Extend the Shelf-Life of Oral Solid Doses with Activ-Blister™ Solutions

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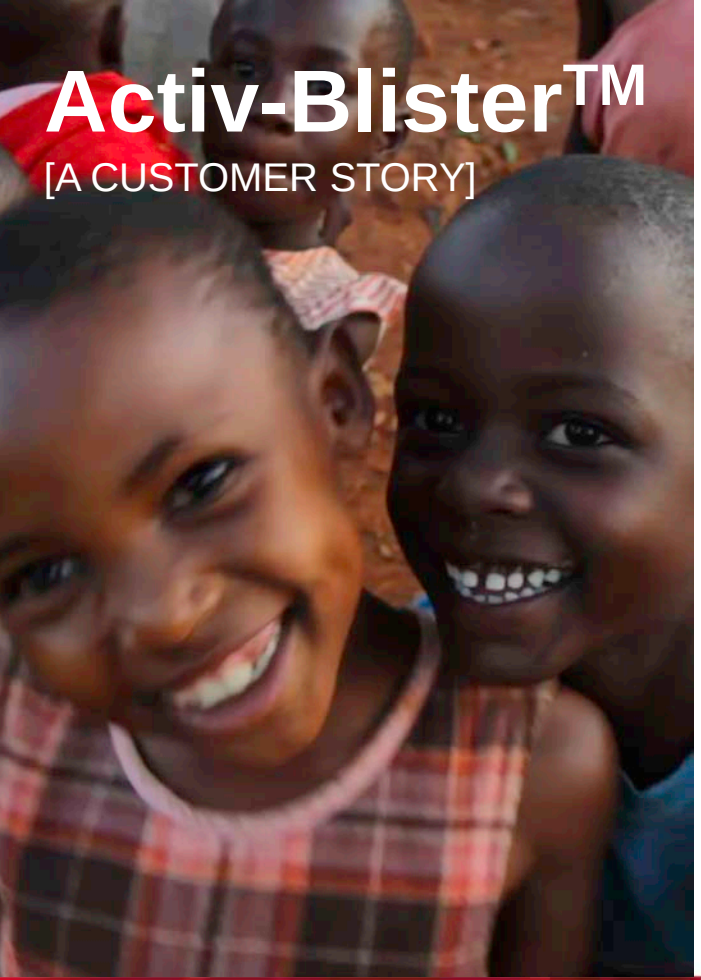
Activ-Blister™ Overview



Activ-Blister™

[A CUSTOMER STORY]

CHALLENGE

Active Pharmaceutical Ingredient (API) was highly sensitive to moisture and oxygen and extremely unstable in adverse conditions. Conventional blister packaging technologies were not viable shelf life options.

SOLUTION

- Aptar CSP Technologies developed a customized Activ-Blister™ solution to extend drug's shelf-life.
- PCI executed Activ-Blister™ runs, starting on a small-scale and ultimately scaled up from stability to clinical to commercial production.

OUTCOME

Activ-Blister™ extended the shelf-life of the drug from several months to up to 3 years. It allowed for a compact packaging design, maximizing blister real-estate and optimizing material cost. Activ-Blister™ improved patient usage by allowing a 'tear' design in the blister wallet to accommodate single dosage opportunities.

Poll Question #1

- What is your main stability concern?
  - Moisture
  - Oxygen
  - VOCs
  - Moisture and Oxygen

Poll Question #2

- Which part of the development cycle are you in?
  - Early drug discovery
  - Preclinical studies
  - Clinical Development
  - Existing Product

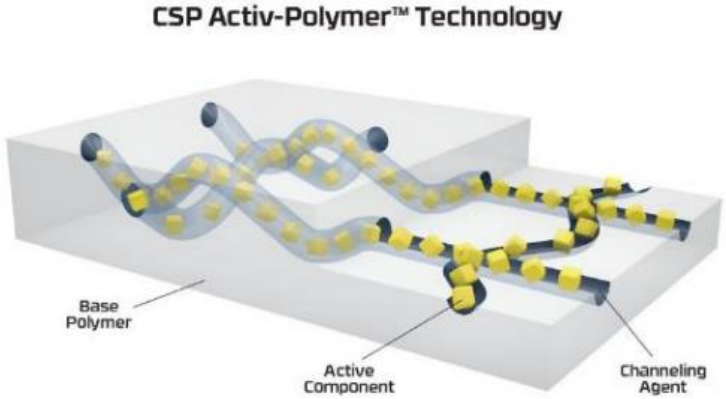
Agenda

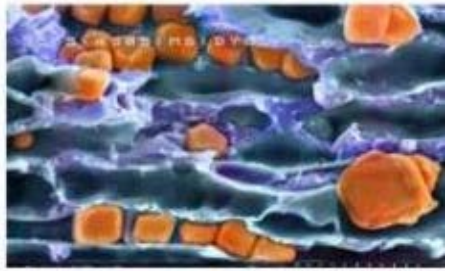
- **Oral solid dose active packaging**: The Basics
- **Active product protection**: Value proposition
- **New solution to an old problem**
- **Xcelerate development services with FreeThink and PCI**
- **Supply chain and go-to-market solution**
- **Q&A**

