

Behavior of Uptake of Moisture by Drugs and Excipients under Accelerated Conditions of Temperature and Humidity in the Absence and the Presence of Light

Part II: Packaged and Unpackaged Antituberculosis Drug Products

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In this article, the influence of light on the moisture gain of packaged and unpackaged formulations was investigated using marketed antituberculosis products containing ethambutol. The products were stored in darkened and lighted chambers at 40 °C and 75% RH for three months. Samples were withdrawn periodically, and their change in weight was recorded. Although formulations packaged in strip packs were stable, formulations packaged in blister packs and all unpackaged tablets gained moisture at a higher rate in the presence of light.

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One of the major changes brought about by the introduction of the International Conference on Harmonization (ICH) guidelines for stability testing of pharmaceutical products has been to standardize temperature and humidity testing conditions (1). Although the environment typically consists of temperature, humidity, and light, the ICH still preferred to develop a separate photostability testing guideline because products in ICH member countries are sold in secondary packages, which eliminates the necessity for light testing along with temperature and humidity (2). Although light isn't considered a main testing factor in several ICH member regions (e.g., United States, Europe, and Japan), it is an important factor with respect to the sale of products in several countries outside the ICH's influence. Many tropical countries have adverse environmental conditions, including high temperature, humidity, and intense light. Products are usually sold without secondary packages in shops that don't have air conditioning. Pharmaceutical manufacturers in ICH member countries are now shifting their focus toward global marketing as the incomes of individuals are rising in various parts of the world. With this shift in focus, global storage-testing conditions have come into intense discussion (3–6). Hence the question arises: Should pharmaceutical products marketed in tropical countries be tested for stability using the combination of temperature, humidity, and light?

In a previous study, the authors found that the cross-linking of gelatin in its preparations was accelerated when products were exposed to all three environmental conditions instead of exposure to only one or two (7). In a recent study on ethambutol (hygroscopic) and other antituberculosis agents, the au-

Table I: Description of formulations investigated in the study.

Drugs	Drug content (mg)				Package	Type of product	Date of manufacture (period of expiry)
	R	H	Z	E			
E	—	—	—	800	Strip (50 μ m aluminum)	Uncoated	December 2001 (5 years)
H + E	—	300	—	800	Strip (40 μ m aluminum)	Uncoated	December 2001 (5 years)
H + E	—	300	—	800	Blister I (PVC ^a /PVDC ^b , orange/25 μ m aluminum + VMCH ^c)	Uncoated	November 2001 (2 years)
H + E	—	300	—	800	Blister II (PVC/PVDC, orange/29 μ m aluminum + VMCH)	Uncoated	October 2001 (2 years)
R + H + E	450	300	—	800	Strip (40 μ m aluminum)	Film coated	February 2002 (2 years)
R + H + E	450	300	—	800	Blister (PVC, orange/47 μ m aluminum + VMCH)	Film coated	January 2002 (2 years)
R + H + Z + E	225	150	750	400	Strip (50 μ m aluminum)	Film coated	November 2001 (2 years)
R + H + Z + E	225	150	750	400	Blister I (PVC/PVDC, glass clear/30 μ m aluminum + VMCH)	Film coated	December 2001 (2 years)
R + H + Z + E	150	100	500	267	Blister II (PVC/PVDC, orange/25 μ m aluminum + VMCH)	Film coated	December 2001 (2 years)

^aPolyvinyl chloride

^bPolyvinylidene chloride

^cA high molecular weight resin containing 86% vinyl chloride, 13% vinyl acetate, and 1% maleic acid acts as a heat-sealable packaging coating.

thors observed that light could even accelerate the rate of moisture gain by a hygroscopic drug (8).

Because the acceleration of moisture gain in the presence of light was a new phenomenon, the authors began investigating whether light, along with moisture and humidity, influenced moisture gain of packaged products. For this study, tablets containing ethambutol and other antituberculosis drugs were procured and stored with and without light under accelerated temperature and humidity conditions. The investigations were conducted on products packaged in strip and blister packs and unpackaged formulations. The results of this study are described in this article.

