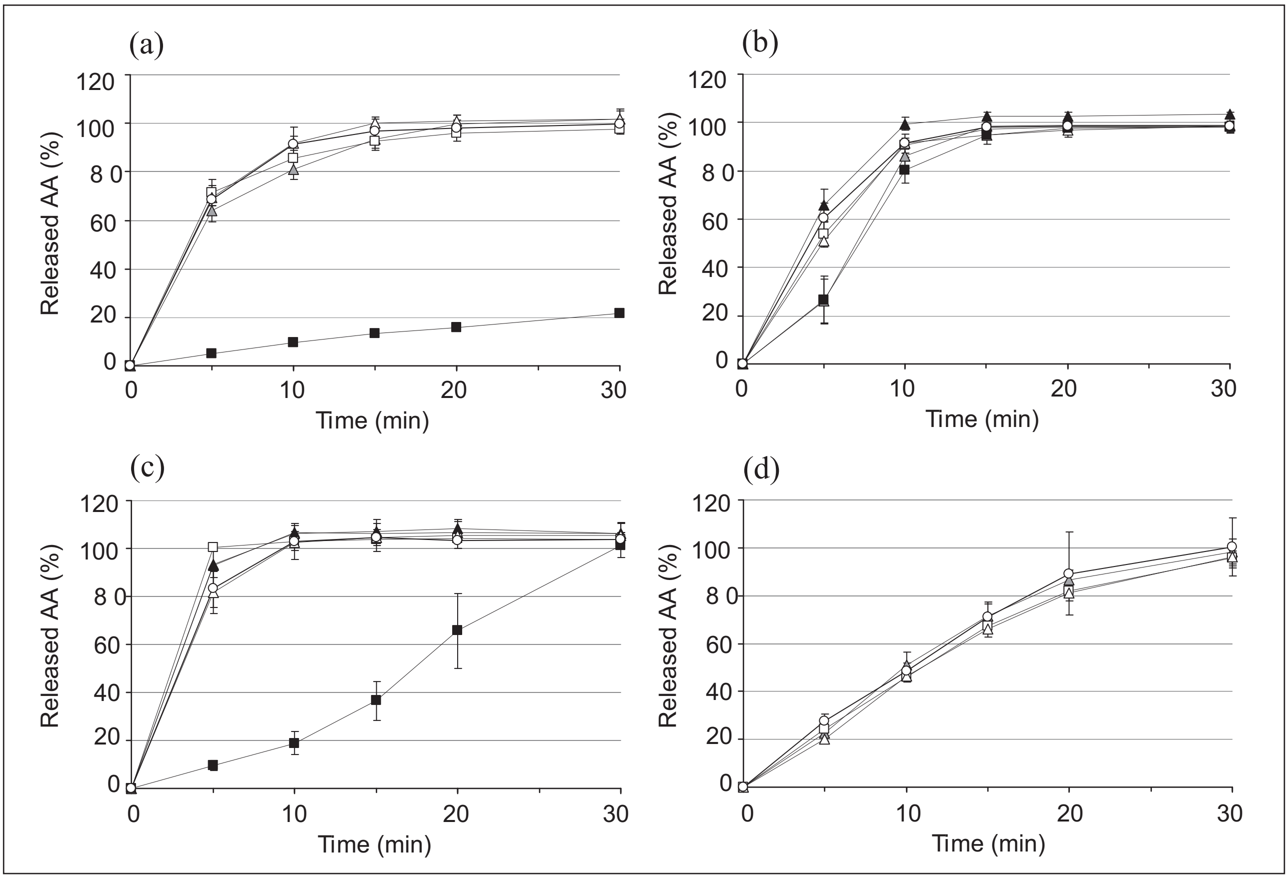



Fig. 2: Dissolution rate profiles of OTC Drugs; (a) OTC tablet A, (b) OTC tablet B, (c) OTC tablet C, (d) OTC tablet D; ○: intact, : Storage Condition 1 (80 °C, 68 % RH), △: condition 2 (50 °C, 40 % RH), : condition 3 (20 °C, 68 % RH), ▲: condition 4 (50 °C 95 % RH), ▲: condition 5 (50 °C, 68 % RH). Each point represents the mean ± S.D. ($n = 6$)

