

The effects of packaging on the stability of a moisture sensitive compound

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Abstract

Packages that provided stability (less than a 10% loss in potency) of a moisture sensitive compound (PGE-7762928) in tablet form at accelerated conditions for 6 months were identified. The equilibrium moisture content of the tablets at 25°C/60%RH, 30°C/60%RH and 40°C/75%RH were 2.3, 2.4, and 2.9%, respectively. The tablet equilibrium moisture content, degradation rate of unpackaged product, and the moisture barrier properties of the packages were used to predict the stability of the packaged product. The physical and chemical stability (HPLC assay) of the products were measured after 2, 4, 6, 8, 12, and 24 weeks at ICH conditions. The Containers-Permeation¹ of polyvinyl chloride blisters, cyclic olefin blisters, aclar blisters, cold-form aluminum blisters was 0.259, 0.040, 0.008 and 0.001 mg per blister per day, respectively. At 6 months at 40°C/75%RH, the percent active was 84% in polyvinyl chloride blisters, 91% in cyclic olefin blisters, 97% in aclar blisters, 100% in cold-form aluminum blisters and 99% in an high density polyethylene bottle with a foil induction seal. The stability results for the packaged product were fairly consistent with the predictions based on the moisture sensitivity of the product and the moisture barrier properties of the respective package. To gain a better prediction, the flux value determined by the Containers-Permeation procedure was adjusted for the internal moisture concentration of the blister. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Stability testing demonstrates the physical and chemical stability of a drug product at a variety of

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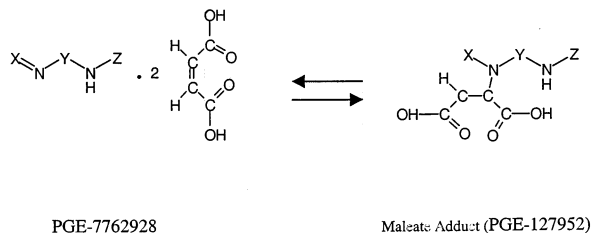
environmental conditions including temperature, humidity and light (USP24/NF18, 2000). Requirements for stability studies are defined in several International Conference on Harmonization guidelines and include storage conditions of 25°C/60%, 30°C/60%RH and 40°C/75% relative humidity (ICH Steering Committee, 1994, 1998).

The challenge for a moisture sensitive compound is to demonstrate stability at the acceler-

ated condition of 40°C/75%RH for 6 months. Many compounds are moisture sensitive and exposure at the accelerated condition results in significant degradation (Carstensen, 1993). Stability studies have been published on moisture sensitive drug products such as aspirin (Snaveley et al., 1993) and seproxetine (Schildcrout et al., 1993).

In the pharmaceutical industry the preferred package options are bottles or blisters. The most common blister materials are polyvinyl chloride, polyvinyl dichloride, Aclar (polychlorotrifluoroethylene), aluminum foil and more recently, cyclic olefin copolymer (Allen, 1999). Polyvinyl chloride is often preferred for drug products primarily due to its low cost and ease of processability (Hunt, 1999). However, a disadvantage of polyvinyl chloride is that it has minimal moisture barrier properties. Aclar, comprised of laminated polyvinyl chloride, has superior moisture protection properties than either polyvinyl chloride or polyvinyl dichloride. Another disadvantage of polyvinyl chloride is the environmental issues associated with the disposal of films containing polyvinyl chloride (Korab, 1999). A relatively new environmentally acceptable blister film is copolymer of ethylene and cyclic olefins (cyclic olefin copolymer). The most impermeable moisture barrier is provided by cold-form aluminum foil.

PGE-7762928 is a proprietary compound under development at Procter & Gamble Pharmaceuticals. The results of PGE-7762928 preformulation data demonstrated dilute solution stability, solid state stability, non-hygroscopicity of the drug substance and significant degradation of prototype tablet formulations at 40°C/75%RH. The degradation mechanism was subsequently identified and the following schematic shows the mois-



ture related degradation of PGE-7762928 (Gazda et al., 1998):

In the immediate release tablet formulation the degradation mechanism is postulated as follows: (a) moisture uptake by the hygroscopic excipients (microcrystalline cellulose, crospovidone) enabling drug dissolution; and (b) the reaction of a weakly basic nitrogen on the drug substance with the maleic acid counter ion via a second order pH-dependent Michael addition reaction to form a maleate adduct (Gazda et al., 1998).

