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Comparative stability of repackaged metoprolol tartrate tablets☆

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ABSTRACT

The stability of metoprolol tartrate tablets packaged in original high density polyethylene containers and repackaged in USP Class A unit-dose blister packs was investigated. Studies were conducted at 25 °C/60% relative humidity (RH) for 52 weeks and at 40 °C/75% RH for 13 weeks. The potency, dissolution, water content, loss on drying and hardness of the drug products were analyzed. Results indicated no differences in the stability between the tablets in both packages stored under 25 °C/60% RH. No difference in potency was found in both packages under either condition. However, a significant weight increase due to moisture uptake was observed for the repackaged tablets stored under 40 °C/75% RH. The weight increase was accompanied by a decrease in tablet hardness (6.5–0 kp) and a increase in dissolution rate (51–92%) in 5 min. Near-infrared (NIR) chemical imaging also monitored moisture uptake of the tablet non-invasively through the package. The observed changes in product stability may adversely affect the products bioavailability profile, even though the potency of the active drug remained within USP specification range of 90–110%. Study results suggest product quality can be negatively impacted even when using USP Class A repackaging materials.

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1. Introduction

Repackaging of solid oral drug products, such as tablets and capsules into unit-dose containers is a common practice both for the pharmacist and the pharmaceutical repackaging firm (Pedersen et al., 2003; ASHP Guidelines, 1977; ASHP Guidelines, 1983; Janes, 1983). For the original package the preferred container is a bottle made of glass or HDPE, while the most common container for unit-dose is the blister package. Various packaging materials are used to create blister package which consists of two components: the blister, which is the cavity that holds the product, and the lid stock, which is the material that seals to the blister. The commonly used materials for the blister are polyvinyl chloride, polyvinyl dichloride, polychlorotrifluoroethylene, aluminum foil and more recently, cyclic olefin copolymer (Allen, 1999). The unit-dose package may be very different from the original one in their physical and chemical properties, especially in the moisture barrier properties. Thus it may lead to a change in the stability profile of a drug product repackaged in a unit-dose package (Das Gupta et al., 1980).

The approaches and requirements for drug stability studies are outlined in the International Conference on Harmonization guidelines (ICH Q1A, Revision 2, 2003; ICH Q1B, 2003). To permit an informed judgment regarding the suitability of the packaging for a particular type of product, methods and a classification scheme for evaluating the moisture-permeation characteristics of single-unit and unit-dose containers are recommended by the U.S. Pharmacopeia (Containers-Permeation <671>, USP, 2008). The individual unit-dose containers as tested in *Method I* are designated *Class A*, *B*, *C* or *D* based on the rate of moisture permeation rate across the packaging material (Containers-Permeation <671>, USP, 2008). Numerous types of packages have been tested for their moisture permeation properties according the USP method (Reamer et al., 1977; Reamer and Grady, 1978). The USP also states that for non-sterile solid dosage forms packaged in unit-dose containers, the beyond-use date shall be one year from the date the drug is packaged into the unit-dose container or the expiration date on the manufacturer's container, whichever is earlier, unless stability data or the manufacturer's labeling indicates otherwise (Packaging practice <1146>, USP, 2008). FDA Draft Guidance "Expiration Dating of unit-Dose Repackaged Drugs: Compliance Policy Guide" has considered the USP beyond-use standard if: (1) the drug product being repackaged is a solid oral dosage form, and the

☆ This scientific contribution is intended to support regulatory policy development. The views presented in this article have not been adopted as regulatory policies by the Food and Drug Administration at this time.

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unit-dose container complies with the Class A standard described in the USP; (2) the original bulk container of drug product has not been opened previously and the entire contents are repackaged in one operation; and (3) the repackaging and storage of the drug product are accomplished in a controlled environment that is consistent with the conditions described in the labeling for the original drug product and the repackaged drug product (FDA Draft Guidance for Industry, 2005). However, two repackaging firms requested that the draft FDA guidance should be revised to allow one year dating on unit-dose packages using Class B material (Webview, 2005). In order to address regulatory concerns about the time extension and to identify potential stability issues associated with repackaged drug products the FDA has conducted research studies on repackaged drug products. The first of these studies tested the stability of ranitidine syrup repackaged in unit-dose containers (Shah et al., 2008). The second FDA repackaging study evaluated the stability differences between a gabapentin capsule product in its original bulk containers and in repackaged unit-dose blister strips (Gupta et al., 2009). The current study evaluates the differences that may result from metoprolol tartrate tablets packaged in original high density polyethylene containers and repackaged in USP Class A unit-dose blister packs.