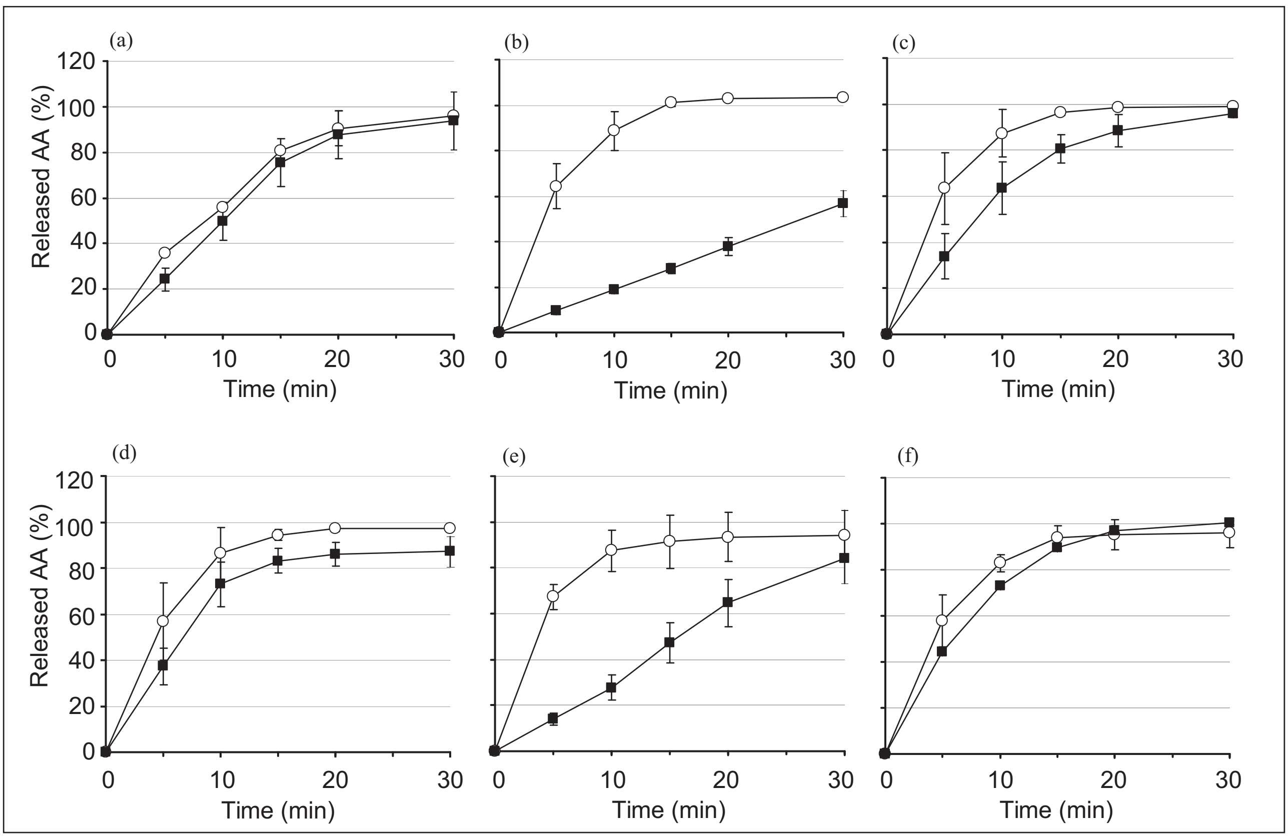



Fig. 3: Dissolution rate profiles of model tablets; (a) formulation A, (b) formulation B, (c) formulation C, (d) formulation D, (e) formulation E, (f) formulation F; ○: intact, : stored (Storage Condition 1). Each point represents the mean ± S.D. ($n = 3$)

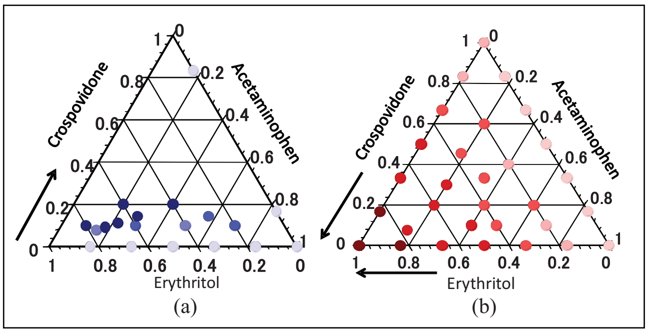



Fig. 4: Triangular phase diagram of model formulation of AA, ET and CP; (a) dissolution rate; ●: < −10%, ●: −10 ∼ −20%, ●: −20 ∼ −30%, ●: > −30%, (b) apparent water sorption rate; ●: > 25%, ●: 15 ∼ 25%, ●: 5 ∼ 15%, ●: 5 ∼ −5%

dissolution of formulation E was obtained after 30 min. Furthermore, in formulations C and F, in which MT was used rather than ET, although a slight drop in dissolution was found immediately after the start of the post-storage dissolution tests, no difference was found after 30 min.