The objective of this research was to use the drug product and package characterization data to predict and subsequently confirm the package material that provided adequate stability of PGE-7762928 at accelerated conditions (40°C/75%RH). The success criterion for these studies was less than a 10% loss in potency at accelerated conditions.

2. Materials and methods

2.1. Materials

The following materials were used in this study: PGE-7762928 (Procter & Gamble Pharmaceuticals, Norwich, NY), lactose monohydrate DCL-11 (DMV, Veghel Netherlands), microcrystalline cellulose PH 101 (FMC, Philadelphia, PA), crospovidone (ISP, Wayne, NJ) and magnesium stearate (Ackros Chemicals, New York, NY). The packaging materials used in this study were as follows: 10 mil polyvinyl chloride (Klockner, Gordonsville, VA), 12 mil Aclar (TekniPlex, Somerville, NJ), 13 mil cyclic olefin copolymer (Klockner, Gordonsville, VA), 6 mil aluminum foil (Lawson Mardon, Shelbyville, KY) and high density polyethylene bottles (West, Puerto Rico).

2.2. Methods

2.2.1. Tablet manufacture

A 1 kg batch of 5 mg PGE-7762928 tablets was manufactured by direct compression. The immediate release tablet formulation was as follows:

Ingredient	Amount per tablet (mg)
PGE-776928	5.0
Lactose monohydrate	156.0
Microcrystalline cellulose	71.0
Crospovidone	7.0
Magnesium stearate	1.0
Total	240.0

The PGE-7762928 was ground in a mortar and pestle. The microcrystalline cellulose and PGE-7762928 were then passed through a 30 mesh screen. The microcrystalline cellulose and PGE-7762928 were then blended in a glass jar in a Turbula mixer (Impandex T2C, Maywood, NJ) at the high speed mixer setting for 5 min. The crospovidone and lactose were added to the mixture and blended for an additional 10 min at the high speed mixer setting. The magnesium stearate was then added to the mixture and blended for an additional 3 min at the high speed mixer setting. Modified oval tablets (11.7 mm × 5.8 mm) were then compressed with an F-press (Stokes-Merrill F-4, 900-S21-2, Bristol, PA) to a final target tablet weight of 240 mg. The tablets were collected and stored in a tightly sealed glass bottle and stored at 5°C until packaged.

2.2.2. Tablet analysis

Tablets were analyzed using an isocratic HPLC method with UV detection. An Inertsil™ column was used to quantitate both the parent PGE-7762928 and maleate adduct degradant (area%). Mobile phase consisting of 0.1% pentafluoropropionic acid, 8.9% acetonitrile and 99% purified water was prepared. Standard stock solutions of PGE-7762928 were prepared at concentrations of 0.6, 0.3, 0.15, 0.0755 µg/ml. The retention times of the parent PGE-7762928

and the maleate adduct degradant were 8 and 4.5 min, respectively. The standard curve was constructed using the mean of the absorbance values obtained from each standard solution. The linear range was 0.3–0.6 µg/ml with a limit of quantitation of 0.3 µg/ml PGE-776928.

For each assay two sets of ten tablets were placed in 100 ml volumetric flasks containing purified water. Each flask was shaken for 20 min on a wrist action shaker (Burrell 75, Pittsburg PA) and sonicated for 10 min in a Ultrasonic Cleaner (Branson 5510, Danbury, CN). The solution was filtered to remove insoluble excipients and assayed for PGE-776928 and PGE-127952.

2.2.3. Unpackaged tablet stability

Unpackaged tablets were stored at 5°C, RT/80%RH, 25°C/60%RH, 30°C/60%RH and 40°C/75%RH. The relative amounts of PGE-7762928 and the maleate adduct degradant (PG-127952) were determined at 2, 4, 6, 8 and 12 weeks.