Material Science: Adding Chemistry to Polymers

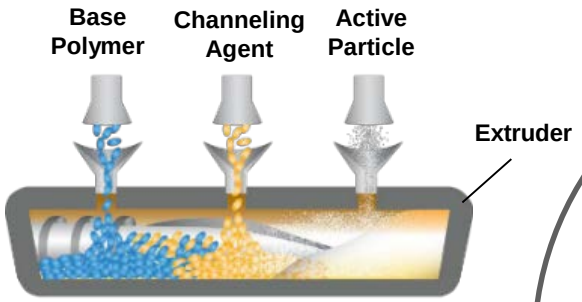
3-Phase Activ-Polymer™ Material

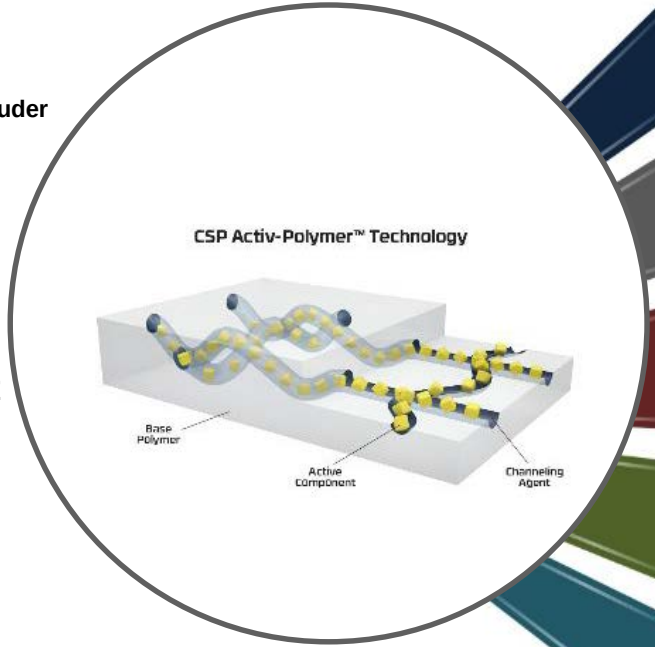
- Channels created within a polymer allow movement of gases
- “Active” particles are added to the polymer in order to:
  - **Adsorb** or **Absorb** (moisture, gases, reactive impurities, odors, formaldehyde and other volatiles)
  - **Release** (aromas, biocides, nutrients, carbon dioxide)
- **Gas diffusion** is controlled through the channel composition