### 2.2.2. *Effect of excipient composition ratio on drug dissolution and hygroscopy*

Model tablet formulations with different composition ratios were prepared using AA, ET and CP for a more detailed investigation of the relationship between the composition ratios of the excipients and dissolution. No large drop in dissolution was found even when the ET content was increased, but a considerable drop occurred with the addition of CP (direction of the arrow in Fig. 4a). Clearly, disintegration and dissolution decreased when both ET and CP were added to AA, and as with the OTC drug products, disintegration of the model tablet formulations was incomplete by the end of the dissolution test (30 min).
In general, the porosity of a formulation increases as the amount of excipients increases. CP creates microscopic voids inside a tablet. The mechanism that weakens the connections within the tablet, causing disintegration, is believed to involve the uptake of moisture into the tablet soon after ingestion, causing the tablet to swell and thus increase the size of the particles (Nakai et al. 1977; Tagawa et al. 2003; Li et al. 2009). It has been reported that at least 80% of the active ingredient is released within 30 min (Li and Sakamoto 2007). Apparently, therefore, the amount of CP in model tablet formulations that exhibit delayed release is sufficient to affect the disintegration properties of CP. However, because delayed release tends to accompany an increase in CP content, it appears that there is an optimal value for disintegrant content. The bulk density and tapped density measurements on CP (Table 2) indicate that the apparent volume of CP is three times that of AA and ET, suggesting that both the mass ratio and the volume ratio of CP in a tablet must be taken into consideration.
The effect of the change in mass between intact and stored formulations on hygroscopy was determined by calculating and plotting the sorption rate for each composition ratio in the model product formulations (Fig. 4b). The results showed that hygroscopy increases as the composition ratios of ET and CP increase (direction of arrow in Fig. 4b). In contrast, no change in mass was found with MT alone or in formulations containing MT as a control (data not shown). For reference purposes, Fig. 5 shows the results of water vapor adsorption measurements conducted at 25 °C for AA, ET, CP, MT, AA + ET (weight ratio 1:1) and AA + CP (weight ratio 1:1). No change in hygroscopy was found for AA and MT (<0.1%), but a sharp increase in hygroscopy at 80 % RH or higher was found for ET, and CP exhibited a change in hygroscopy in response to the relative humidity which encompassed the entire measurement range. In the mixtures containing AA, isotherms for water vapor sorption, which reflect the hygroscopic properties of ET and CP, were observed.
Although these findings did not reveal a definitive correlation between composition ratios with a delayed release and an increase in hygroscopy, the results do indicate that sorption occurred in the powders stored under Storage Condition 1, thereby possibly contributing to structural changes in the formulation that bring about a delay in drug release.

**Table 2: Density of the powder pharmaceutical ingredients**

| Sample | Bulk density (g/cm$^3$) | Tapped density (g/cm$^3$) |
|---|---|---|
| AA | 0.61 ± 0.02 | 0.84 ± 0.03 |
| ET | 0.83 ± 0.00 | 0.90 ± 0.02 |
| CP | 0.23 ± 0.01 | 0.30 ± 0.00 |

Each value represents the mean ± S.D. (n = 3)

### 2.2.3. *Observation of moisture absorption and crystallization process by polarized light microscopy*

To visually observe the changes occurring in test materials that absorbed moisture during storage, polarized light microscopy was used to compare the state of intact and stored simulated product formulation E. A liquid state or a slurry suspension was observed immediately after storage under Storage Condition 1 (Fig. 6e). ET appeared translucent because it had deliquesced, and crystals believed to be AA (circles in Fig. 6e) and amorphous CP were observed as black particles (arrows, Fig. 6e). After approximately 10 min, ET was observed to recrystallize rapidly and form aggregates while incorporating AA and CP (Fig. 6f, g). In contrast, in formulation D, which did not contain CP, ET remained a liquid after 10 min (Fig. 6i), and recrystallization was observed after approximately 90 min (Fig. 6j). The above findings revealed that CP greatly decreases the time required for ET recrystallization. Because the moisture absorption properties of CP are dependent on the relative humidity (Fig. 5), it appears that when the preparation is moved from a high humidity storage environment to a room temperature environment, the absorbed moisture is released into the atmosphere (i.e., the preparation dries), thereby promoting the rapid recrystallization of ET. Moreover, the experimental samples were powders of model tablet formulations that lay in a shallow indention on a glass plate. Voids between particles were observed before storage (Fig. 6g, arrows), but these voids disappeared as recrystallization occurred after storage.

### 2.2.4. *Pharmaceutical evaluation of intact and stored AA-containing OTC tablets on the market*

SEM observations were carried out on the surface of OTC drug product formulation A (Fig. 7). After storage, fissures were visible that were not seen before storage (Fig. 7b, circle). Moreover, intraparticle voids (micropores) formed after compression of the test sample in the tableting process were observed on the surface of the tablet before storage (Fig. 7c, arrows), and particles adhering to the tablet surface were observed after storage (Fig. 7d, circle).
Increases in micropore diameter and volume were observed, perhaps corresponding to the post-storage fissures observed by SEM (Fig. 8, Table 3). A cumulative micropore volume of 30,000 Å or less was seen before storage, whereas after storage this number had clearly decreased (Fig. 8, dotted line). More-