2.2.4. Equilibrium moisture content determination

The equilibrium moisture content of three tablets was analyzed on a moisture balance (VTI SGA-100, Hialeah, FL) at each storage condition (25°C/60%RH, 30°C/60%RH and 40°C/75%RH). For each condition, the chamber was purged for approximately 2–3 h at 60°C until the weight of the tablets was constant. The system was then ramped to each temperature and humidity conditions to determine the equilibrium moisture content. Results are expressed as percent of the purged tablet weight.

2.2.5. Packaging

Tablets were packaged into blisters on a standard blister machine (Klockner EAS2, Clearwater, FL). Tablets were also hand packaged into standard high density polyethylene bottles with an 0.001 inch aluminum foil seal.

The following conditions were used to form and seal the blister materials into 13.3 mm × 7.5 mm × 4.4 mm (length × width × height) cavities:

Blister material	Forming temperature (°C)	Sealing temperature (°C)	Pressure (PSI)
Polyvinyl chloride	145	150	70
Aclar	144	185	75
Cyclic olefin copolymer	144	168	70

No forming temperature is used for aluminum foil as this material is formed by physical deformation (cold-forming). The aluminum foil was then sealed at 240°C.

2.2.6. Package characterization

2.2.6.1. Moisture permeability. The moisture permeability of cold-form aluminum, polyvinyl chloride, Aclar, and cyclic olefin copolymer blisters were determined according to the Containers-Permeation procedure (USP24/NF18, <671>, 2000). Blisters containing anhydrous calcium chloride desiccant pellets were stored at 23°C/75%RH and monitored for weight gain at four intervals over a period of 28 days. The weight gain was used to determine the moisture permeability through the container and was expressed as mg per blister per day.

2.2.6.2. Leak testing. Leak testing for the blisters was conducted to ensure that a sufficient seal was formed between the film or foil and the aluminum foil lidding (ASTM Method D 3078-94, 1994). The samples were submerged in a vacuum chamber containing dye solution and a 10 mmHg vacuum was drawn on the chamber. Using this method, leaks were detected if a steady flow of bubbles originates from the blisters, or by the presence of dye solution within the test blisters once the vacuum has been removed.

2.2.7. Packaged stability

Tablets packaged in polyvinyl chloride blisters, cyclic olefin blisters, Aclar blisters, cold-form alu-

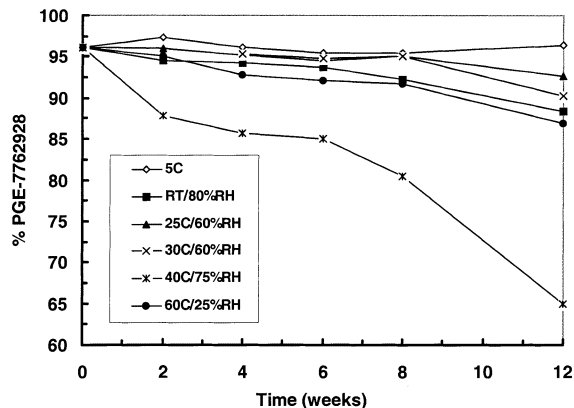


Fig. 1. The effect storage conditions on unpackaged PGE-7762928 tablet assay.

minum blisters and in high density polyethylene bottle with a foil induction seal were stored at 25°C/60%RH, 30°C/60%RH, 40°C/75%RH (Hotpak Stability Chambers 417532, Cincinnati, OH). Unpackaged (open dish) tablets were also stored at the same conditions. Tablet content uniformity and assay were determined at the start of the stability program, and assay was determined at 2, 4, 6, 8, 12 and 24 weeks.

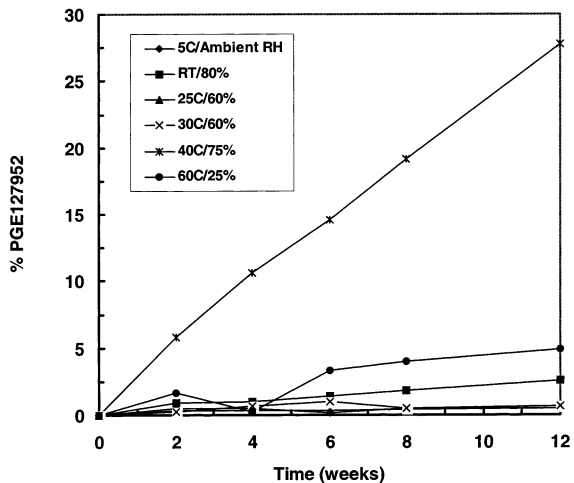


Fig. 2. The effect of storage conditions on unpackaged PGE-127952 maleate adduct formation.