Experiment

Materials. Nine tablet formulations of antituberculosis drugs packaged in strip and blister packs were purchased from the local market. The formulations were from the same batch in each case. The tablets contained ethambutol (E) alone; combinations of isoniazid and ethambutol (H + E); rifampicin, isoniazid, and ethambutol (R + H + E); and rifampicin, isoniazid, pyrazinamide, and ethambutol (R + H + Z + E). The tablets with H + E were not sold in blister packs but were taken from antituberculosis kits. Table I describes each formulation, including the drugs present and their strengths, the types of

packaging, the nature of the products, and the dates of manufacture and expiry.

Equipment. The formulations were charged to a humidity chamber (KBF720, WTB Binder, Tuttlingen, Germany) and a photostability chamber (KBWF240, WTB Binder) for moisture gain studies. The chambers' temperature and humidity data were recorded on a personal computer using APT-COM communication software (version 1.0, WTB Binder). The photostability chamber was equipped with an illumination bank on the inside top that consisted of four white fluorescent lamps (L20, OSRAM GmbH, Munich, Germany) and two black-light UV lamps (L73, OSRAM GmbH) according to option 2 of the ICH guideline Q1B (2). Lux (model 545, Testo, Lenzkirch, Germany) and UV meters (Dr Honle AG, Grafelfing, Germany) were used for measuring the intensities of fluorescent and UV light, respectively. A precision analytical balance (AG 135, Mettler Toledo, Greifensee, Switzerland) was used for weight gain studies. Scanning electron microscopy (SEM) studies were performed by a JEOL 6100 microscope (JEOL Scientific, Tokyo, Japan).

Methods. For moisture gain studies, strip and blister packs were cut to obtain individually packed tablets, but a sufficient sealed portion existed on all sides. Also, some of the tablets were removed from the packaging to investigate the tablets' moisture

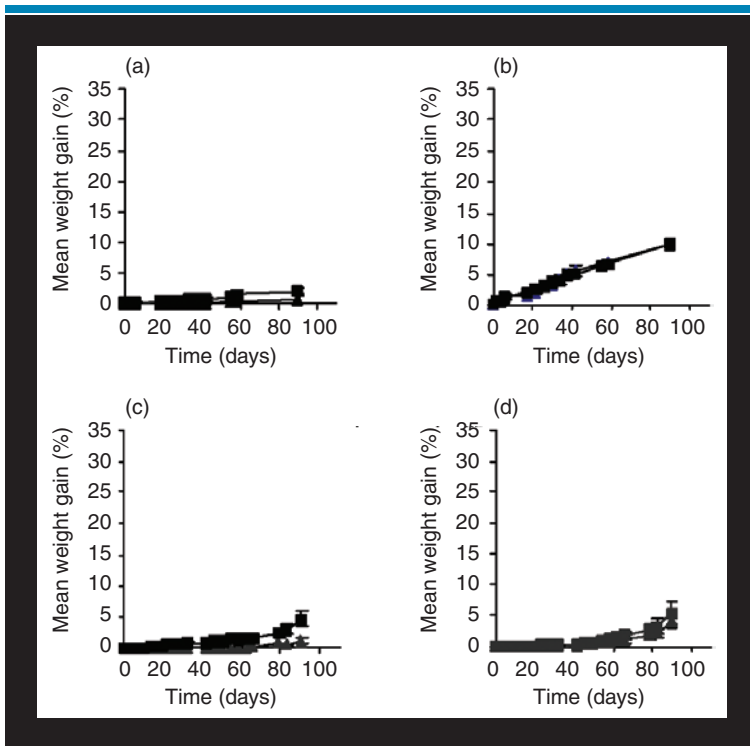


Figure 1: Behavior of weight gain by tablets packaged in strip packs containing E (a) alone, (b) H + E, (c) R + H + E, and (d) R + H + Z + E over time while exposed to stability chambers with (■) and without (▲) light.

lamps were turned on simultaneously in the photostability chamber. The wavelength of the UV lamps ranged from 345 to 410 nm with a maximum at ~365 nm. The output of the fluorescent lamp was similar to that specified in ISO 10977. The distance between the samples and the light bank was 9 in. The overall illumination at the point of placement was 5500 lux fluorescent light and 0.5 W/m² UV light.

