Optimizing Dermal Drug Delivery with Material Science: A Case Study

Aptar
CSP Technologies

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Microneedle & Transdermal Delivery Virtual Summit | October 5th, 2021

About Aptar CSP Technologies

- Joined **AptarGroup** in August 2018
- Premier active **material science solutions expert** delivering innovative, highly-engineered, **active packaging** solutions
- Headquarters Auburn, Alabama, USA, with **+500** dedicated employees in **4** countries
- **+1.2** billion components manufactured annually, **4** manufacturing locations worldwide (US, France & China)
- **+500** worldwide patents
- **ISO-9001**, **ISO-13485** and **ISO-14001** certified

Platform Technology Serving Broad Therapeutic Areas

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Oral Solid Dose	Dermal Drug Delivery	Drug Delivery Systems	Diagnostics	Probiotics	Medical Device & Implants
Immunodeficiency Treatment	Hormone Patch/ MAP Device	Inhalation/ Nasal Drug Delivery	Blood Glucose Testing/COVID Testing	Dietary Supplement	Implant Neurostimulator

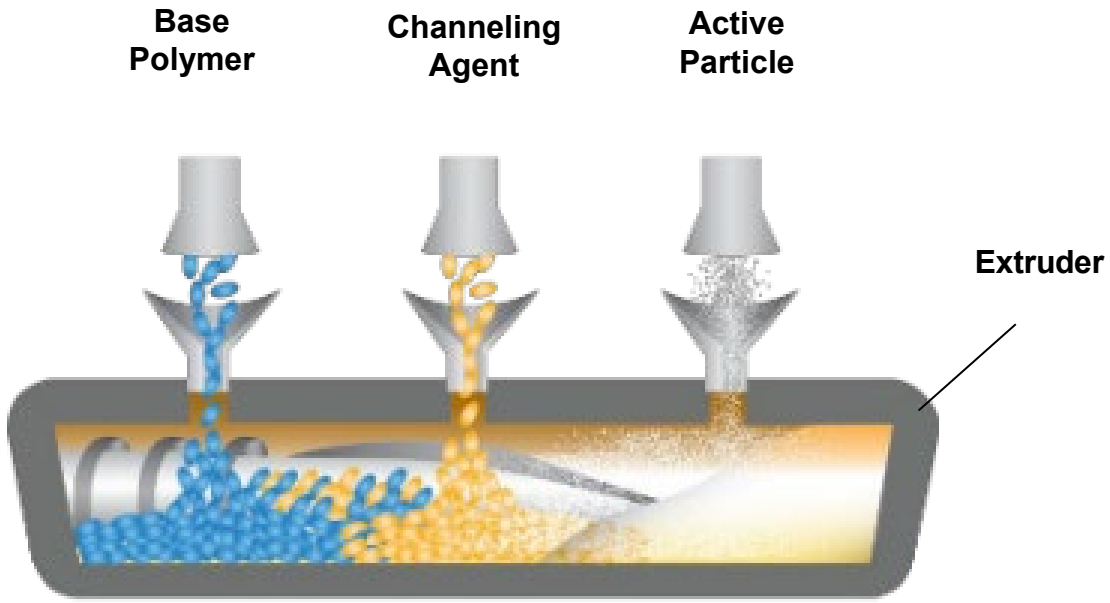
3-Phase Activ-Polymer™ Technology

3-Phase Activ-Polymer™ Material = Platform Material

Material Science: Adding Chemistry to Polymers

3-Phase Polymers

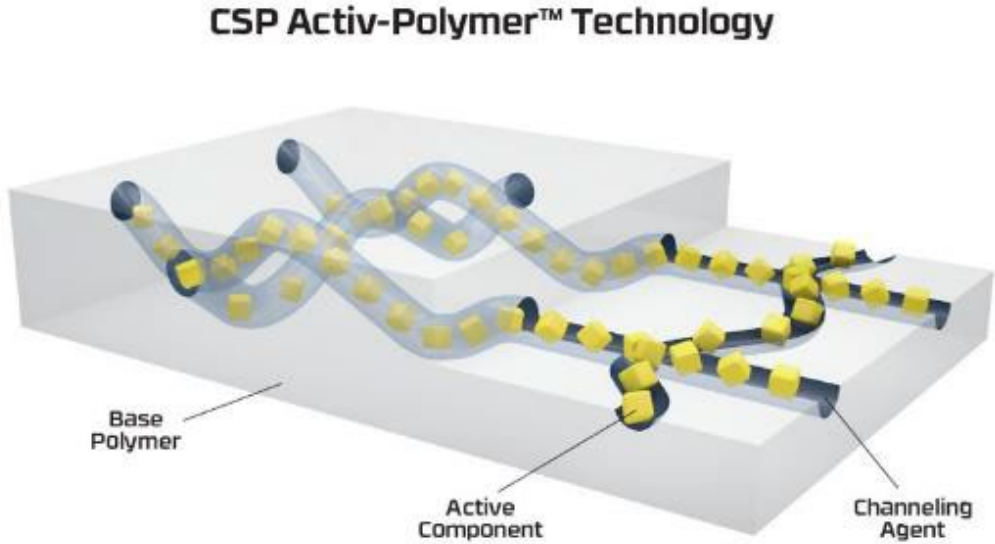
1. Majority Polymer: Base structure component
2. Particle: Adsorbing/absorbing – active component
3. Minority Polymer/Channeling Agent: Immiscible in majority polymer