Three Phase Material = Platform Material





Active Packaging Management

- Moisture Control
- Scavenging
- Antimicrobial
- Emitters
- Odor removers

Injection molding

Thermoforming

Extrusion film

Extrusion blow molding

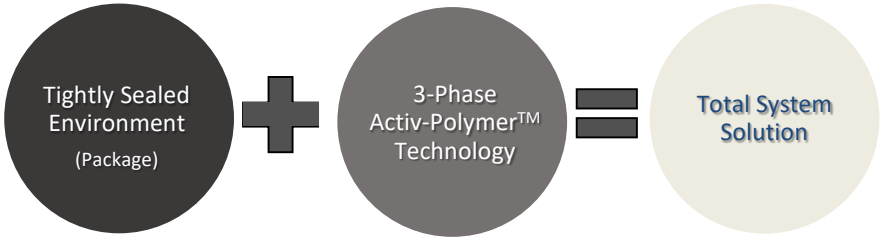
Hot melt

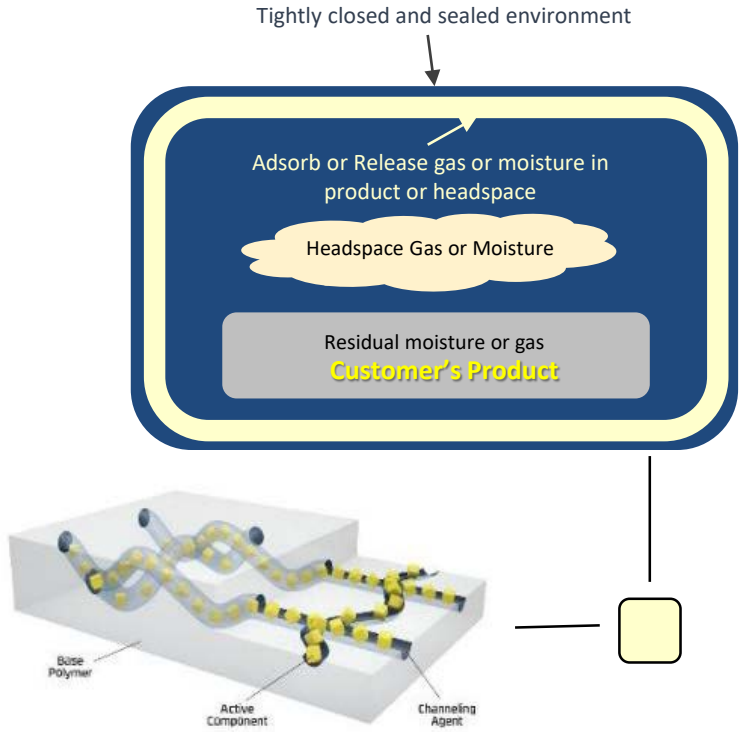
Active Packaging – Putting Chemistry into Polymers

Tightly Sealed Environment

Utilizing 3-Phase Activ-Polymer™ technology requires a tightly sealed environment

- Chemistry required determined
- Gas or moisture transmission rates are reviewed
- Focus on seals associated with package
- Amount of ***3-phase material*** required will depend on how ***tight*** of an ***environment*** it will be placed in





Platform Technology Serving Broad Therapeutic Areas

Material science deployed in key therapeutic areas → **Activ-Vial™, Activ-Seal™, Pharmapuck™, and Activ-Film™**

Oral Solid Dose	Transdermal	Drug Delivery	Diagnostics	Probiotics	Medical Device
Immunodeficiency Treatment	Hormone Patch	Anti-Fungal	Blood Glucose Testing	Dietary Supplement	Implant Neurostimulator

Why Are We Here Today?

Oral Solid Doses have long faced stability challenges associated with moisture and oxygen, and these challenges are only projected to increase due to the development of:

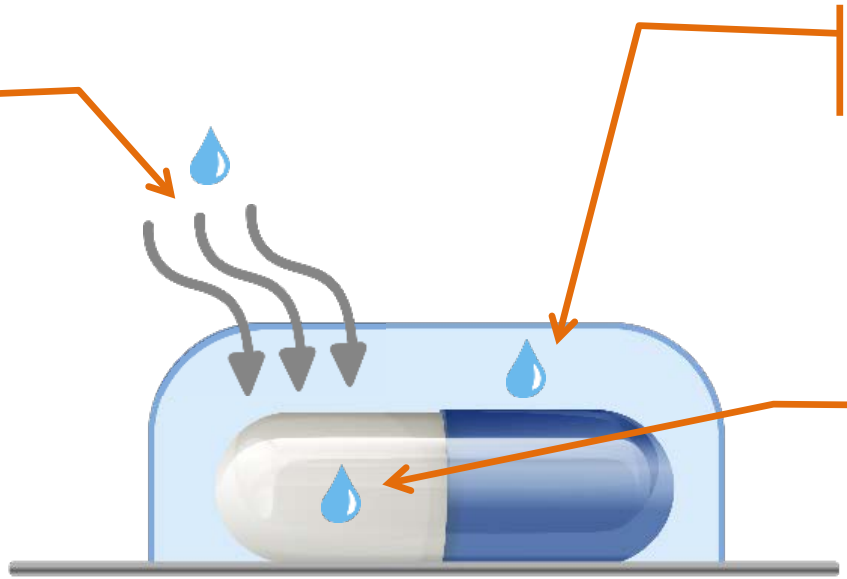
- Larger / lower solubility molecules
- New controlled release technologies
- More potent API’s

Further, regulations and standards for stability are getting tougher.

Together, these trends/developments are creating demand for more effective and efficient packaging solutions for moisture and oxygen management.