Weight gain studies. The samples were withdrawn from the humidity and photostability chambers periodically. The packaged formulations were stored for a total duration of three months. The studies on unpackaged products continued for as long as the samples gained moisture and were discontinued once the equilibrium was attained.

Results and discussion

Moisture uptake behavior of tablets packaged in strip packs.

Figure 1 shows the moisture uptake behavior of strip-packed products. Figures 1a, 1c, and 1d indicate that a minimal moisture gain existed in darkness and light by tablets containing E, R + H + E, and R + H + Z + E, respectively. The minimal moisture gain is understandable because aluminum is supposedly im-

permeous to moisture as well as light. However, the tablets with H + E (see Figure 1b) showed a steady gain of moisture both in the absence and the presence of light. Also, when fresh strip packs of these tablets were opened for studies on unpackaged formulations, a fine sheet of white powder was found inside the pockets, which caused the authors to postulate that the foil had pinholes. To confirm this speculation, SEM studies were conducted on aluminum foil samples cut from the strip. The results are shown in the photographs in Figure 2. The region of the foil in which no pinholes were observed is shown in Figure 2a. Two places in which pinholes were observed are shown in Figures 2b and 2c. Figure 2d shows a magnified view of a pinhole.

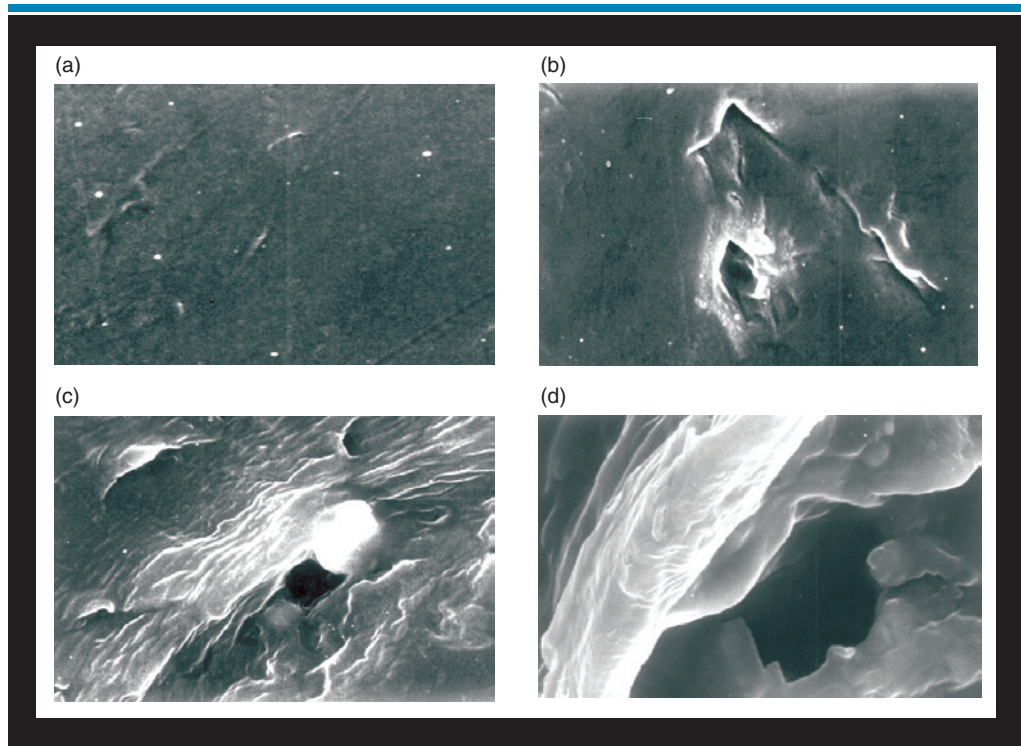


Figure 2: Photographs showing presence of pinholes in a strip pack in which a white coat of powder was seen in the tablet pockets. Region of the strip pack (a) without pinholes; (b and c) portions of the strip pack with pinholes; and (d) a magnified view of the pinhole in c.

