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The most appropriate storage method in unit-dose package and correlation between color change and decomposition rate of aspirin tablets

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ABSTRACT

The most appropriate method to preserve Bufferin 81-mg tablets dispensed for unit-dose packaging in the hospital pharmacy was examined. The surface color change of the tablets was investigated over time by spectrophotometry, and the decomposition rate of aspirin was measured by high-performance liquid chromatography (HPLC). To overcome these, it was found that we can effectively prevent color changes and preserve the quality by maintaining the humidity as 55% or less, storage with drying agent in a plastic or aluminum pack. It was revealed that the color changes became greater and the decomposition rate became higher as time passed. Color changes markedly affect the patients' compliance, and are found to be a very important factor. It was considered that the clarity of the correlation between the color change and decomposition rate may contribute to a decrease in the number of tablets discarded before the expiration date.

1. Introduction

Since "Bufferin 81-mg tablets" (The proprietary name was changed to "Bufferin combination tablets A81" in September 2009.), as an anti-platelet agent, were manufactured/sold by LION Co., Ltd. (Tokyo; Japan) in 2000, they have been routinely employed in clinical practice as 2-layer, light orange tablets containing 81 mg of aspirin and 33 mg of dialuminate (aluminum glycinate: 11 mg, magnesium carbonate: 22 mg) in respective layers. In addition, Corn Starch, Saccharin, Sodium Saccharin, Talc, D-Mannitol and Gelatin, as the excipients or additives, are included in these tablets. However, actually, "Bufferin 81-mg tablets" became commercially available as "Children's bufferin" in 1963. After Weiss et al. reported the anti-platelet actions of aspirin in 1967 (Mann and Plummer, 1994), "Children's bufferin" was also selected as an anti-platelet agent beyond its approved indications from the 1970s in Japan (Hirasawa, 2001). In 1999, it was approved as an anti-platelet agent to eliminate its extra-indication use. In 2000, it was manufactured/sold with a modified name.

In the "Indications" column of Bufferin 81-mg tablets, the following contents are described: "① inhibition of thrombus/embolus formation related to the following disorders: angina pectoris (chronic stable angina, unstable angina), myocardial infarction, and ischemic cerebrovascular disorder (transient ischemic attack (TIA), cerebral infarction) and ② inhibition of thrombus/embolus formation after coronary aortic bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA)". In particular, the frequency of elderly persons taking this preparation is high, and compliance as prophylactic administration requiring regular once-a-day dosing may be important.

The principal component of Bufferin 81-mg tablets, aspirin (acetylsalicylic acid), is known to gradually decompose into salicylic and acetic acids in the presence of moist air. In the package inserts of Bufferin 81-mg tablets, it is also described that this product is decomposed via moistening, and should be handed to patients with its aluminum-sheet package remaining intact, as "Precautions for handling". However, in clinical practice, Bufferin 81-mg tablets may be taken out of the aluminum sheet, dispensed for unit-dose packaging, and delivered to patients in some hospitals/drugstores, considering compliance, difficulty in SP-sheet opening (Owaki et al., 2004), and availability in nursing facilities. In the interview form (IF) (Lion Co., Ltd., 2003) of Bufferin 81-mg tablets, the standard free salicylic acid content is established as 3% or less of the aspirin content. The stability of these tablets after unit-dose packaging has been reported. However, the relationship between color changes and the decomposition rate remains to be clarified.

Target pharmacists working in hospitals/drugstores, we conducted a questionnaire survey regarding the presence or absence of Bufferin 81-mg tablet dispensing for unit-dose packaging, changes in the color of tablets taken out of the aluminum sheet, and guidance for patients regarding storage methods. Based on the results, we examined the most appropriate storage method to reduce the rate of aspirin decomposition, as the principal component of re-

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packaged Bufferin 81-mg tablets, to 3% or less, as well as the correlation between color changes and the rate of aspirin decomposition, and evaluated whether the rate of decomposition can be estimated based on color changes.