Sources of Moisture and Oxygen in Blister Packaging

Moisture within the package has <u>three</u> sources:

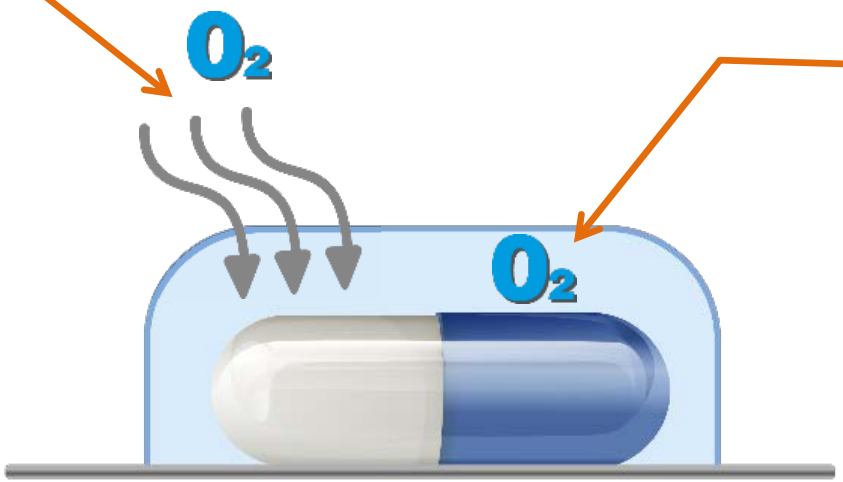


1. Within the initial headspace of the blister
2. Ingress thru the package over time
3. Initial water content of the oral solid dose

Sources of Moisture and Oxygen in Blister Packaging

Oxygen within the package has <u>two</u> sources:

2. Ingress thru the package over time



1. Within the initial headspace of the blister

Protecting Oral Solid Doses from O_2 / Moisture

Blister Headspace Management Challenges:

- Confined space of packaging
- Possible need to minimize oxygen and moisture
- Minimize production impact
- Avoid complicated packaging
- Avoid lengthy development and reformulation

Protecting Oral Solid Doses from O_2 / Moisture

Blister Headspace Management:

- Secondary packaging with sachets
  - Adds materials and size to packaging
  - Complexity for end-user

- Fishbone Designs
  - Adds materials and size to packaging
  - Complexity for end-user

Protecting Oral Solid Doses from O_2 / Moisture

Blister Headspace Management:

- Cold form foil
  - Excellent barrier protection
  - Does not address initial water content of the tablet / capsule or headspace moisture / oxygen
  - Increased blister card size vs thermoform
  - Capsule/Tablet is not visible

- Foils with integrated desiccants
  - Mitigates ingress thru edges
  - Fixed desiccant capacity per blister

Protecting Oral Solid Doses from O_2 / Moisture

Blister Headspace Management:

- Nitrogen Purging (reduce / eliminate oxygen)
  - Difficult to validate; often a custom solution
  - Adds time to line stoppages
  - Operator Safety – monitor room oxygen levels
  - Below 8 - 10% oxygen, can be difficult to achieve
  - Does not address oxygen ingress

Protecting Oral Solid Doses from O_2 / Moisture

Activ-Blister™ Solutions

- Management of all sources of moisture & oxygen
  - Silica Gel and Molecular Sieve desiccants
  - Combination options available (e.g. moisture + oxygen)
- Customized capacity and uptake rates
- Oxygen products do not require moisture to be active
- Integrate into existing and new packaging lines

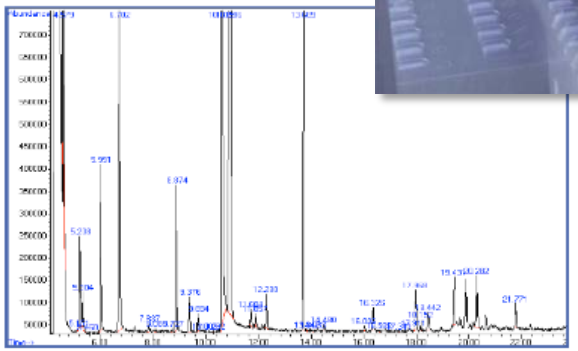
Proprietary Heat-Staking Process

Heat-stake Formulations provide Adhesive-Free attachment within blister

- No adhesive residual solvents
- Eliminates adhesive and backing material
- Helps to meet ICH guidelines for residual solvents

Adhesive Residual Solvents can:

- Migrate into package headspace or product
- Show up in analytical tests as impurities
- Adversely react with the drug product
- Create odors