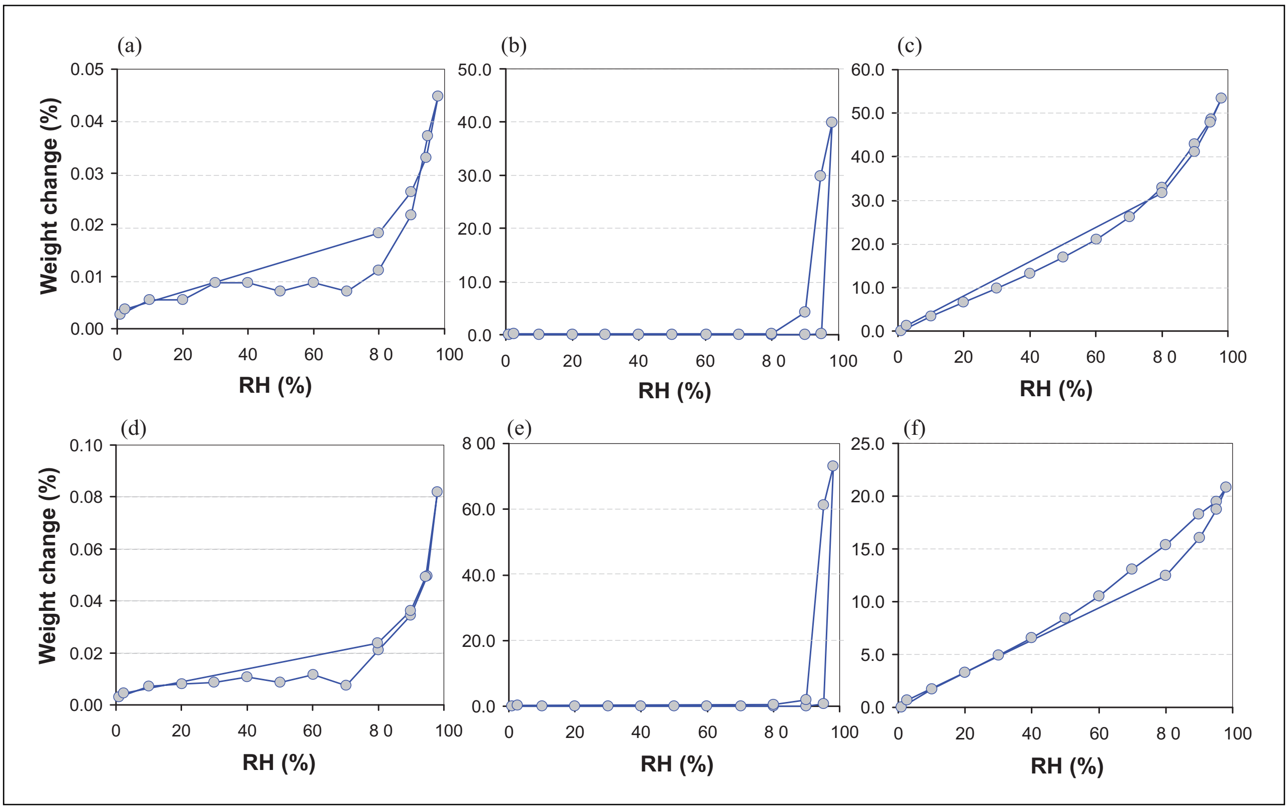



Fig. 5: Water vapor sorption isotherms; (a) AA, (b) ET, (c) CP, (d) MT, (e) AA + ET (weight ratio of 1:1), (f) AA + CP (weight ratio of 1:1)

**Table 3: Micropore size distribution**

| Sample | Total volume of pore ($cm^3/g$) | Total specific surface area ($m^2/g$) | Average pore diameter (Å) |
|---|---|---|---|
| Intact | 0.1313 | 6.423 | 8359 |
| After stored | 0.3329 | 7.661 | 118440 |

over, measurements of the true density before and after storage revealed that the volume increased and the true density decreased in stored product formulation A (Table 4).

These findings indicate that one factor causing delayed release in these pharmaceutical product formulations may be a change in the micropore structure, both on the surface and within the particles, resulting in a decrease in the solvent infiltration pathways leading to the interior of the preparation. It appears that deliquescence of ET under high temperature, high humidity conditions triggers recrystallization**.** During recrystallization, intraparticle crosslinks or agglomerations are formed, the solvent cannot infiltrate, disintegration due to swelling by CP decreases, and release of the drug is delayed (Fig. 9).

### *2.3. Conclustions*

We investigated the mechanisms involved in the pharmaceutical stability and deterioration of orally disintegrating tablets. We chose several OTC drugs which were poorly studied in this regard. Orally disintegrating tablets are extremely useful pharmaceutical preparations not only for patients with dysphagia, but for patients in general because they can be taken immediately without water when symptoms appear. However, as this study demonstrated, tablets that may have a delayed release cannot be distinguished by their appearance, so it is of concern that patients are likely to use such tablets. Because OTC drugs can easily be purchased, it is increasingly important to provide information regarding their proper use. Moreover, as the health needs of patients diversify, it is vitally important to develop drug products that meet those needs and promote the effective utilization of OTC drugs. The basic knowledge obtained from the current study should aid the development of more physically stable pharmaceutical preparations and thus aid the future development of many improved formulations for orally disintegrating tablets.