2. Materials and methods

2.1. Materials

Bufferin®81-mg tablets manufactured/sold by Lion Co., Ltd. (Tokyo), which were for 33–36 months before the expiration date were used. Powder packaging paper used machine, which was E Ueda Cello-Poly® (polyethylene (PE) 0.04 mm thick) obtained from Meg Co. (Tokyo), plastic pack (Uni-pack® I-4: 0.04 mm × 200 mm × 280 mm, PE) and aluminum pack (Lami-zip® AL-22: 0.134 mm × 220 mm × 300 mm + gusset 64 mm, polyethylene terephthalate (PET)/aluminum (AL)/PE) supplied from Seisannipponsha, Ltd. (Tokyo), Silica gel S-5 (5 g, 60 mm × 50 mm) purchased from TachibanaYa Shouji Inc. (Kouchi, Japan), and raw lime drying agent S237270H (20 g, 7 cm × 9 cm) obtained from Sakamotosekkai Co., Ltd. (Kumamoto, Japan) were used. Columns used HPLC was Inertsil®ODS-3 (5 μm, 150 mm × 4.6 mm I.D.) manufactured by GL Sciences Inc. (Tokyo). Membrane filter (Omnipore™: 0.2-μm JG) used Millipore Co. (MA, USA). The reagents used were all of special class grade available on the market.

2.2. Questionnaire survey

A questionnaire survey regarding Bufferin 81-mg tablets by inquiry was conducted involving hospital/drugstore pharmacists who attended the North Tama North-Medical-Area Medical/Pharmaceutical Study Meeting (Yamazaki et al., 2008), which was held in Meiji Pharmaceutical University on February 14, 2008, and consented to cooperate. The question items are shown in Table 1. Concerning color changes in comparison with that immediately after opening, photographs of Bufferin 81-mg tablets with ① slight, ② appreciable, and ③ much changes, which could be evaluated under direct vision, were presented, and the following question was addressed: "What color leads to you discarding the tablet?"(refer to Photo 1).

2.3. Experiment [I]

Temperature/humidity: Tablets were simultaneously stored in a thermohygrostat (Enviros KCL-2000W: Tokyo Rikakikai Co., Ltd., Tokyo), while maintaining the temperature and humidity at 27 °C and 65%, respectively, with reference to the mean temperature/humidity in hospital pharmacies in which optimal conditions may be maintained for medicinal storage (Japanese Society of Hospital Pharmacists, 2005).

Packaging method: Based on the results of this questionnaire survey, tablets were taken out of the aluminum sheet, and the following 7 types ((A)–(G)) of packaging form were employed with reference to routine methods after unit-dose packaging. When storing unit-dose-packaged products in a plastic pack, can, or aluminum pack, 84 packages per lot were simultaneously stored, considering the maximum interval of 12 weeks measured in this study: (A) uncovered tablets, (B) unit-dose-packaged products alone, (C) unit-dose-packaged products stored in a can, (D) unit-dose-packaged products stored in a plastic pack, (E) unit-dose-packaged products stored with silica gel (drying agent) in a plastic pack, (F) unit-dose-packaged products stored with a raw lime drying agent in a plastic pack, and (G) unit-dose-packaged products stored in an aluminum pack.

Table 1
Questionnaire regarding Bufferin 81-mg tablets (LION Co., Ltd.).

Workplace: Hospital, Drugstore, Others
Question 1. Have you ever taken Bufferin 81-mg tablets from their aluminum-sheet package for unit-dose packaging?
→ Yes, No → Persons who selected "No" please skip to Questions 5 and 6.
Persons who selected "Yes": Is a Bufferin 81-mg cassette installed?
→ Yes, No

Question 2. Have you ever prepared preliminary unit-dose packages before the date of scheduled patient consultation (visit)?
→ Yes, No
Persons who selected "Yes": How were the preliminary unit-dose packages stored?
→Uncovered, Unipack, Unipack + a drying agent, Aluminum bag,
Others ( )
Question 3. Have you ever discarded tablets taken out of their aluminum sheet due to color changes before administration? (before the expiration date)
→ Yes, No
Persons who selected "Yes": How about the condition?
→ In a cassette for unit-dose package, Preliminarily prepared products, In a Unipack,
Others ( )

Question 4. Did you instruct patients on storage methods?
→ No special instruction, Use of a Unipack, Use of an empty can, Use of a drying agent, Others ( )

Question 5. Have you ever been consulted about color changes by patients?
→ Yes, No
Persons who selected "Yes": How did you answer (evaluate)?
→ Evaluate whether or not tablets should be discarded based on the color (self-assessment, others)
Evaluate based on the administration period
Evaluate based on the expiration date
Others ( )

Question 6. What color leads to you discarding the tablet?

