Case study: Activ-Blister™ solutions provide superior protection of a model drug product over cold-form foil

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EXECUTIVE SUMMARY

FreeThink Technologies, Inc., Aptar CSP Technologies, and PCI Pharma Services compared the efficacy of Activ-Blister™ packaging configurations with cold-form foil in maintaining the stability of a model tableted drug product. An Accelerated Stability Assessment Program (ASAP) study was carried out and growth of the main degradant of the active ingredient was quantified. The data were modeled using the ASAP*prime*® software and included four different packaging configurations: cold-form foil blisters, thermoform incorporating Activ-Blister™ technology with molecular sieve, thermoform incorporating Activ-Blister™ technology with silica gel and thermoform blisters alone. Four typical ICH storage conditions were also evaluated: 25°C/60% RH, 30°C/65% RH, 30°C/75% RH and 40°C/75% RH. Two different initial relative humidities were modeled to assess the impact of starting water content on shelf-life. To confirm the modeling results, tablets were packaged and stored under these conditions for up to 6 months prior to analysis. As predicted from the ASAP study, the packaging configurations can be ranked from most protective to least protective towards degradation in the following way: Activ-Blister™ technology with molecular sieve > Activ-Blister™ technology with silica gel > coldform foil > thermoform blister alone. The advantage of Activ-Blister™ solutions over cold-form foil was particularly pronounced when the drug product had a high initial water content. ASAP*prime*® predictions of degradant growth within packaging agreed with the data generated from the stressed blistered tablets at all packaging, storage and initial water conditions. ASAP*prime*® can effectively model packaging configurations incorporating molecular sieve and silica gel versions of Activ-Blister™ packaging and predict the shelf-life of a product using Activ-Blister™ technology.

System	ln A	E_a (kcal/mol)	B	R^2	Q^2
Model tablet	43.8 ± 5	30.1 ± 3.4	0.038 ± 0.012	0.96	0.85

Table 1. Modified Arrhenius parameters for the sample drug product tablet.

OBJECTIVES

- To compare the efficacy of Activ-Blister™ packaging configurations with cold-form foil in maintaining the stability of a model tableted drug product.

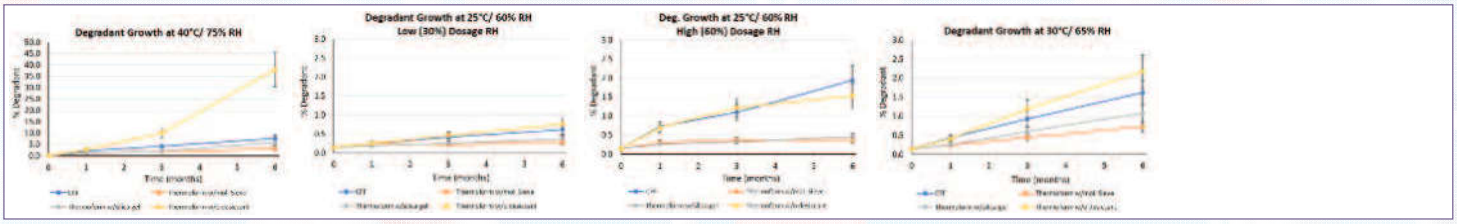

Figure 1. Probability of passing with a 2-yr shelf life at 25°C/60% RH, 30% dosage RH: Molecular sieve: 99%, Silica gel: 95%, Cold-form foil: 71%, Thermoform alone: 24%. Activ-Blister™ with molecular sieve results in the lowest degradant growth. The impact of Activ-Blister™ packaging configurations is highest with high dosage RH (60% RH).

- To examine the role of starting water content in the efficacy of Activ-Blister™ packaging configurations.
- To demonstrate that ASAP and the ASAP*prime*® software can accurately model packaging configurations incorporating molecular sieve and silica gel versions of Activ-Blister™ packaging and predict the shelf-life of a product using Activ-Blister™ technology.