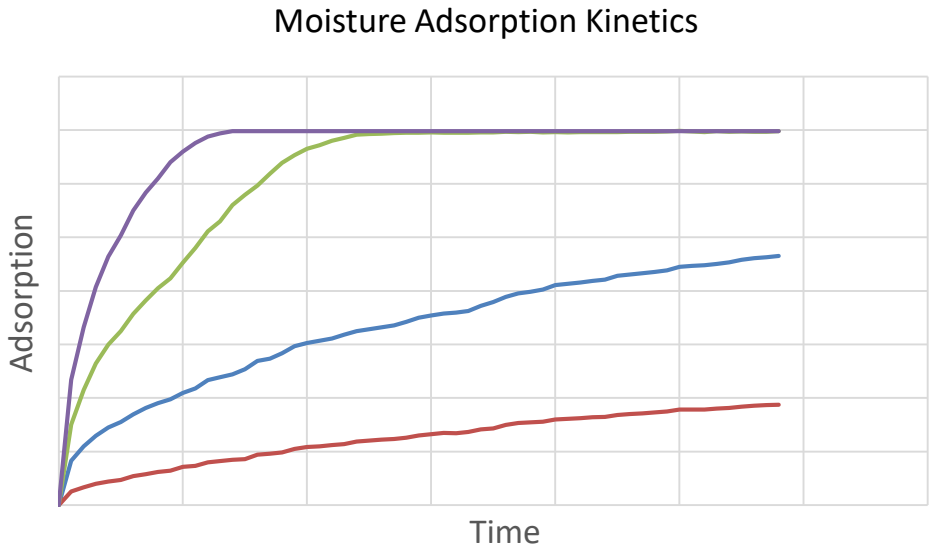


Major solvent peaks: Ethyl alcohol (class 3), Isopropyl alcohol (class 3), Benzene (class 1) and Toulene (class 2)

Chart above shows a typical GC chromatogram of solvent outgassing from a medical grade adhesive.

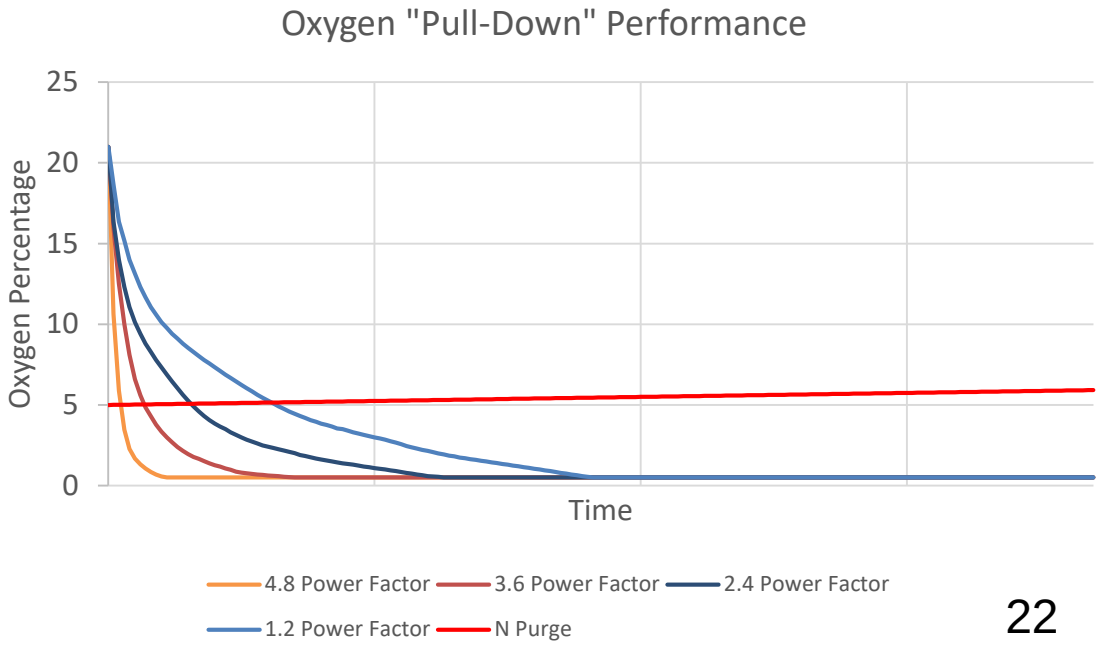
Controlling Moisture Kinetics

- Capacity: Moisture from headspace + product + ingress
- Kinetics: How quickly moisture is adsorbed



Controlling Oxygen Kinetics

- Capacity: Oxygen from headspace + ingress
- Kinetics: How quickly oxygen is scavenged
- Non iron based formulation
- Moisture not required for activation