① or higher, ② or higher, ③ or higher

2.4. Experiment [II]

Temperature/humidity: When storing tablets, the temperature and humidity in the thermohygrostat were maintained at 27 °C and 55%, respectively, as it is described that the rate of aspirin decomposition on pulverization decreases at a humidity of 56% or less, in the IF of Bufferin 81-mg tablets.

Packaging method: Of the above 7 types, 4 ((B), (D), (E), and (G)) were selected.

2.5. Quantification of aspirin and salicylic acid

Aspirin was quantified using high-performance liquid chromatography (HPLC, HPLC JASCO 2000-Plus system, Japan Spectroscopic Co., Ltd.). The column temperature was 40 °C, and the flow rate was 1.2 mL/min. As a mobile phase, monobasic potassium phosphate/methanol solution (3:2) (pH 2.0) was used at a measurement wavelength of 295 nm.

Four Bufferin 81-mg tablets were ground, and 0.5 g of powder was accurately weighed as a sample. The sample was mixed with 10 mL of dehydrated ethanol, agitated, and filtered using a 0.2-μm membrane filter. The filtrate was mixed with purified water to accurately prepare a volume of 50 mL. It was used as sample solution.

The peak area per 10 μL of sample/standard solution was measured using HPLC, and the levels of aspirin and salicylic acid were calculated based on the assay lines for the two prepared from standard solution. Furthermore, the sample aspirin decomposition rate was calculated using the following formula by converting the sample level of salicylic acid to the aspirin level (converted

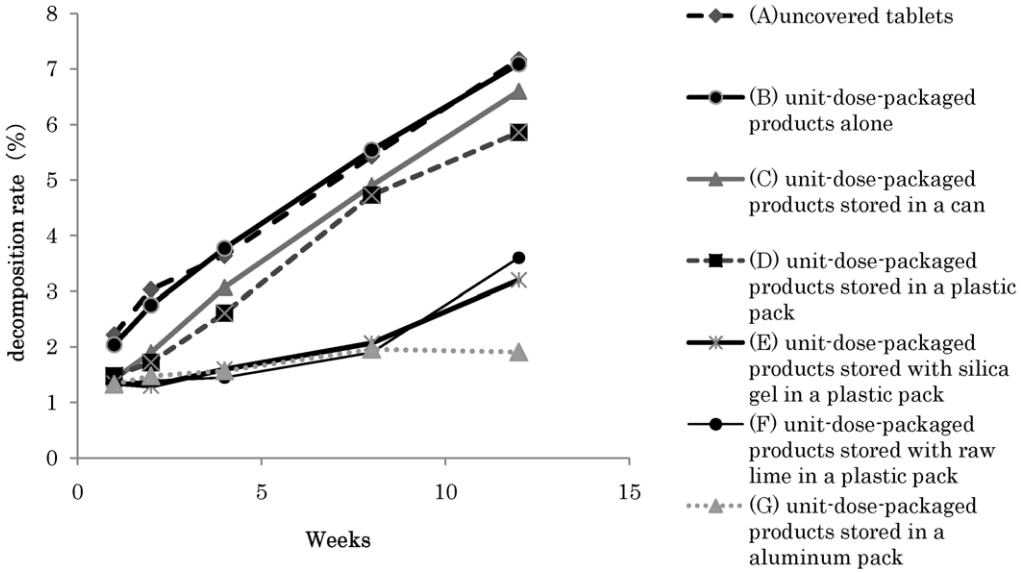

Fig. 1. Experiment [I]: the aspirin decomposition rate in tablets with each package form stored in a thermohygrostat (temperature: 27 °C, humidity: 65%): at the start of measurement, the decomposition rate was 1.3%.

aspirin level):

$$\text{Aspirin decomposition rate}\,(\%) = \frac{\text{Converted aspirin level}}{\text{Actual aspirin level} + \text{converted aspirin level}} \times 100$$

Measurement was performed immediately after tablet removal from the aluminum sheet (at the start of the experiment) and 1, 2, 4, 8, and 12 weeks after unit-dose packaging, establishing a maximum interval as 3 months, which may be indicated in prescriptions.