2. Materials and methods

2.1. Materials

Metoprolol tartrate tablets (50 mg) were manufactured by Caraco Pharmaceutical Laboratories, Ltd. (Detroit, MI) and were repackaged by Dispensing Solutions, Inc. (Santa Ana, CA). The USP metoprolol tartrate reference standard and oxprenolol hydrochloride resolution standard were obtained from USP (Rockville, MD). All other chemicals used are of reagent grade.

2.2. Sample preparation

An appropriate number of metoprolol tartrate tablets in the original, white, round HDPE bottle with child-resistant polypropylene caps, containing 100 tablets/bottle, and the unit-dose repackaged blister strips which consist of two parts, USP Class A certified, foil/paper backing with a clear plastic cover material, formed into a unit-dose packet and sealed on all four sides, were stored under long term storage conditions (25 °C/60% RH) for 52 weeks and under accelerated storage conditions (40 °C/75% RH) for 13 weeks. Samples were stored in carefully monitored and regulated incubators (Hotpack, Warminster, PA). Samples stored under long term storage conditions were removed and analyzed at 0, 4, 13, 26, 39 and 52 weeks. Samples stored under accelerated storage conditions were removed and analyzed at 0, 4, 8 and 13 weeks. At the appropriate time points, one original sealed bulk container and appropriate number of repackaged unit-dose blister strips were removed from the stability chambers for analysis. Samples were analyzed for water content, loss on drying and tablet hardness immediately after removal from the stability chambers and for potency and dissolution after equilibrating at room conditions for one hour.

2.3. Loss on drying

Loss on drying was tested according to the USP method (Loss on drying <731>, USP, 2008). Four tablets (about 700 mg) were quickly removed from containers and loaded onto MB 35 Moisture Analyzer (Ohaus Corporation, NJ). The tablets were dried at 105 °C for two hours and the loss of weight (%) was recorded.

2.4. Water content determination

Water content was determined by method 1a (direct titration) described in the USP using Karl Fischer Titrator (Mettler Toledo DL 38, Switzerland) (Water determination <921>, USP, 2008). Ten tablets were finely ground in a mortar and pestle under room conditions. A weighed portion of the powder estimated to contain not less than 5 mg of water was quickly added to the titration vessel, mixed thoroughly, and again titrated with the KF reagent to the electrometric endpoint. The water content (%) was automatically calculated by the instrument. All tests were done in triplicate.

2.5. Weight change during storage

Ten individual repackaged units of the metoprolol were weighed and placed under both storage conditions. The individual repackaged units were weighed again at each time point to determine the change in sample weight due to the permeation of moisture across the packaging material used for repackaging the tablets.

2.6. Tablet hardness

Hardness of ten tablets at each time point was measured using a VK-200 Tablet Hardness Tester (Varian Instruments, CA). Each tablet was loaded such that the scoring on the surface was always oriented perpendicular to the sensing and power jaws.

2.7. Potency testing

The potency testing was performed using a validated USP monograph liquid chromatography method for the metoprolol tartrate tablets using 20 tablets at each time point (Metoprolol tartrate tablets, USP, 2008). The quantity, in mg, of metoprolol tartrate present in the portion of tablets taken for analysis was calculated using the formula:

$$100 \times C \times \left(\frac{r_U}{r_S}\right)$$

in which C is the concentration, in mg per mL, of the USP Metoprolol Tartrate RS in the standard solution; and r_U and r_S are the metoprolol peak responses obtained from the test samples and the standard solution, respectively.

2.8. Dissolution testing

Dissolution testing was carried out according to the USP method using apparatus I (Van Kel, Cary, NC) (Dissolution <711>, USP, 2008). Nine hundred millilitres of the degassed dissolution medium at 37 ± 1 °C was used in each vessel. Six tablets each of the original drug product and the repackaged drug product were analyzed at 275 nm every 5 min for 30 min using a flow-thru UV–vis spectrophotometer accessory attached to the dissolution apparatus. The amount dissolved was automatically calculated by the spectrophotometer by comparing the absorbance of the test samples against that of a reference standard solution of metoprolol tartrate.