Value for Oral Solid Dose Packaging

1. Move from bottle to blister
   - Discrete headspace management in each blister

2. Enhance shelf life of coldform and thermoforms

3. Reduce packaging complexity and costs
   - Eliminate purging / secondary and fishbone packaging

4. Move from coldform to thermoform
   - Visible capsule / tablet
   - Smaller footprint (40-60% size reduction)

Case Study

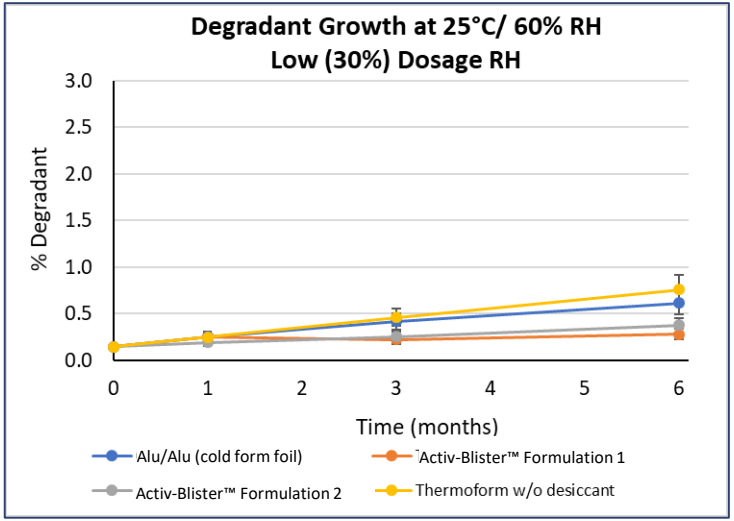
Objective: Compare efficacy of Activ-Blister™ packaging configurations with cold-form foil in maintaining the stability of a model tableted drug product.

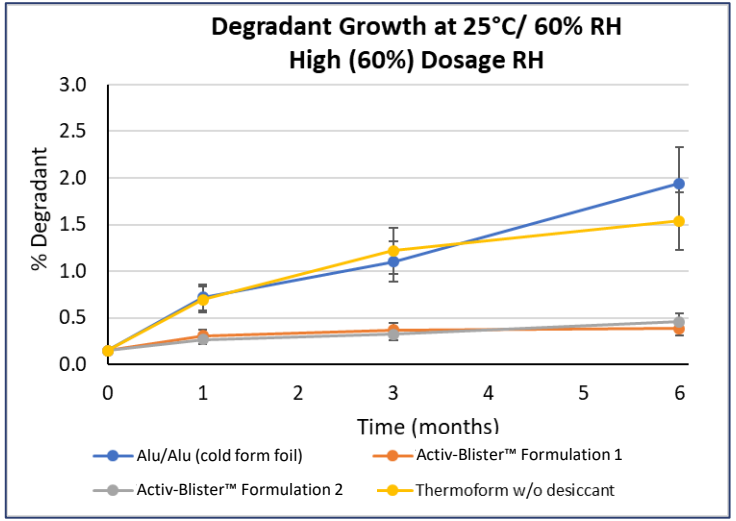
Blistering & Storage Conditions for Stability Study:

Packaging Configuration	Low Water Content, 25°C/60% RH	Low Water Content, 30°C/65% RH	Low Water Content, 30°C/75% RH	Low Water Content, 40°C/75% RH	High Water Content, 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 Activ-Film™ Formulation 1 (Activ-Blister™)	X	X	X	X	X
Thermoform Activ-Film™ Formulation 2 (Activ-Blister™)	X	X	X	X	X
Cold-form foil	X	X	X	X	X
Thermoform without Activ-Film™ (Activ-Blister™)	X	X	X	X	X

Case Study - Data

Growth of main degradant in tables stored under ICH stability conditions under different packaging configurations





Data courtesy of joint study with FreeThink Technologies and PCI Pharma Services

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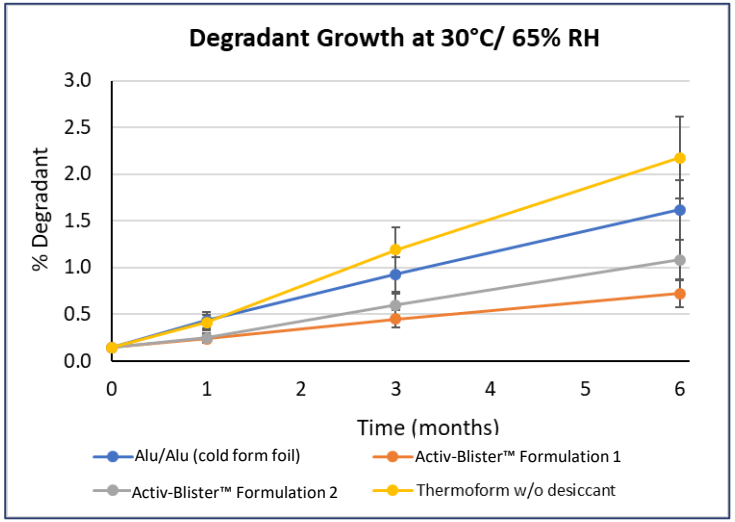