In all experiments, these substances were quantified 3 times per lot using 3 different lots of Bufferin 81-mg tablets. The mean of 9 measurements was employed.

2.6. Color changes

In Experiment I, Bufferin 81-mg tablets were taken out of the aluminum sheet, separately packaged by unit-dose, and stored in a thermohygrostat (temperature: 27 °C, humidity: 65%). Apparent changes on the tablet surface were investigated using photography and spectrophotometry at the start of this experiment and after 2, 4, 8, and 12 weeks, as described below. At each point, 4 tablets per lot (total: 12 tablets) were evaluated. The bilateral sides were assessed using a spectrophotometer, and the mean was employed. The aspirin decomposition rate at each point was calculated, as described above (Section 4).

① Photography

Photographs were taken using a digital steel camera (Cyber-Shot DSC-T9: Sony Co., Ltd.) under an illuminance of 20,000 lx.

② Spectrophotometer

The color of tablets was measured through the L*a*b* coloring system using a spectrophotometer (CM-2002: Konica Minolta Co., Ltd.). Color differences related to serial changes of the tablet (ΔE^*ab) were calculated employing the following formula:

$$\Delta E * ab = \sqrt{(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2}$$

In this formula, ΔL^* and (Δa^*; Δb^*) indicate differences in brightness and color (Δa^*: red-green direction; Δb^*: yellow-blue direction), respectively.

3. Results

3.1. Results of the questionnaire survey

Twenty-four pharmacists (16 hospital and 8 drugstore pharmacists) responded to the "Questionnaire regarding Bufferin 81-mg Tablets" presented in Table 1. Of these, 14 (58.3%) reported that Bufferin 81-mg tablets were taken out of the aluminum-sheet package for unit-dose packaging. Of the 14 pharmacists, 8 (57.1%) indicated the preparation of preliminary packages before drug delivery to patients. Only 2 (14.3%) reported guidance for patients regarding the storage of unit-dose-packaged Bufferin. Furthermore, 12 (85.7%) had discarded tablets taken out of the aluminum sheet due to color changes before the expiration date. Question 6, "What color leads to you discarding the tablet?", was raised, while presenting a photograph of Bufferin 81-mg tablets with color changes (Photograph 1). Ten pharmacists (41.7%) selected grade 1 or higher tablets, 12 (50.0%) selected grade 2 or higher tablets, and 2 (8.3%) selected grade 3 tablets.

3.2. Rate of aspirin decomposition

3.2.1. Experiment [I]

The serial changes in the aspirin decomposition rate in tablets with each package form stored in a thermohygrostat (temperature: 27 °C, humidity: 65%) are shown in Fig. 1. At the start of measurement, the decomposition rate was 1.3%. In uncovered tablets, the decomposition rate exceeded 3% 2 weeks after unit-dose packaging; the tablets did not meet the standards. In unit-dose-packaged products alone/unit-dose-packaged products stored in a can, a similar tendency was noted 4 weeks after unit-dose packaging. In unit-dose-packaged products stored in a plastic pack, the decomposition rate was less than 3% 4 weeks after unit-dose packaging, but exceeded 4.7% after 8 weeks; the tablets did not meet the standards. In unit-dose-packaged products stored with a drying agent (silica gel/raw lime) in a plastic pack, the decomposition rate was approximately 2% after 8 weeks, although it exceeded 3% after 12 weeks. On the other hand, in unit-dose-packaged products stored in an aluminum pack, the decomposition rate was approximately 2% or less after 12 weeks.

