International Journal of Pharmaceutics 396 (2010) 105–110

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

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

Noriko Yamazaki, Kumiko Taya, Ken-ichi Shimokawa, Fumiyoshi Ishii*

Department of Health Care and Sciences, Faculty of Pharmaceutical Sciences, Meiji Pharmaceutical University, 2-522-1, Noshio, Kiyose, Tokyo 204-8588, Japan

ARTICLE INFO

Article history:
Received 24 March 2010
Received in revised form 29 May 2010
Accepted 18 June 2010
Available online 25 June 2010

Keywords:
Aspirin tablet
Color change
Decomposition rate
Discard
Storage method

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-

* Corresponding author. Tel.: +81 42 495 8468; fax: +81 42 495 8468.
E-mail address: fishii@my-pharm.ac.jp (F. Ishii).

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.06.031

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