ASAP STUDY

- **A** model tablet drug product was produced and an Accelerated Stability Assessment Program (ASAP) study was conducted at FreeThink Technologies.
- Tablets were stressed (open) over a temperature range of 35°C - 60°C and a relative humidity range of 11% RH - 75% RH.
- Related substances were quantified by HPLC and the growth of the main degradant modeled using the moisture-modified Arrhenius equation, assuming a 3% specification limit.
- A good model was obtained with E_a (activation energy, i.e. temperature sensitivity) and B (moisture sensitivity) values in the average range for similar products (Table 1). The model was used to predict product shelf-life under different storage conditions.

Moisture-Modified Arrhenius Equation:

$$lnk = lnA - \frac{E_a}{RT} + B \times RH$$

PRODUCT PACKAGING AND STORAGE

- **B**lister packaging of the drug product tablets was performed by PCI Pharma Services.
- Tablets were divided into two categories:
  1. Low % RH: Stored in presence of silica gel desiccant until blistering.
  2. High % RH: Equilibrated in a 25°C/60% RH stability chamber for 24 hours before blistering.
- Materials used:
  1. Molecular sieve desiccant film, Aptar CSP Technologies (M-0035, 0.8 mm thickness, 8 mm x 8 mm).
  2. Silica gel desiccant film, Aptar CSP Technologies (M-0020, 0.8 mm thickness, 8 mm x 8 mm).

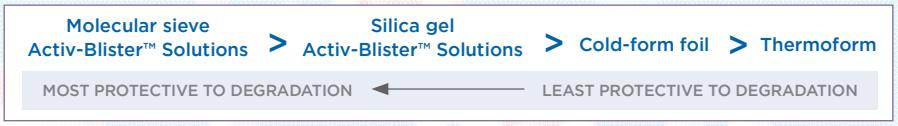

Figure 2.