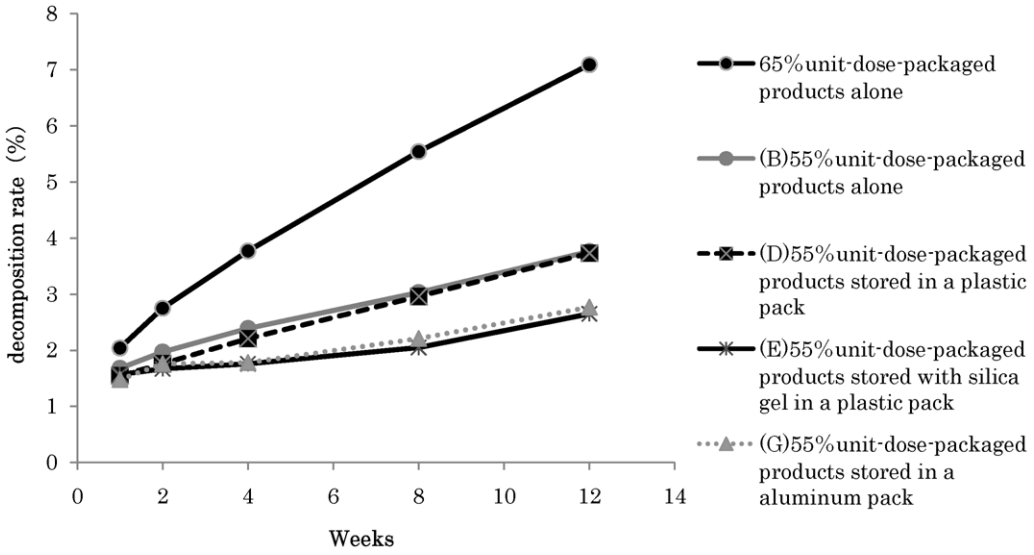

Fig. 2. Experiment [II]: the aspirin decomposition rate in tablets with each package form stored in a thermohygrostat (temperature: 27 °C, humidity: 55%): at the start of measurement, the decomposition rate was 1.3%.

3.2.2. Experiment [II]

As it is described that the rate of aspirin decomposition on pulverization decreases at a humidity of 56% or less, in the IF of Bufferin 81-mg tablets, this experiment was conducted, while maintaining the thermohygrostat temperature and humidity at 27 °C and 55%, respectively. For storage, 4 package forms ((B), (D), (E), and (G)) were employed. The serial changes in the decomposition rate for each package form in comparison with that for the (B) package form obtained at a temperature and humidity of 27 °C and 65%, respectively, in Experiment I are shown in Fig. 2.

Concerning the (B) package form, the results were compared between 2 different humidity conditions: 65 and 55%. At a humidity of 65%, the decomposition rate was 3.8% 4 weeks after unit-dose packaging, as described above. However, it was 2.4% at a humidity of 55%. Concerning the (D) package form, the decomposition rate after 8 weeks was 4.7% at a humidity of 65%, whereas it was 3% at a humidity of 55%. Concerning the (E) and (G) package forms, the decomposition rates after 12 weeks were approximately 3% or less. These results confirmed that the aspirin decomposition rate at a humidity of 55% was lower than at a humidity of 65% regardless of the presence or absence of pulverization.

3.2.3. Color changes

The changes in the appearance/color of unit-dose-packaged Bufferin 81-mg tablets at the start of the experiment and after a specific period (2, 4, 8, and 12 weeks) of storage in a thermohygrostat (temperature: 27 °C, humidity: 65%) are shown in Photo 2.

The color of tablets immediately after being taken out of the aluminum sheet (at the start of the experiment) was light orange. The white color of the dialuminate-containing layer was slightly more marked. At this point, the decomposition rate was 1.3%. After 2 weeks, the circumference became slightly dark orange, showing a change in the appearance. However, the decomposition rate was 2.8%. After 4 weeks, the sides and circumference became dark orange, and the decomposition rate was 3.8%; the tablets did not meet the standards. After 8 weeks, a portion of the center became dark orange in addition to the sides and circumference, with a decomposition rate of 5.5%. In addition, after 12 weeks, dark orange spots extending at the center were observed, and the corner was affected in some tablets. The decomposition rate was 7.1%.