gain behavior in an unpackaged state. The unpackaged tablets were placed in 10-mL beakers. In each case, triplicate samples were put in humidity and photostability chambers, both of which were set at 40 ± 1 °C and 75 ± 3% RH. The UV and fluorescent

searchers concluded that the pinholes in the aluminum film were responsible for the spread of powder inside the strip-pack pockets and this particular product's moisture gain in the stability chamber.

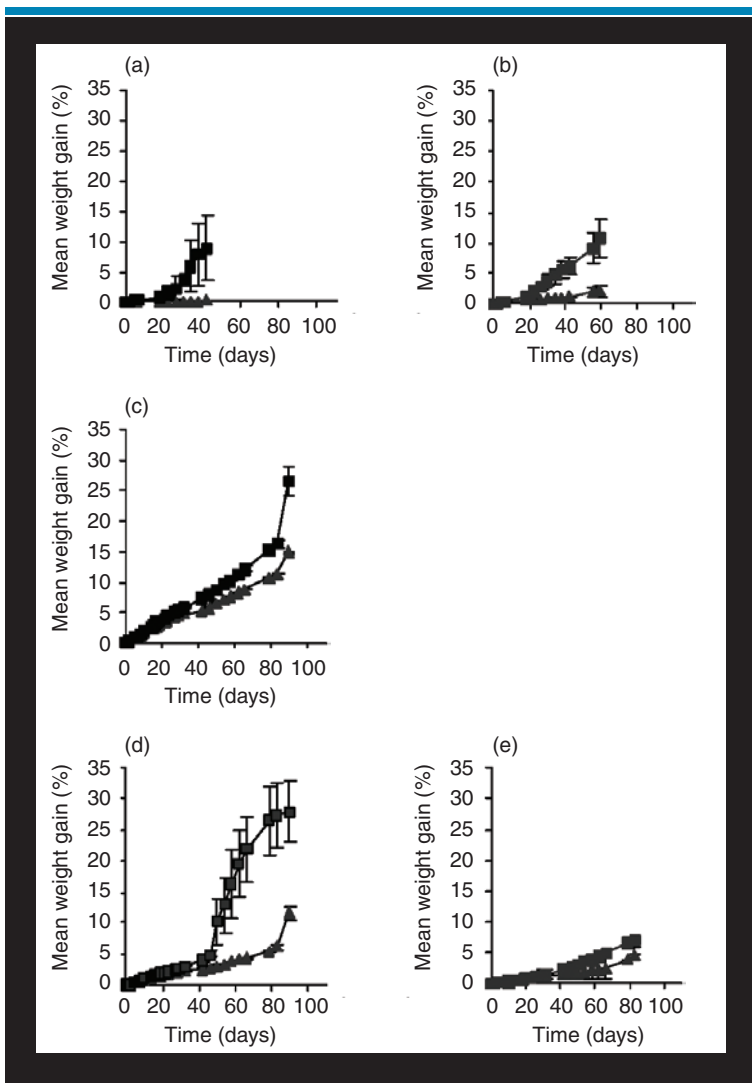


Figure 3: Behavior of weight gain by tablets packaged in blister packs containing (a, b) H + E, (c) R + H + E, and (d, e) R + H + Z + E over time while exposed to stability chambers with (■) and without (▲) light.