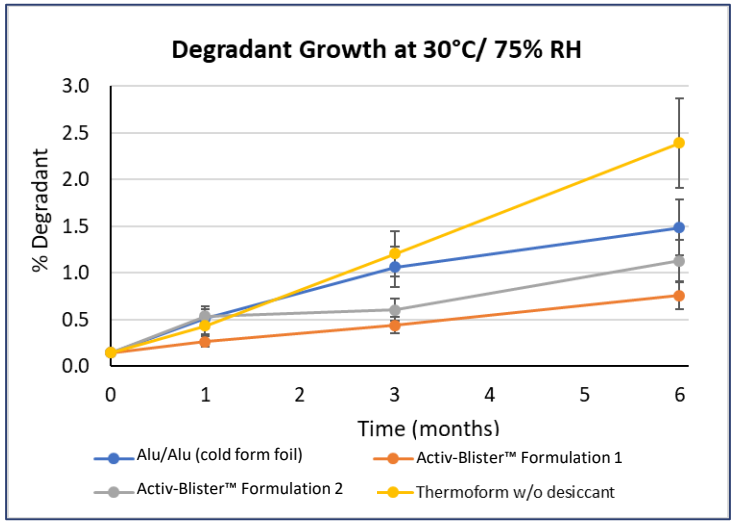

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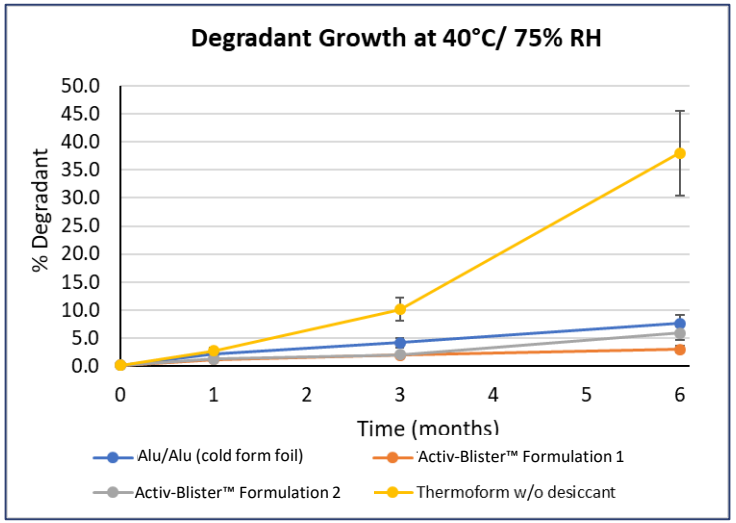
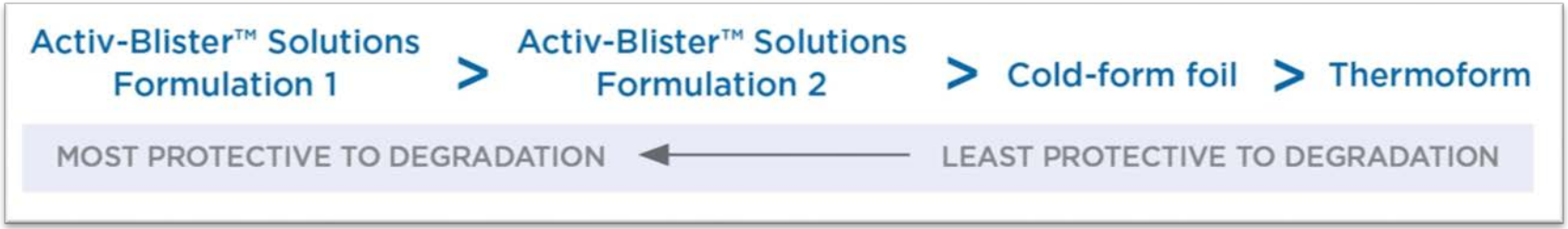


Data courtesy of joint study with FreeThink Technologies and PCI Pharma Services

Case Study – Conclusions

The packaging configurations can be ranked in the following way:

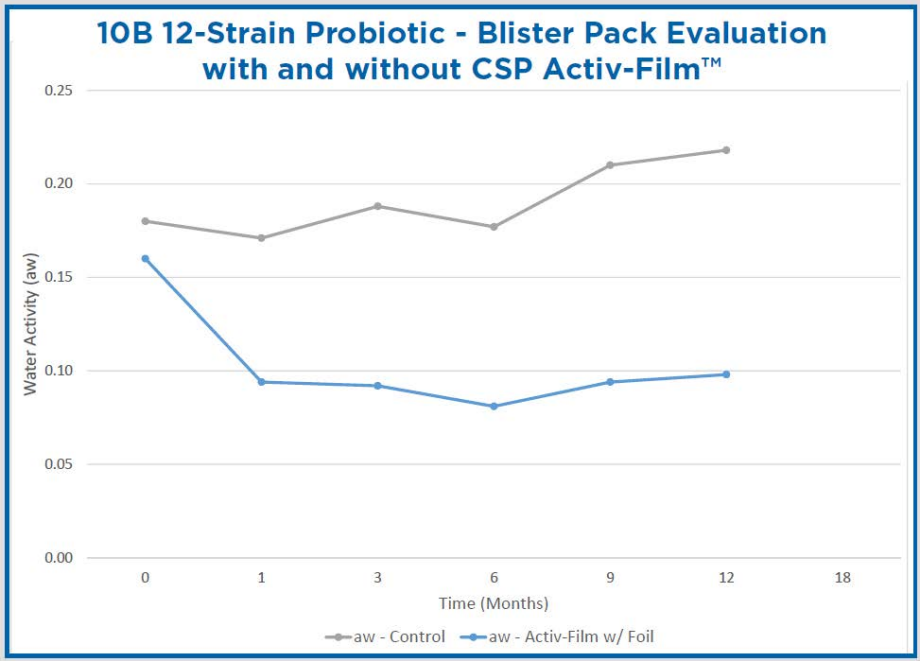


- The advantage of thermoform combined with Activ-Blister™ Solutions over cold-form foil is particularly pronounced for drug product with a high initial water content.
- Activ-Blister™ packaging combines the practical advantages of thermoform blisters with the moisture protection provided by desiccant in order to provide a thermoform option for moisture-sensitive drug products.

Case Study

Probiotic Capsule - Water Activity

(Standard Blister Packaging vs. Activ-Blister™ Packaging with CSP Activ-Film™)



Storage Conditions:

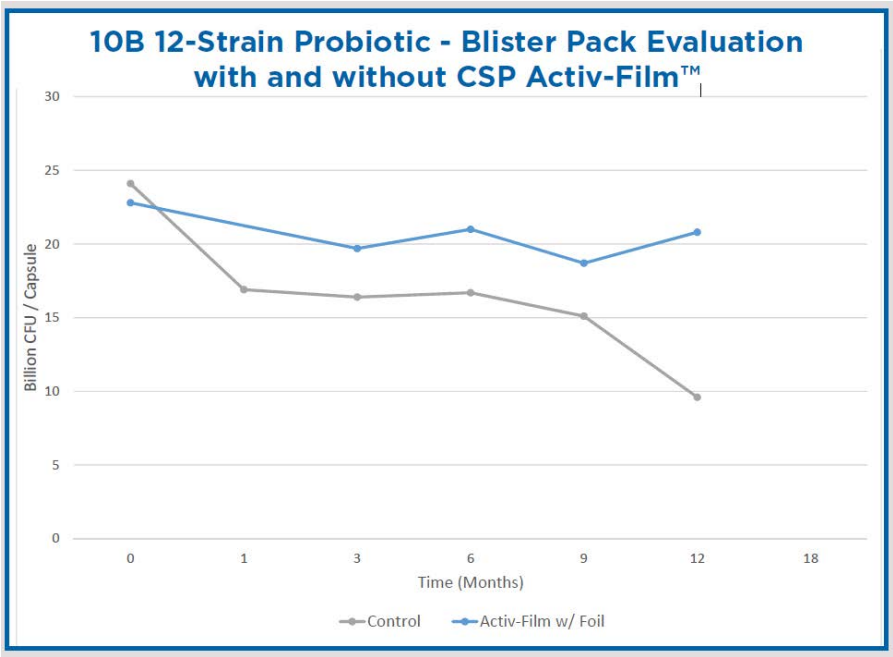
22°C ± 2°C

40% ± 5% RH

Data courtesy of Merical

Case Study

Probiotic Capsule - Potency
(Standard Blister Packaging vs. Activ-Blister™ Packaging with CSP Activ-Film™)



Storage Conditions:
22°C ± 2°C
40% ± 5% RH

Data courtesy of Merical
CFU=Colony Forming Units

Xcelerate Development Services

Complete solution from Stability Challenge to Production Launch

- Designed for new applications and existing packaged products

FreeThink Technologies

pci PHARMA SERVICES

Key Takeaways

1. Activ-Blister™ solutions provide comprehensive oxygen and moisture management; all sources can be mitigated with sufficient capacity.

2. Determining shelf-life characteristics and design an Activ-Blister™ packaging solution to achieve desired shelf life.

3. Along with our trusted partner, PCI, we can take a product from R&D all the way to market.

4. Clinical and commercial packaging with Activ-Blister™ solutions is available at PCI Pharma Services.

Thank you for your attention

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Q & A session

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