The relationship among the color difference (ΔE^*ab) measured using a spectrophotometer, criteria for color differences established by the National Bureau of Standards (NBS unit), and decomposition rate is shown in Fig. 3. The color difference and decomposition rate serially increased. According to the NBS criteria, the color of tablets was evaluated as "noticeably different" after 2 weeks and "appreciable different" after 4, 8, and 12 weeks. The decomposition rate reached 3% more than 2 weeks after the start of the experiment; the tablets did not meet the standards.

4. Discussion

In clinical practice, Bayaspirin® 100-mg (Bayer Schering Pharma Co., Ltd. 2008), which exhibit the same effects as Bufferin 81-mg tablets, are commercially available. These are enteric-coated tablets, and non-sealed tablets are also commercially available as a preparation that can be utilized for unit-dose packaging. When packaging tablets by unit-dose, the stability may be maintained by selecting coated tablets, because their hygroscopic property is lower. However, actually, Bufferin 81-mg tablets, which show a marked hygroscopic property, are separately packaged by unit-dose in some hospitals, as indicated by the results of this questionnaire survey. This may be because prescribing physicians are accustomed to Bufferin 81-mg tablets, with a 40-year history from 1963, and because even elderly persons with reduced vision can distinguish light orange tablets. However, based on the results of this questionnaire survey, there are limitations: Bufferin 81-mg tablets are dispensed for unit-dose packaging, although it is described that this product should be handed to patients with its aluminum-sheet package remaining intact, in the package inserts of this agent; and color changes related to unit-dose packaging require discarding before administration in some cases. To overcome these limitations, an optimal storage method at the mean temperature/humidity in hospital pharmacies should be reviewed, and patients should be instructed on storage at home so that the conditions may be maintained.

In this study, the rate of aspirin decomposition for each packaging form was measured under Experiment I (mean temperature/humidity in hospital pharmacies: 27 °C and 65%, respectively) and Experiment II (27 °C and 55%, respectively, in accordance with a humidity of 56% or less at which the rate of aspirin decomposition decreases) conditions. The results of Experiment II showed that the aspirin decomposition rate in Bufferin 81-mg tablets was inhibited when the humidity on storage was established as 55%

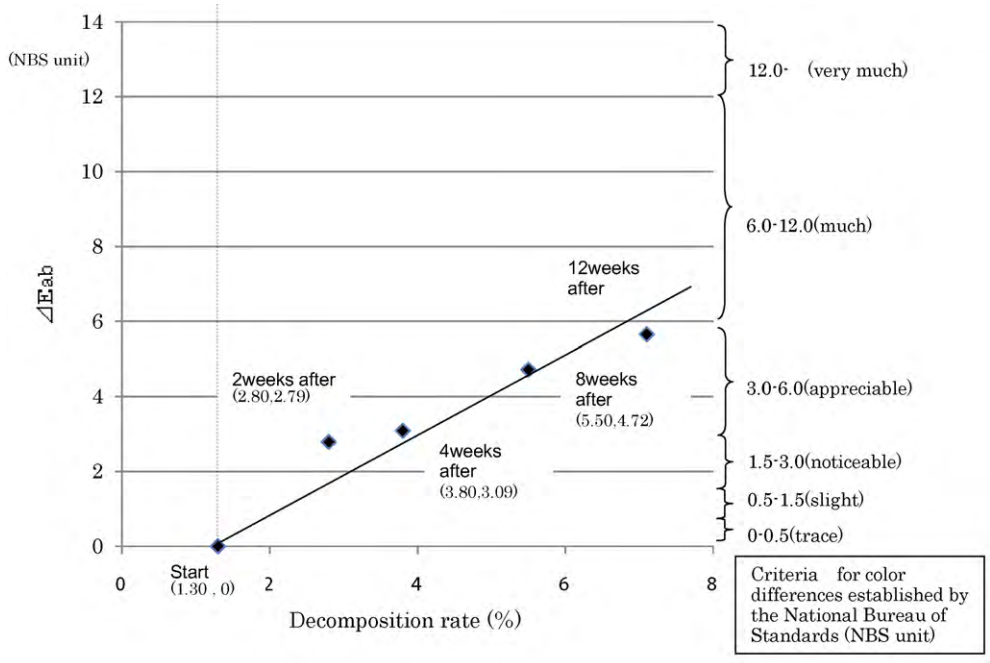

Fig. 3. The relationship among the color difference (ΔE^*ab) measured using a spectrophotometer, criteria for color differences established by the National Bureau of Standards (NBS unit), and aspirin decomposition rate.