**Table 4: True density of OTC tablet A**

| Sample | Volume ($cm^3$) | Weight (g) | Density ($g/cm^3$) |
|---|---|---|---|
| Before storage | 0.836 | 1.192 | $1.425 \pm 0.001$ |
| After storage | 0.841 | 1.196 | $1.422 \pm 0.001$ |

mean ± S.D. (n = 10)

## 3. Experimental

### *3.1. Reagents*

The AA-containing OTC drugs we used were: Ringl Satto for children (Lot. ZXAX, Sato Pharmaceutical Co., Ltd., Tokyo, Japan), Children's Bufferin $_{CII}$ 33 mg (Lot. 00941, Lion Corp., Tokyo, Japan), Tylenol® A 300 mg and Tylenol® FD 150 mg (Lots. L06NA and Lot D031, Johnson & Johnson K.K., Tokyo, Japan). In this report we assigned these OTC drugs the designations A, B, C and D, respectively. Formulations A, C and D are orally disintegrating tablets, and formulation B is a conventional tablet. AA, erythritol (ET) and D-mannitol (MT) were special reagent grade products from Wako Pure Chemical Industries (Osaka, Japan). Crospovidone (CP), procured as Kollidon® CL-F from BASF Japan, is widely used as a disintegrant in orally disintegrating tablets (Kakiguchi et al. 2006).

### *3.2. Preparation of model tablet formulations*

We prepared model tablet formulations using the excipients erythritol (ET) and crospovidone (CP), contained in all the pharmaceutical formulations of OTC drugs in which a delayed release was found, to investigate their effect on the release properties of AA. MT was selected as a control for ET, and model tablet formulations with formulations A to F were prepared. The formulations shown in Table 1 were prepared to take into account both the

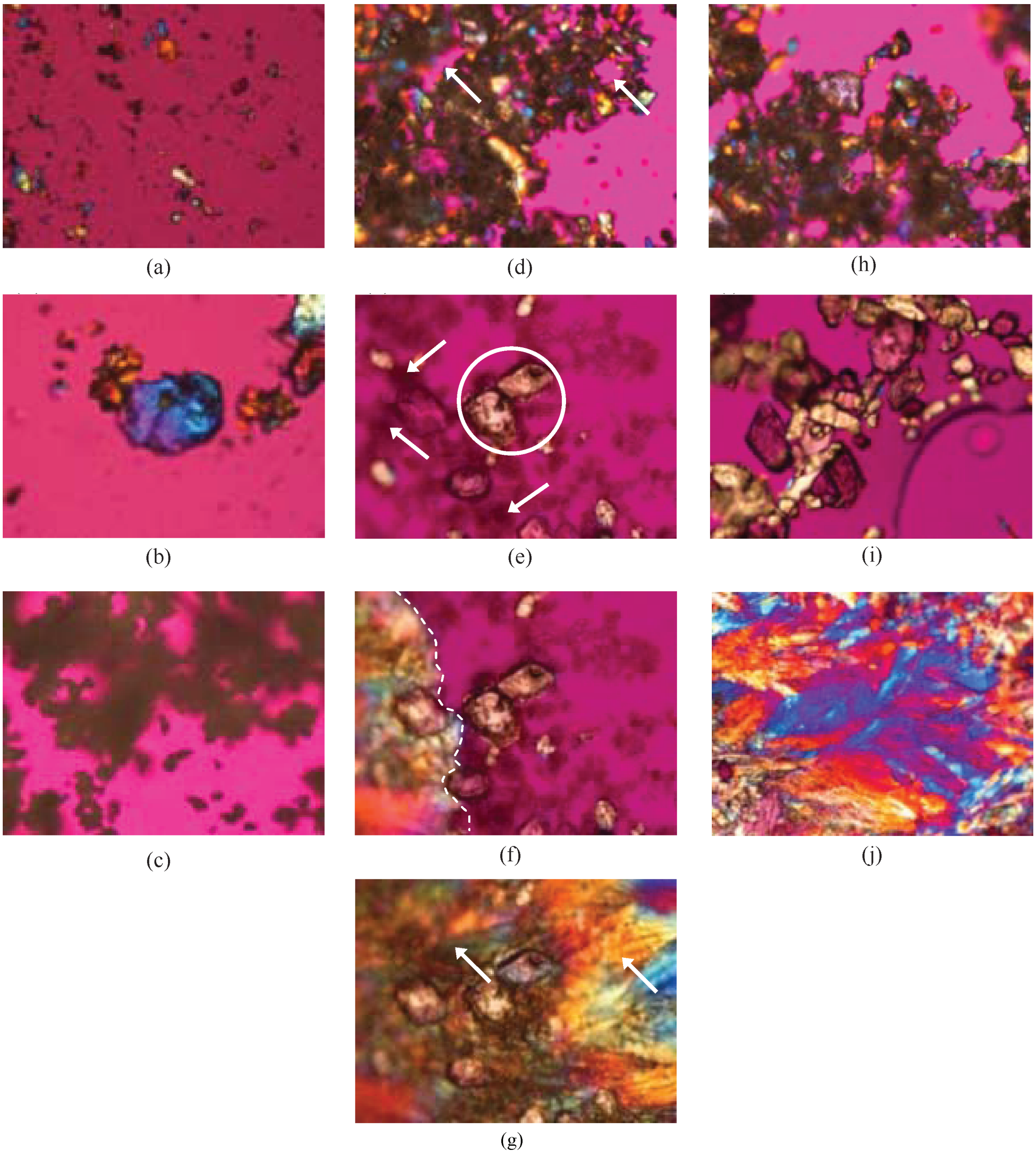


Fig. 6: Polarizing microscope photographs of model formulations; (a) AA, (b) ET, (c) CP; formulation E of (d) intact, (e) after 5 min, (f) 10 min, (g) 15 min; formulation D of (h) intact, (i) 10 min, (j) 90 min