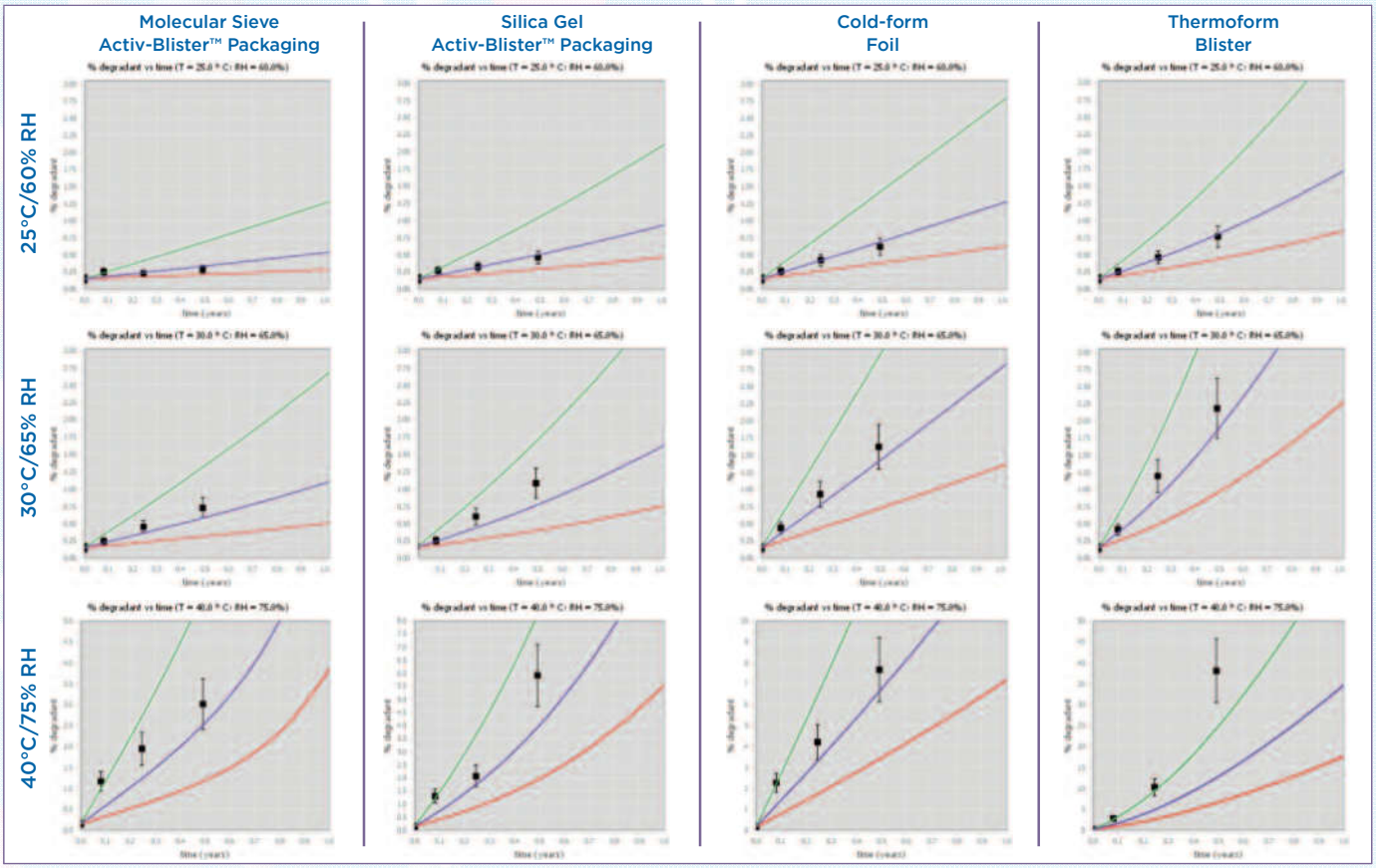

Figure 3. The 40°C/75% RH conditions have differing scales due to the wide range of degradation.

3. Thermoform, Tekniplex (Tekniflex® VPA10400 triplex with PVC, PE, 4 mil PCTFE (Aclar® UltRx4000)).
4. Aluminum foil lidding, Amcor Flexibles (20 µm thickness).
5. Cold-form foil.

- Blistered tablets were stored in reach-in stability chambers (Darwin PH030) at FreeThink Technologies (Table 2).
- At initial set-up, the dosage RH was determined for a subset of tablets.
- After stressing, growth of the primary degradant was measured by HPLC..

Packaging Configuration	Low RH, 25°C/60 % RH	Low RH, 30°C/65 % RH	Low RH, 30°C/75% RH	Low RH, 40°C/75% RH	High RH, 25°C/60% RH
	1, 3, 6 months	1, 3, 6 months	1, 3, 6 months	1, 3, 6 months	1, 3, 6 months
Thermoform w/ molecular sieve desiccant film M-0035	X	X	X	X	X
Thermoform w/ silica gel desiccant film M-0020	X	X	X	X	X
Cold-form Foil	X	X	X	X	X
Thermoform without desiccant film	X	X	X	X	X

Table 2. Blistering and storage conditions used for the stability study.

RESULTS

Growth of the main degradant in tablets stored under ICH stability conditions under different packaging configurations is shown in Figure 1.
Selected ASAP*prime*® predictions compared to degradant growth in tablets stored under ICH stability conditions is shown in Figure 3.

CONCLUSIONS

The packaging configurations can be ranked in the following way as shown in Figure 2:

- The advantage of thermoform combined with an active desiccant film (Activ-Blister™ Solutions) over cold-form foil is particularly pronounced for drug product with a high initial water content.
- The ASAP*prime*® program can be used to effectively model packaging configurations incorporating molecular sieve and silica gel versions of Activ-Blister™ packaging to predict the probability of passing with a particular shelf-life.
- Activ-Blister™ packaging combines the practical advantages of thermoform blisters with the moisture protection provided by desiccant in order to provide a thermoform option for moisture-sensitive drug products.