Table 1
The equilibrium moisture content of 5 mg PGE-7762928 tablets at ICH conditions

Condition	Equilibrium moisture content (%)
25°C/60%RH	2.3
30°C/60%RH	2.4
40°C/75%RH	2.9

3. Results and discussion

3.1. Unpackaged tablet stability

The assay and maleate adduct formation of unpackaged PGE-7762928 tablets at 2, 4, 6, 8 and 12 weeks is shown in Figs. 1 and 2. As expected, the highest temperature and humidity condition (40°C/75%RH) resulted in the greatest amount of degradation, with a 12 week assay of 65% PGE-7762928. The formation of the maleate adduct PG-127952 corresponds well with the loss of potency (28% PG-127952 at 12 weeks). After 12 weeks at the RT/80%RH condition the assay was 88% and at 60°C/25%RH the assay was 87%. At 5°C, 25°C/60%RH and 30°C/60%RH there was minimal degradation with a PGE-7762928 assay value greater than 90%.

3.2. Equilibrium moisture content

The equilibrium moisture content at each ICH stability condition is shown in Table 1. As expected, at 40°C/75%RH the tablets had the highest moisture content of 2.9%. Since PGE-7762928 is non-hygroscopic, the tablet water uptake is attributed to the microcrystalline cellulose and crospovidone in the tablets.

3.3. Packaging characterization

No leaks were observed for any sample for all blister packages. The moisture permeability of polyvinyl chloride, cyclic olefin copolymer, Aclar and cold-form aluminum blisters by the USP24/NF Containers-Permeation test is shown in Table 2. The four blister materials have very different moisture permeability properties. As expected, the

Table 2
USP Container-Permeation results

Material	Container-Permeation (mg per blister per day)
Polyvinyl chloride	0.259
Cyclic olefin copolymer	0.040
Aclar RX160	0.008
Aluminum foil	0.001

aluminum foil has the lowest permeability followed by Aclar, then cyclic olefin copolymer and finally, polyvinyl chloride. Aluminum foil had a Containers-Permeation value of 0.001 mg per blister per day and polyvinyl chloride had a containers permeation value of 0.259 mg per blister per day, approximately a 200-fold difference. The new cyclic olefin copolymer material container's permeation value is nearly seven times lower than that of polyvinyl chloride at 0.040 mg per blister per day.

3.4. Flux calculations and stability predictions

The Flux (J) across the blister was determined using the Containers-Permeation moisture permeability (mg per blister per day) and the surface area of the blister cavity ($2.8 \times 10^4/\text{m}^2$). Blister permeability (P_m) of each material (m/s) was then calculated using a reduced version of Fick's law (Amidon and Middleton, 1988):

$$J = P(C_o - C_i)$$

where J , Flux (mg/m^2 per day); P_m , Blister Permeability (m/s); C_o , Concentration of water outside blister (mg/m^3); C_i , Concentration of water inside blister (mg/m^3).

Table 3
Blister permeability (P_m) calculation results

Material	Blister Permeability, P_m (cm/s)
Polyvinyl chloride	6.7×10^{-5}
Cyclic olefin copolymer	1.0×10^{-5}
Aclar	2.2×10^{-6}
Aluminum foil	3.6×10^{-7}

Table 4
Flux (J) calculation results

Material	Flux for C_i (mg per blister per day)		
	30%RH	35%RH	70%RH
Polyvinyl chloride	0.1443	0.1291	0.0156
Cyclic olefin copolymer	0.0219	0.0196	0.0024
Aclar	0.0047	0.0042	0.0005
Aluminum foil	0.0008	0.0007	0.0001

Since a desiccant was used in the containers permeation test, the relative humidity in the blister cavity (C_i) is assumed to be zero. Thus the blister permeability for each material was calculated using $C_i = 0$ and the results are shown in Table 3. The blister permeability (P_m) of polyvinyl chloride (6.7×10^{-5} cm/s) was much higher than the blister permeability (P_m) of foil blisters at (3.7×10^{-7} cm/s), an approximate 200-fold difference. The blister permeability (P_m) data is used to directly compare the inherent water vapor permeability properties each blister.