2.9. Equilibrium moisture content

Equilibrium moisture content of the excipients present in the tablet formulation were determined gravimetrically at 25 and 40 °C on a Symmetrical Gravimetric Analyzer (Model SGA-100, VTI Corporation, Hialeah, FL) from 5% to 95% RH in increments of 5% RH. Sample size was between 5 and 10 mg. The air flow rate was set at 100 cm^3/min. All samples were dried in the instrument at 60 °C

for one hour prior to the water sorption experiment. A weight change of less than 0.05% in 20 min was used as the equilibrium criteria.

2.10. Near-infrared spectroscopy—forced hydration of drug product and formulation

2.10.1. Ingredients

To understand better the impact of humidity and assess the hygroscopic nature of the formulation ingredients; the metoprolol drug product, the metoprolol API and the major excipients were studied by NIR chemical imaging. A pure compact (approx. 300 mg) of each major ingredient – API (metoprolol tartrate), sodium starch glycolate (SSG), microcrystalline cellulose (MCC), lactose monohydrate, and hydroxypropyl methylcellulose (HPMC) – was produced using a benchtop hydraulic press (Carver model 3889, Wabash, IN) at 2000 lb, 40% pump speed, 1 min dwell time with a 3/8in diameter stainless steel cylindrical punch and die set (The Elizabeth Companies, McKeesport, PA). The compacts were exposed to accelerated conditions 40 °C, 75% RH for 14 days without packaging protection. A Sapphire™ NIR Chemical Imaging System (Malvern, United Kingdom) was used to acquire near-infrared (NIR) chemical images of the compacts prior to exposure, and on days 1, 2, 4, 8, and 14. Near-infrared reflectance data was collected at 1400–2200 nm, with a spectral resolution of 10 nm. Similarly, three metoprolol drug product tablets were exposed and imaged for 14 days and reflectance spectra were generated. Malvern's ISys™ (v. 3.1) software was used for spectral analysis.

2.10.2. Near-infrared chemical imaging—drug products

A Spectral Dimensions Sapphire™ NIR Chemical Imaging System was used to acquire near-infrared chemical images of the drug product tablet. The manufacturer's SapphireGo Software was used to process the images. Six tablets from the original container and 6 tablets from the unit-dose repackaged blister strips were scanned at each time point. Images were collected from the top and bottom side of each tablet. For each side, 8 spectral images were collected across 1400–2450 nm range with a spectral resolution of 10 nm and a spatial resolution (i.e., pixel size) of 39 μm.

2.10.3. A statistical analysis

A Students *t*-test was used with a 5% significance level ($\alpha = 0.05$).

3. Results and discussion

3.1. Loss on drying

Tablets in the original containers stored under both storage conditions and in the repackaged unit-dose blister strips stored at 25 °C/60% RH showed little change in the loss on drying during the study period. However, a significant increase in water content from the initial 3.5 to 9.4%, 9.5% and 10.5%, respectively after 4, 8, and 13 weeks was observed with the repackaged tablets stored at 40 °C/75% RH ($p < 0.01$).

3.2. Water content determination

Tablets in the original containers under both storage conditions and in the repackaged unit-dose blister strips stored at 25 °C/60% RH conditions showed no change in water content during the study period. However, the repackaged metoprolol tablets showed an increase in water content from the initial 4.0% at the beginning of the study to 8.5%, 7.3% and 7.7%, respectively, after 4, 8, and 13 weeks of storage at 40 °C/75% RH conditions. These data confirm a significant moisture uptake by the repackaged tablets under elevated temperature and humidity conditions ($p < 0.01$).

3.3. Weight change during storage

Only metoprolol tablets in repackaged unit-dose blister strips stored at 40 °C/75% RH showed significant increase in the tablet weights. The mean tablet weight ($n = 6$) increased from the initial weight of 175 mg to 185, 186 and 186 mg at week 4, 8, and 13, respectively ($p < 0.05$), representing an increase of 5.7%. This was similar to the weight change observed with the loss on drying and water content data. This direct correlation suggests that the moisture was penetrating the package and was being absorbed by the tablets, thus compromising the integrity and quality of the metoprolol tablets repackaged in the unit-dose blister strips.