Moisture uptake behavior of tablets packaged in blister packs. Figure 3 shows the moisture uptake behavior of blister-packed formulations. Tablets containing E alone were not available in blister packs. The two blister formulations containing H + E (see Figures 3a and 3b) were profoundly influenced by light, and the result is similar for both products. The profiles of these two products are shown only for 40 and 60 days of testing, respectively, because the studies were abandoned when the tablets dissolved as a result of the gained moisture and the liquid contents leaked from the packs. Thereafter, the correct weights could not be determined because of content loss. Such a drastic instability occurred in the samples despite the fact that the blister films were colored. Because the samples did not gain moisture for almost 20 days in darkness and light, the results indicated that the integrity of the pockets was not affected initially when a particular portion was cut from the kit package. The change in the samples' stability was caused by prolonged exposure to the environmental conditions in the stability chamber, which was noted visually in the blister film's softening and peeling from

the edges, thereby causing the formation of channels through which the contents flowed out. This observation may indicate that light combined with the accelerated conditions of temperature and humidity brings a faster adverse influence on package material integrity, especially in the case of formulations containing H + E. Separate in-depth investigations of the stability of packaging materials under the combined influence of humidity, temperature, and light are currently underway.

The profile in Figure 3c for R + H + E tablets shows that this blister-packed product also exhibited profound moisture gain overall both in dark and lighted conditions. Over time, moisture droplets were found inside the intact blisters. The moisture ingress apparently resulted from the use of a pervious polyvinyl chloride (PVC) film (see Table I), which is typically used only for non-moisture-sensitive drugs.

The moisture gain behavior of two blister packs containing all four drugs (R + H + Z + E) is shown in Figures 3d and 3e. The blister pack in Figure 3d exhibited a profound moisture gain in the presence of light, which is explained by the fact that this blister pack's film was clear (see Table I). On the other hand, the presence of light affected the blister pack in Figure 3e much less, which can mainly be attributed to the correspondingly lower strength of ethambutol and other drugs (see Table I).

Moisture uptake behavior of unpackaged tablets. Figure 4 shows the profiles of unpackaged tablets that were tested using similar conditions as the packaged tablets. The unpackaged products gained maximum moisture in only 60–150 h. The presence of light accelerated the rate of moisture gain in all cases (packaged and unpackaged), which is similar to an observation made in a previous study of pure drugs and their combinations (8).

Tablets containing H + E (see Figures 4b–4d) gained more moisture overall than did tablets containing E alone (see Figure 4a) or other drug combinations (see Figures 4e–4i). The low moisture gain by tablets containing R + H + Z + E (see Figures 4g and 4h) can be explained by the low E strength in the formulation (see Table I). A decrease in moisture sensitivity with a decrease in E strength in the tablet is proven further by Figure 4i, which shows that even less time was required for the samples to reach a moisture-gain plateau as a result of a still lower quantity of E, along with other drugs.

Conclusion

This study demonstrates that marketed blister-packed anti-tuberculosis products that contain ethambutol gain more moisture when exposed to accelerated stability test conditions. Therefore, manufacturers should use packaging materials that can provide strong barriers. Strip packs are preferred over blister packs because strip packs showed a much lower moisture gain in the studies presented in this article. The fact that moisture gain did occur in one of the tested strip packs suggests that the aluminum

aging materials of the marketed products.