or less. Briefly, aspirin decomposition depends on humidity; an environmental humidity maintained at 55% or less during the storage period may be useful for inhibiting decomposition. Based on these results, it is important to maintain the humidity in hospital pharmacies at 55% or less. However, the mean hospital pharmacy temperature and humidity in June were reported to be 27 °C and 65% (Japanese Society of Hospital Pharmacists, 2005), respectively, by the Japanese Society of Hospital Pharmacists. During specific hours or in some areas, the mean humidity was 70% or more. Considering this, an optimal storage method under the Experiment I conditions was reviewed. After Bufferin 81-mg tablets were taken out of the aluminum sheet, the rate of aspirin decomposition rapidly increased, as shown in Fig. 1. In addition, there were no marked differences in the decomposition rate among several storage methods: unit-dose-packaged tablets, those stored in a plastic pack, and those stored in a can. Briefly, the 0.04-mm thick plastic pack employed in this study did not exhibit any anti-hygroscopic effects even when sealed with a zipper, and the aspirin decomposition rate was similar to that in unit-dose-packaged or uncovered tablets. However, as shown in Fig. 1, the decomposition rate was markedly inhibited when a drying agent was placed in the plastic pack. When employing an aluminum pack, it was further inhibited. The introduction of these storage methods in each hospital/drugstore may make it possible to maintain the stability of this preparation over a longer period even if Bufferin 81-mg tablets are taken out of their sealed packaging.

In this experiment, silica gel and raw lime were used as drying agents. The volume of these drying agents required to maintain their effects for 12 weeks was calculated using a formula (JIS Z0301) regarding anti-hygroscopic packaging methods. Products immediately after arrival from the manufacturers were employed. However, in clinical practice, storage conditions may vary: an insufficient volume of drying agents, and the use of drying agents absorbing moisture to some degree. In such cases, the rate of aspirin decomposition may be higher than in this experiment. Silica gel must be dried using a microwave oven, and used at a sufficient volume. Furthermore, an aluminum pack inhibits the decomposition rate in the absence of drying agents; therefore, it should be positively introduced, although it is expensive.

Concerning color changes, this experiment confirmed that both the color difference (ΔE^*ab) on the tablet surface and aspirin decomposition rate serially increased. A spectrophotometer may not be installed in clinical practice; color differences may be visually assessed.

Based on the results of this questionnaire survey, 41.7% of the pharmacists reported that tablets with "slight changes ①" in color were discarded (Photograph 1). The slight changes were evaluated as color differences ranging from 0.5 to 1.5 according to the NBS criteria. As shown in Fig. 3, the aspirin decomposition rate was 2% or less, meeting the standards. With this color, the pharmacists discarded tablets, possibly because they considered that even slight color changes showed an elevated aspirin decomposition rate beyond the standards, or because they paid attention to the tablet's color at the time of drug delivery to patients to prevent the reduction of compliance related to post-delivery color changes, considering the humidity level on storage at home.

A review of the relationship between color changes and the decomposition rate obtained in this experiment may contribute to a decrease in the number of tablets discarded before the expiration date (Fig. 3). Briefly, when color differences are trace or slight, the decomposition rate may be 3% or less, meeting the standards. When they are appreciable, it may exceed 3%. However, when administering aspirin for the secondary prevention of myocardial infarction, the dose ranges from 50 to 162 mg (Japanese Circulation Society, 2006); its anti-platelet actions may not be markedly reduced even if the decomposition rate exceeds 3%. However, to prevent Bufferin 81-mg tablets' deviation from the standards and maintain patient compliance, tablets should be dispensed for unit-dose packaging immediately before administration. When preparing preliminary unit-dose packages for specific reasons, storage methods are important. Quality control with the above storage methods at an optimal humidity and guidance regarding appropriate storage at home after drug delivery may prevent color changes, maintaining compliance.

These results may provide information useful for health care professionals and patients, improving future medicinal management.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2010.06.031.

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