3.4. Tablet hardness

No change in hardness was observed for the metoprolol tablets from the original container stored under both conditions or from the repackaged unit-dose blister strips stored at 25 °C/60% RH. However, the hardness of the repackaged metoprolol tablets stored at 40 °C/75% RH showed a significant decrease from initial 6.5 kp (at week 0) to 0 kp after 4 weeks ($p < 0.01$). This loss in the tablet hardness of repackaged metoprolol tables appears to be due to the significant moisture uptake by these tables during storage at 40 °C/75% RH. These data highlight the importance of controlling the permeation of moisture through the packaging material being used to repackage drug products. It should be noted that tablets exposed to excess moisture do not always exhibit a decrease in hardness. Sometime, an increase in hardness may occur too, depending on the pharmaceutical excipients and the active drug substance. For example, tolbutamide tablets harden after two to four weeks of exposure to a temperature of 49 °C/100% RH, while phenindione tablets harden to different degrees depending on the binder used in the formulation (Khalil et al., 1973, 1974). Of concern would be drug products that contain highly hydroscopic excipients which might be more vulnerable to the moisture permeation, thus the product quality would be negatively impacted.

3.5. Potency

No significant differences were observed in the potency of the repackaged tablets as compared to the tablets stored in the original container during the study period under both storage conditions. All samples had a potency between 96% and 104%, which is well within the USP requirements of 90–110% labeled claim for the tablet potency (Table 1). In addition, no impurity or degradation product was detected for any samples stored under either storage condition.

Table 1
Potency of metoprolol tartrate tablets in original containers and repackaged unit-dose blister strips after storage under 25 °C/60% RH and 40 °C/75% RH conditions ($n = 3$). Values are mean ± SD.

Time (weeks)	25 °C/60% RH		40 °C/75% RH	
	Original	Repackaged	Original	Repackaged
0	99.2 ± 0.5	101.2 ± 0.4	99.9 ± 0.9	102.0 ± 0.3
4	99.4 ± 0.1	100.4 ± 1.2	100.6 ± 0.6	104.9 ± 0.6
8	–	–	97.2 ± 1.3	101.9 ± 1.2
13	100.9 ± 1.1	100.2 ± 1.0	100.7 ± 1.5	102.42 ± 1.6
26	98.1 ± 0.5	100.2 ± 0.8	–	–
39	96.6 ± 1.0	97.8 ± 2.2	–	–
52	98.7 ± 1.0	99.4 ± 1.0	–	–

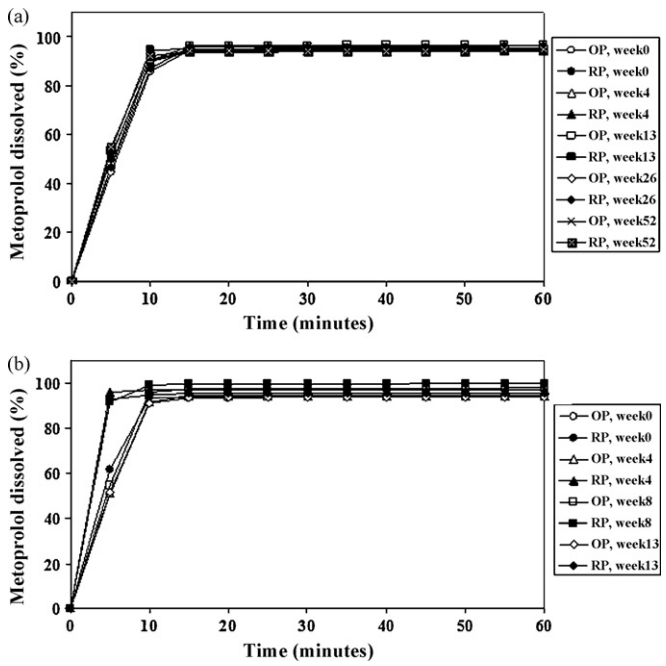

Fig. 1. Mean ($n = 6$) dissolution profiles of original and repackaged metoprolol tartrate tablet at (a) 25 °C/60% RH and (b) 40 °C/75% RH. The standard deviation bars are not displayed because they are smaller than symbol. OP: original package; RP: repackage.

3.6. Dissolution

All tablets at all time points met the USP dissolution criteria of Q NLT 75% in 20 min. The repackaged metoprolol tablets stored at 40 °C/75% RH for 4, 8 and 13 weeks showed a faster dissolution of 92% within 5 min as compared to 51% dissolution at the start of the study. Tablets stored in the original package at 40 °C/75% RH, however, showed no change in the dissolution profile, as well as all tablets (original and repackaged) stored at 25 °C/60% RH for 52 weeks (Fig. 1). The results clearly show that altered dissolution of the repackaged metoprolol tablets could be a major product quality concern in ICH climate zone IV (hot/humid) (Dietz et al., 1993).