composition ratio of the active ingredient to the total mass of the formulation and the results of the dissolution tests. The ingredients were powdered in an agate mortar, and after sifting through a 150 μm sieve, mixed at the designated ratios using a vortex mixer. Fifty milligrams of AA and the appropriate amount of other powders were weighed out for each preparation, then the sample material was placed in a disk type tableting machine and a pressure of 1 t was applied for 5 min to form the tablets. All model tablet formulations have a cylinder shape of 12.0 mm in diameter. The hardness varies by each model tablet formulation with a range of 2.1–14.5 kg (n = 3).

### *3.3. Product formulation storage conditions*

Temperature and humidity affect the release of the active ingredient from tablets. To investigate formulation storage conditions, we designed a composite experimental matrix (Iwata et al. 1994; Takayama and Nagai 1991) in which temperature (X1, 20 °C to 80 °C) and humidity (X2, 40 % to 95 %) were varied simultaneously (Fig. 1). The formulated products were removed from a PTP or strip package (SP) and immediately stored for 24 h in a constant temperature, constant humidity chamber (LH21-11 M, ESPEC Corp., Osaka, Japan).

### *3.4. Measurement of AA content*

The content of the active ingredient in each OTC product was measured in accordance with the content assay described in the Sixteenth Edition of the Japanese Pharmacopoeia (JP16). A calibration curve was prepared by first dissolving AA in the first JP16 dissolution test liquid to make AA standard solutions of 10, 30 and 50 mg/L, then measuring the absorption of each standard at 244 nm using an ultraviolet-visible spectrophotometer (V-660, JASCO Corp., Tokyo, Japan). After powdering each OTC product using an agate mortar and pestle, the powder was placed in a beaker containing 100 mL of the first dissolution test liquid and stirred for 1 h with a magnetic stirrer to obtain the test sample solution. The solutions were diluted 10-fold in the dissolution test liquid, filtered through a membrane filter (0.2 μm pore size), and then the absorption of each filtrate was measured and the amount of AA was determined using the calibration curve. Each measurement was repeated three times, and the average was used as the active ingredient content of the product.

### *3.5. Dissolution profile*

Dissolution tests were carried out on the OTC drugs and the model tablet formulations after 24 h storage. In accordance with the monograph for AA in JP16, the paddle method was used, the dissolution medium was the first dissolution test liquid, and the stirring speed was 50 rpm. Samples (5 mL) of the test medium were collected at 5, 10, 15, 20, and 30 min, and the concentration of AA in the samples was calculated from their absorption. Six samples were measured and a dissolution profile was prepared. To check whether moisture adhering to the surface of OTC drug formulation A would