The blister permeability (P_m) data cannot be directly used to predict the flux across a blister containing a pharmaceutical dosage form. Unlike the Containers-Permeation procedure that used a desiccant, the relative humidity in a tablet blister cavity is not zero and is constantly changing over time. Previously published studies have shown the typical water concentration inside the blister ranges from 30 to 70% for relatively permeable blister packages (Amidon and Middleton, 1988). The stability of unpackaged tablets shows that PGE-7762928 tablets are stable at 30°C/60%RH and the product is not stable at 40°C/75%RH. At an equivalent water vapor pressure for the 30°C/60%RH condition, the percent relative humidity at 40°C is 35%RH. Therefore, the results of the flux (J) calculations of C_i equal to 30, 35 and 70%RH were determined and are shown in Table 4.

Stability predictions for the time to achieve equilibrium moisture content at 30, 35 and 70%RH are shown in Table 5. The stability prediction at $C_i = 30\%$ RH suggest that only aluminum foil will provide a sufficient moisture barrier. At $C_i =$

Table 5
Stability predictions: time (weeks) to equilibrium moisture content @ 40°C/75%RH

Material	$C_i = 30$	$C_i = 35$	C_i = 70
	Polyvinyl chloride	1	1
Cyclic olefin copolymer	5	5	43
Aclar	22	24	204
Aluminum foil	128	146	1275

35%RH, Aclar is also predicted to provide a sufficient moisture barrier. If the product is stable at 40°C/70%RH, predictions for $C_i = 70\%$ RH indicate that foil, Aclar and cyclic olefin copolymer blisters will provide a sufficient moisture barrier to yield acceptable product performance for 6 months at the accelerated condition (40°C/75%RH).

3.5. Packaged stability

The tablet assay and maleate adduct formation at 2, 4, 6, 8, 12 and 24 weeks are shown in Figs. 3 and 4, respectively. Polyvinyl chloride blisters provide minimal moisture protection and was similar to tablets stored unpackaged. After 6 months at 40°C/75%RH the assays for tablets packaged in polyvinyl chloride and unpackaged tablets were 84 with 12% maleate adduct and 82 with 13% maleate adduct, respectively. This result is similar to that found for stability studies conducted with vitamin C tablets packaged in polyvinyl chloride and polyvinyl dichloride blisters (Canefe et al., 1989).

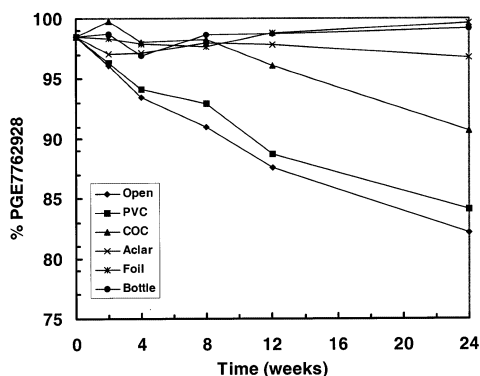


Fig. 3. Effect of the 40°C/75%RH storage condition on the PGE-7762928 tablet assay.

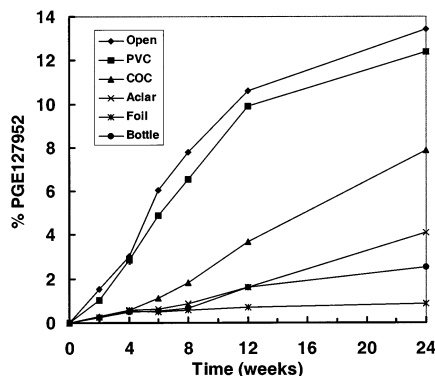


Fig. 4. Effect of the 40°C/75%RH storage condition on the PGE-127952 maleate adduct formation.