Table 2
Equilibrium moisture content of some excipients present in metoprolol tablets.

Excipient	Equilibrium moisture content (% w/w) at	
	25 °C/60% RH	40 °C/75% RH
Povidone	23.7	32.4
Sodium starch glycolate	16.5	25.3
Polysorbate	6.4	13.7
Colloidal silicon dioxide	7.8	11.2
Microcrystalline cellulose	6.6	8.1
Hydroxypropyl methylcellulose	5.2	9.0

The results of water content and loss on drying suggest that the moisture sorption by metoprolol tablets may be responsible for the faster release from these tablets. Whether this faster drug release from the repackaged product presents a clinical significance needs to be further investigated, which was beyond the scope of this work. However, the quality of tablets might be affected because of the lost of hardness and faster dissolution after storage under accelerated storage conditions. Hence caution should be observed if controlled release tablets which are moisture sensitive are repackaged in the similar packaging materials.

3.7. Equilibrium moisture content

This study was performed to determine if the moisture uptake by tablets stored under accelerated storage conditions of temperature and humidity was the result of the hygroscopicity of certain excipients. An increase in the equilibrium moisture content at higher temperature and humidity condition would indicate that the excipients are hygroscopic. The metoprolol tartrate tablets used in this study were formulated using colloidal silicon dioxide, hydroxypropyl methylcellulose, microcrystalline cellulose, polysorbate, povidone and sodium starch glycolate. Statistically significant higher equilibrium moisture content at 40 °C/75% RH as compared to 25 °C/60% RH (Table 2) was observed with all of these excipients which could be the driving force behind the significant moisture uptake by the tablets stored under accelerated storage conditions. Any permeation of moisture across the packaging material under accelerated storage conditions would readily be absorbed by these materials resulting in an increase in the moisture content of the tablets as seen with the metoprolol tablets stored at 40 °C/75% RH.

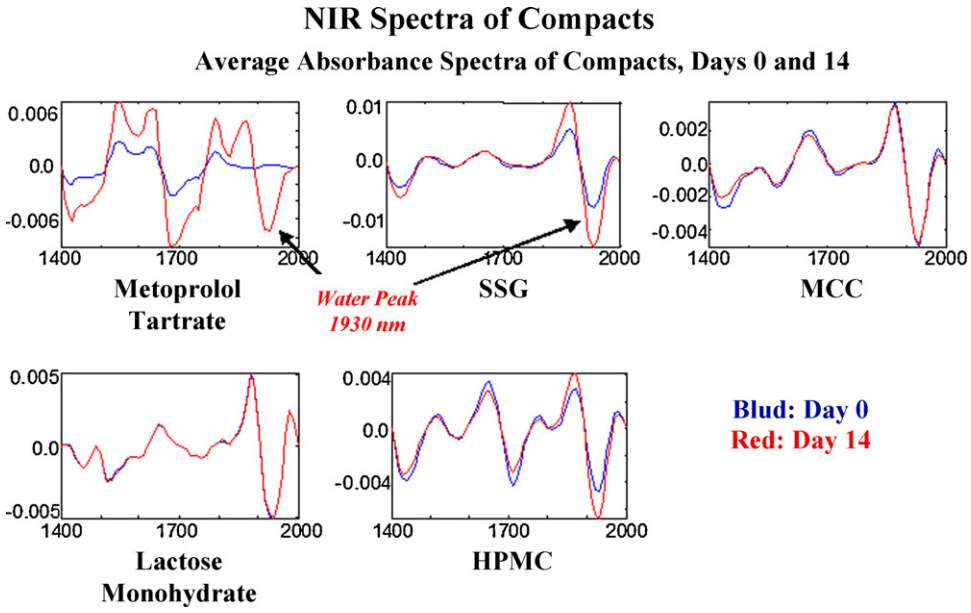

Fig. 2. NIR spectra of the compacts on day 0 and day 14 following unprotected storage at 40 °C/75% RH; metoprolol, SSG, MCC, lactose monohydrate, HPMC.