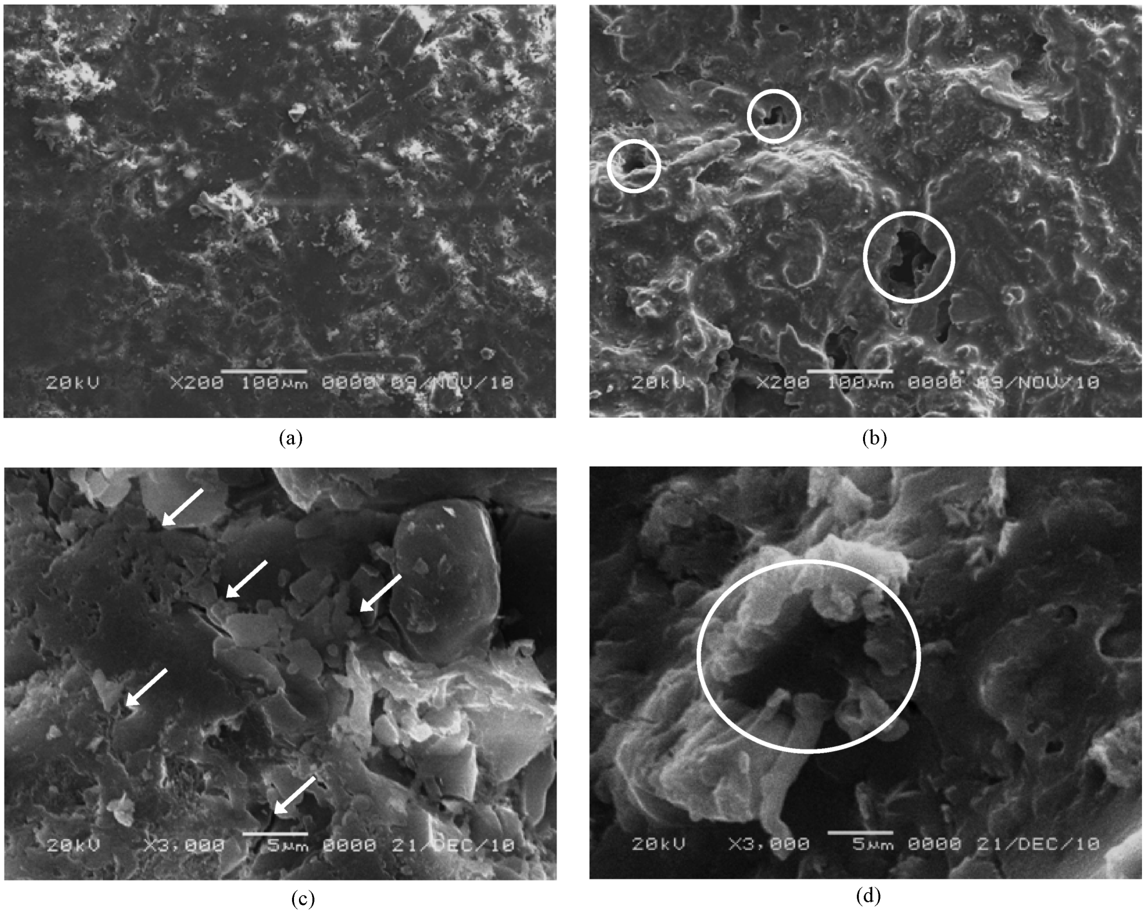



Fig. 7: SEM photographs of OTC tablet A; (a) intact (×200), (b) stored (×200), (c) intact (×3000), (d) stored (×3000)

have any effect, the dissolution test was carried out on this formulation after 24 h under Storage Condition 1 (80 °C, 68 %RH), followed by room temperature conditions for 48 h.

### *3.6. Hygroscopy*

The change in mass after 24 h storage was measured for the model tablet formulations, and for AA, ET, CP and MT alone. To take into account the effect of any moisture adhering to the surface of the test samples, the samples were removed from the constant temperature, constant humidity chamber, and then after 10 min at room conditions their mass was measured and compared to their mass prior to storage. The moisture absorption rate was calculated from the increase in mass due to the increase in moisture content. This measurement method was based on the loss on drying test in JP 16. First, 100 mg of test sample was placed in a weighing bottle, then the bottle was tapped until the height of the sample was no greater than 5 mm. The bottle was stored in a constant temperature, constant humidity chamber. Each measurement was repeated three times, and the average values were compared.

In addition, water sorption analysis was carried out for AA, ET, CP, MT, AA + ET (weight ratio 1:1) and AA + CP (weight ratio 1:1) at 25 °C using an SPS11-10 µ sorption analyzer (PMT Analytical GmbH & Co. KG, Germany).

### *3.7. Bulk density and tapped density*

The bulk density of AA, ET, and CP alone was determined using a device for measuring the decrease in apparent specific volume (model KC-RHK, Konishi Medical Instruments Co, Ltd., Osaka, Japan). Approximately 2 g of each test sample was placed in a 10 mL graduated cylinder, and the bulk density was calculated from the volume of the sample. Using the KC-RHK device, the sample was tapped repeatedly 100 times/min for 5 min and at a

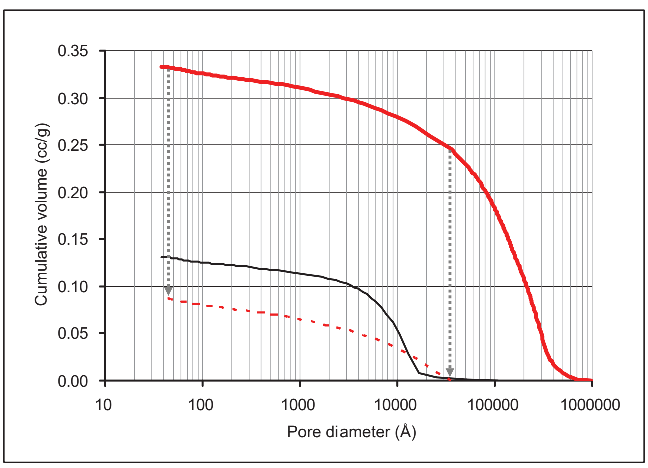



Fig. 8: Micropore distribution of OTC tablet A; black line: intact, red line: stored, red broken line: stored (<30,000 Å)

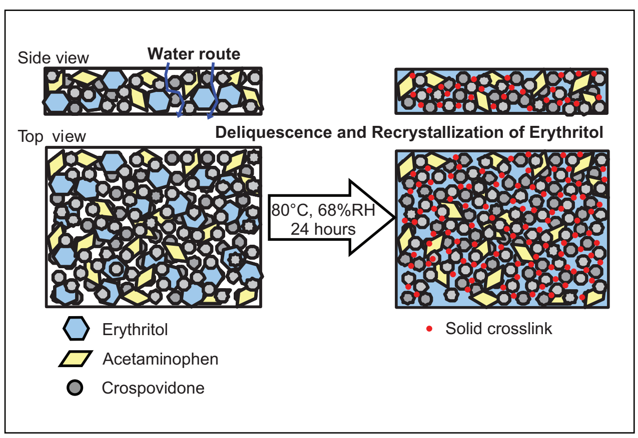



Fig. 9: Schematic diagram outlining the proposed mechanism by which drug release and disintegration of OTC tablet A is retarded

drop height of 2 cm, the volume was measured, and the tapped density was calculated. Each measurement was repeated 3 times, and the mean value and standard deviation (S.D.) were calculated.