Both blister materials were reported to be insufficient to stabilize the drug product. Similar performance in polyvinyl chloride blister was also shown for sultamicillin tablets (Burat et al., 1992) and vitamin A acetate, medazepam and amitriptyline drug substances (Ruz et al., 1995).

The cyclic olefin copolymer film is reported to have better moisture barrier properties than polyvinyl chloride, but inferior to that of Aclar (Phillips, 1996). Therefore, tablet stability in cyclic olefin copolymer blisters was improved versus the stability results in polyvinyl chloride after 6 months at 40°C/75%RH with an assay of 91 with 8% maleate adduct. Although cyclic olefin copolymer meets the stability criteria (> 90% assay), this material would not be chosen for this product as the performance is not robust.

The PGE776292 assay for Aclar blisters is 97% after 6 months at 40°C/75% RH and the amount of maleate adduct degradant in the tablets is minimal (< 4%). These results are in accordance with the moisture protection properties of the blister materials as Aclar has superior moisture protection properties than either polyvinyl chloride or polyvinyl dichloride. Aclar is typically not used alone as a blister film but rather is laminated to PVC, yielding a barrier material that is superior to PVC alone. The water vapor transmission rate (WVTR) of 250 micron polyvinyl chloride with 9 micron of Aclar is 15 times higher than that of 250 micron polyvinyl chloride alone (Korab, 1999).

As with the stability results for Aclar blisters, the PGE776292 assay in cold-form aluminum blisters at all conditions is greater than 90% and the amount of maleate adduct degradant in the tablets is minimal (< 4%). These results are in accordance with the moisture protection properties of cold-form aluminum as the highest moisture barrier blister is provided by cold-form aluminum. However, aluminum is generally reserved for applications where a total moisture, light or gas barrier is required. The disadvantages of aluminum include cost of the material, the cost of cold-form change parts for the blister equipment and processing difficulties (Gander, 1999).

The PGE776292 assay for high density polyethylene bottles with a foil induction seals at all conditions is greater than 90% and the amount of maleate adduct degradant in the tablets is minimal (< 3%). This type of packaging is commonly used in pharmaceutical packaging as it provides a high moisture barrier. Therefore, this data was generated as a control.

4. Conclusion

After 6 months storage at 40°C/75%RH, the PGE-7762928 tablet assay was 82% unpackaged, 84% in polyvinyl chloride blisters, 91% in cyclic olefin blisters, 97% in Aclar blisters, 100% in cold-form aluminum blisters and 99% in an high density polyethylene bottle with a foil induction seal. Based on the goal of 90% assay at 6 months, cold-form aluminum and Aclar blister packaging and high density polyethylene bottles with foil induction seals provide acceptable PGE-7762928 tablet stability.

The stability predictions agreed with the experimental results in terms of the relative order of the length of time the product was stable. The rank order from the longest time stable to least time stable was as follows: foil, Aclar, cyclic olefin copolymer, polyvinyl chloride. However, the PGE-7762928 tablets stability predictions for C_i equal to 30% and 35%RH underestimated the length of time the product would be stable. For example, assuming an internal water concentration of C_i equal to 30%RH yields the prediction

that only foil blisters would provide a sufficient moisture barrier for 6 months at 40°C/75%RH. However, the use of C_i equal to 35% suggests that Aclar would also provide a sufficient moisture barrier in addition to the use of foil blisters. The experimental results demonstrate that foil and Aclar are acceptable materials. Based on these obtained, the internal moisture content of the blisters was greater than 35%.

Use of a conservative estimate of the internal water concentration of 30–35%RH provides greater assurance that a suitable packaging material is recommended. Unfortunately, it is difficult to obtain an accurate estimate of C_i as the percent relative humidity is constantly changing and the product begins degrading before it reach the equilibrium moisture content. The more accurate the assessment of C_i , the more accurate stability predictions can be made.

In summary, stability performance is predicted using the mechanism of degradation, and specifically in the case of moisture sensitive compounds, with the equilibrium moisture content and the permeability of the blister film. The stability performance prediction can be improved with a more accurate estimation of the relative humidity inside the blister cavity.

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