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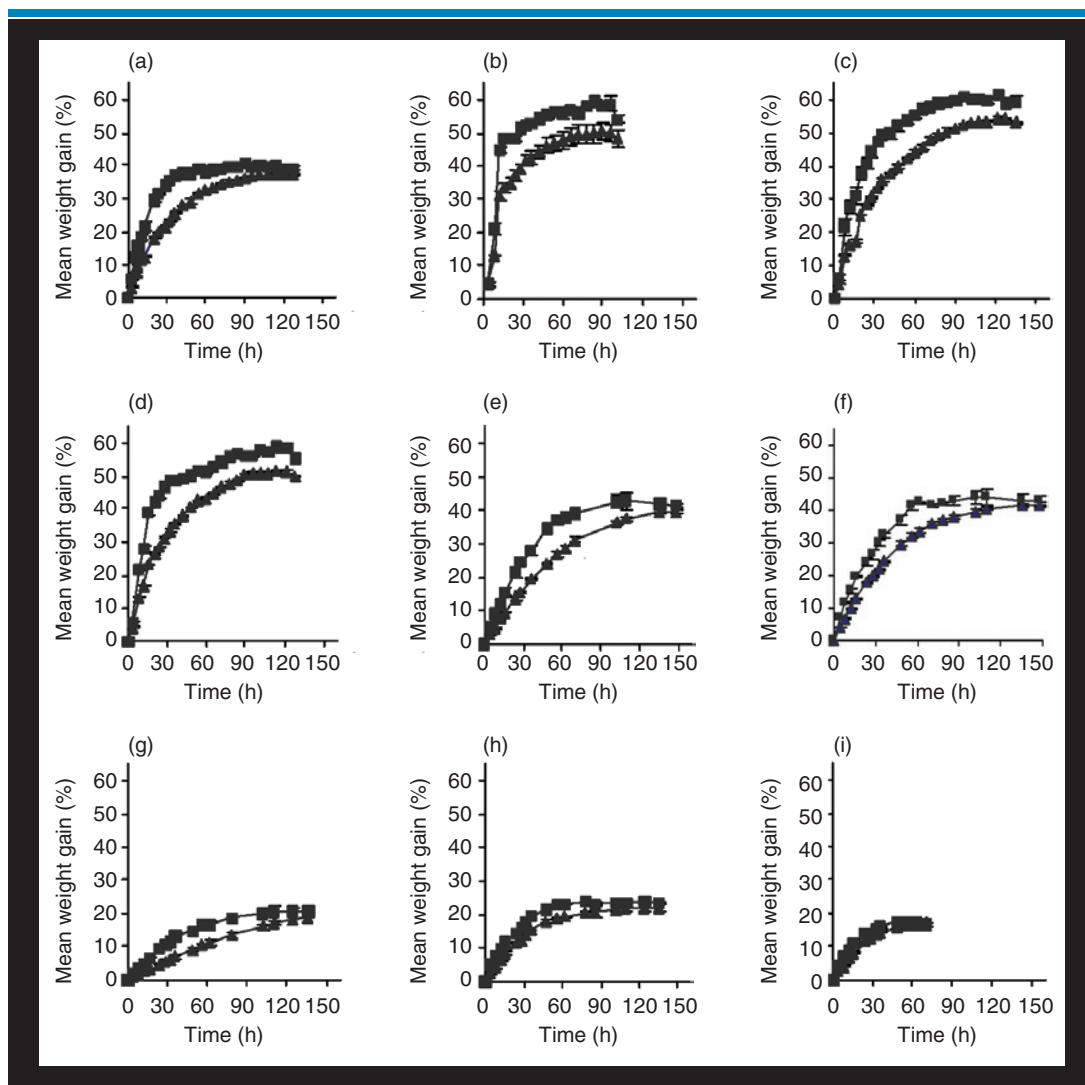


Figure 4: Behavior of weight gain by unpackaged tablets containing (a) E alone, (b–d) H + E, (e and f) R + H + E, and (g–i) R + H + Z + E over time while exposed to stability chambers with (■) and without (▲) light.

foil used in the packaging must be of high quality and free of pinholes. Moreover, the integrity of the packaging material should be monitored during the product's shelf-life. Proper packaging development studies must be conducted because they are of utmost importance regarding the worldwide concern about the quality of antituberculosis products that are already in circulation (9,10).

This study confirms the phenomenon that the rate of moisture gain in the presence of light also applies to blister-packed and unpackaged tablet formulations of the same drugs used in a previous study (8). Accordingly, this study suggests that stability testing of antituberculosis products should be conducted in the presence of light combined with the accelerated conditions of temperature and humidity. This finding may be especially true for products distributed in tropical countries in which heat, humidity, and intense light may contribute to product decay.

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