### 3.8. *Observation of crystallization by polarized light microscopy*

After sieving AA, ET, and CP through a 75 µm sieve, a mixture based on formulation D was spread on a glass slide to a thickness of 0.6 mm. The sample was observed after 24 h storage under Storage Condition 1 (80 °C, 68 % RH), and until the sample reached room temperature, using an E-600-Pol (Nikon Corporation., Tokyo, Japan) polarized light microscope.

### 3.9. *Scanning Electron Microscopy (SEM)*

A JSM-6360LV (JEOL Ltd., Tokyo, Japan) scanning electron microscope was used for SEM measurements. Solid samples were adhered to the sample stage using adhesive tape. A sputter coater, JEC-1600 (JEOL Ltd., Tokyo, Japan) was used to coat the samples with gold/platinum at 20 mA for 30 s.

### 3.10. *Analysis of pore size distribution and surface area*

The pore size distribution and surface area of OTC drug product formulation A, which had the lowest dissolution rate, was measured before and after 24 h storage under Storage Condition 1 (80 °C, 68 % RH) using a mercury intrusion porosimeter (model Pascal 440, Carlo Erba, Italy). The specific surface area was calculated from the micropore distribution and pore volume.

### 3.11. *Analysis of True Density (True Density)*

Test samples of OTC drug product formulation A before and after 24 h storage under Storage Condition 1 (80 °C, 68 % RH) were placed in a 10 mL cell, and the true density was measured using an AccuPyc™ II 1340 Gas Displacement Pycnometer (Micromeritics Co., Norcross, GA, U.S.A.).

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### References

Iyakuhin Seizohanbai Shishin (2008) Japan Pharmacists Education Center, Jiho Inc., Tokyo, p. 673–674.

Iwata M, Shirotake S, Huang CC, Machida Y, Nagai T (1994) Development of release tast method for suppositories using beads and thimble filter. Jpn J Hosp Pharm 20: 273–278.

Kakiguchi Y, Tanabe M, Katsuno T (2006) 23rd Symposium on the division of particulate design and preparations, Symposium papers, Hiroshima, October, p. 267–269.

Kohama H (2008) Trend of pharmaceutical packaging associated with the reform of selling system of OTC drugs. Packag Tech 46: 596–600.

Li C, Sakamoto M (2007) Development of oral rapidly disintegrating tablets. Arch Pract Pharm 67: 133–141.

Li C, Sakamoto M, Kobayashi T (2009) Development of oral rapidly disintegrating tablets (II). Arch Pract Pharm 69: 297–306.

MHLW (Ministry of Health, Labour and Welfare) (2002) The investigative commission for rationalization of the approval review in an over-the-counter drug. http://www.mhlw.go.jp/shingi/2002/11/s1108-4.html, cited 8 November.

Nakai Y, Nakajima S, Fukuoka S (1977) Effect of swelling of disintegrants on tablets disintegration. Yakugaku Zasshi 97: 1058–1063.

Nishioka Y (2003) Significance of stability information in the non-packaging condition of tablet and capsule. Med Drug J 39: 850–854.

Ohtagaki R, Hioki Y (2008) An evalution of green shade effects of pergola for improving car park's thermal environment. J Jpn Soc Reveget Tech 34: 127–132.

Ota M, Takahashi Y, Fukami T, Tomono K, Iwata M, Hidaka S (2010) Physico-pharmaceutical study on stability of over-the-counter drugs containing acetaminophen. J Pharm Health Care Sci 36: 425–435.

Sagawa K (2008) Porphyrization Information; Jouzai Kapuseruzai Funsai Handbook, 5th ed. Jiho Inc., Tokyo.

Shimizu N, Notani J, Nishikawa T, Kitayama H, Shiroishi A, Fujita H, Yamauchi K, Ide M, Koizumi H, Takeyama I, Yamazaki H, Sonobe H, Arime T, Uzawa O (2005) Study on development and evaluation of new over-the-counter drugs by the actual use trial (AUT) using OTC common cold medicine including ibupurofen. Rinsho Hyoka 33: 213–240.

Suzuki H, Onishi H, Hisamatsu S, Masuda K, Takahashi Y, Iwata M, Machida Y (2004) Acetaminophen-containing chewable tablets with suppressed bitterness and improved oral feelings. Int J Pharm 278: 51–61.

Suzuki H, Onishi H, Takahashi Y, Iwata M, Machida Y (2003) Development of oral acetaminophen chewable tablet with inhibited bitter taste. Int J Pharm 251: 123–132.

Tagawa M, Chen R, Chen P, Kobayashi M, Okamoto K, Danjo K (2003) Effect of various disintegrants on drugs release behavior from tablets. Arch Pract Pharm 63: 238–248.

Takayama K, Nagai T (1991) Simultaneous optimization for several characteristics concerning percutaneous absorption and skin damage of ketoprofen hydrogels containing d-limonene. Int J Pharm 74: 115–126.