3.8. Near-infrared spectroscopy—forced hydration of drug product and formulation

3.8.1. Ingredients

To confirm the moisture uptake of metoprolol and formulation excipients the sample compacts were monitored by NIR chemical imaging. Images were preprocessed by converting the data to absorbance data ($A = -\ln(R)$), and applying a Savitzky-Golay second-derivative (11 points, 3rd-order polynomial). Changes in the density of the pure metoprolol compact also necessitated changing the upper spectral limit from 2200 to 2000 nm. It can be clearly seen in the second-derivative spectra (Fig. 2) that following unprotected exposure to storage conditions at 40 °C/75% RH for 14 days, that the compacts of metoprolol tartrate and SSG absorb moisture. MCC also showed a small increase in moisture, while HPMC and lactose monohydrate showed no significant change. In particular, the metoprolol compact absorbed water slowly over the two-week period, while SSG approached peak absorbance in about one day. Likewise when the drug product tablets were studied, they demonstrated rapid water absorption in approximately one day (data not shown) which can now be attributed to the SSG. These results clearly show the utility of NIR spectroscopy for screening of excipients to detect changes in the moisture content of samples placed under high humidity conditions.

3.8.2. Near-infrared chemical imaging-drug products

The moisture uptake can be clearly seen in the NIR chemical images of the repackaged unit-dose tablets after storage at 40 °C/75% RH (Fig. 3). The NIR chemical images of the untreated repackaged tablets, the repackaged tablets stored at 25 °C/60% RH and the tablets from the original container before and after storage under the stability conditions displayed little changes (Fig. 3). These results clearly show the utility of NIR chemical imaging in non-destructively detecting changes in the samples placed on stability study.

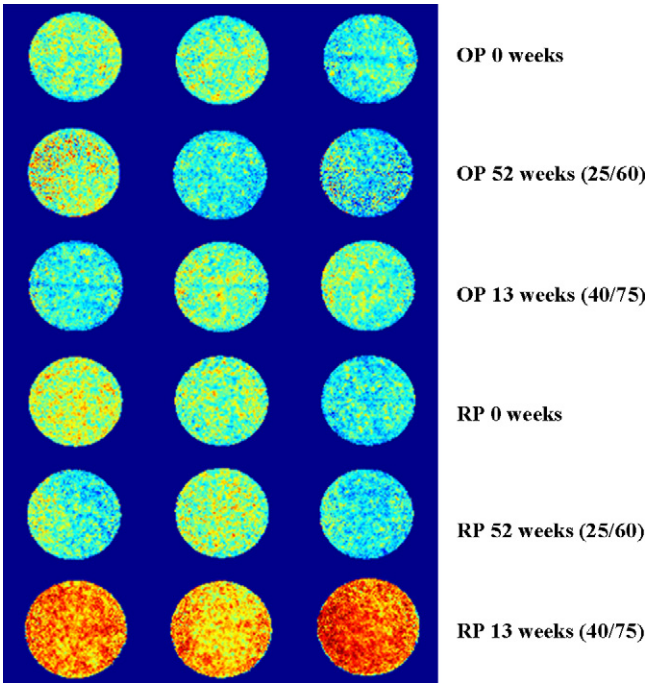

Fig. 3. NIR chemical images of the tablets from the original containers (OP) and repackaged unit-dose blister strips (RP) at the start of the study (0 weeks) and after 52 and 13 weeks storage at 25 °C/60% RH and 40 °C/75% RH.

4. Conclusion

This study compared the stability of metoprolol tartrate tablets repackaged into USP Class A unit-dose containers with the stability of the same drug products stored in the original containers at two storage conditions. The results indicated no differences in the stability during the 12 months storage at 25 °C/60% RH. However, a significant moisture uptake was observed for the metoprolol tablets repackaged using USP Class A material when stored under 40 °C/75% RH conditions. The moisture uptake resulted in changes: (1) an increase in tablet weight, (2) a decrease in tablet hardness and (3) faster tablet dissolution. No such change was observed for tablets stored in the original container. If product quality could be compromised due to permeation of moisture across the USP Class A materials, USP Class B materials with significantly higher moisture permeation should be avoided for repackaging drug products, especially if they are formulated using hygroscopic ingredients.

The results highlight the importance of selecting the packaging material for repackaging a drug product based on the scientific understanding of the equilibrium moisture content of different formulation components, in addition to the active drug substance. This is especially important for those drug products that are formulated using hygroscopic ingredients to assure the physical integrity of the drug product. For these products applying the same expiration to the repackaged drug products without any stability studies could compromise their product quality during storage even when repackaged using USP Class A materials.

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