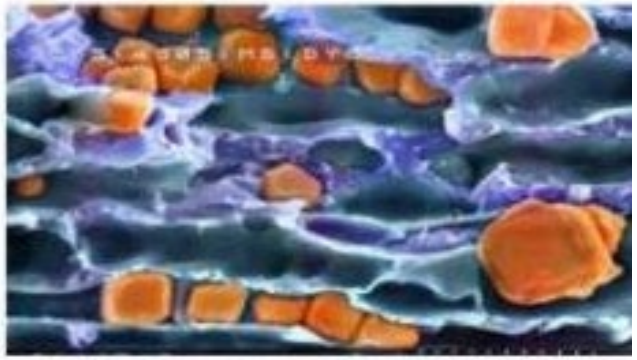


Material Science: Adding Chemistry to Polymers

3-Phase Activ-Polymer™ Material

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





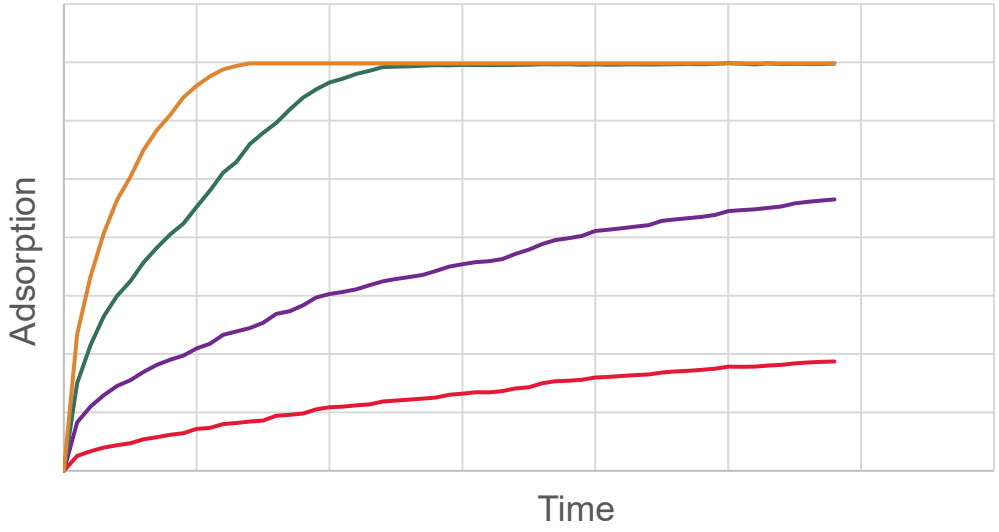
Active Packaging – Putting Chemistry into Polymers

3-Phase Activ-Polymer™ Material

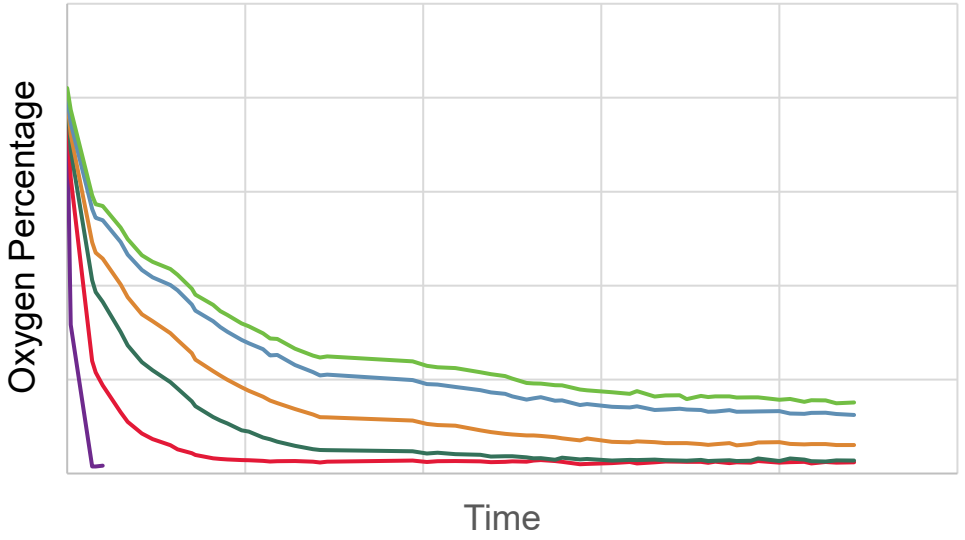
Allows **control of kinetics** based upon formulation:

- Uptake rate can be increased or decreased
- Absorption capacity can be increased or decreased
- Buffered RH solutions for products susceptible to over-drying

Moisture Adsorption Kinetics

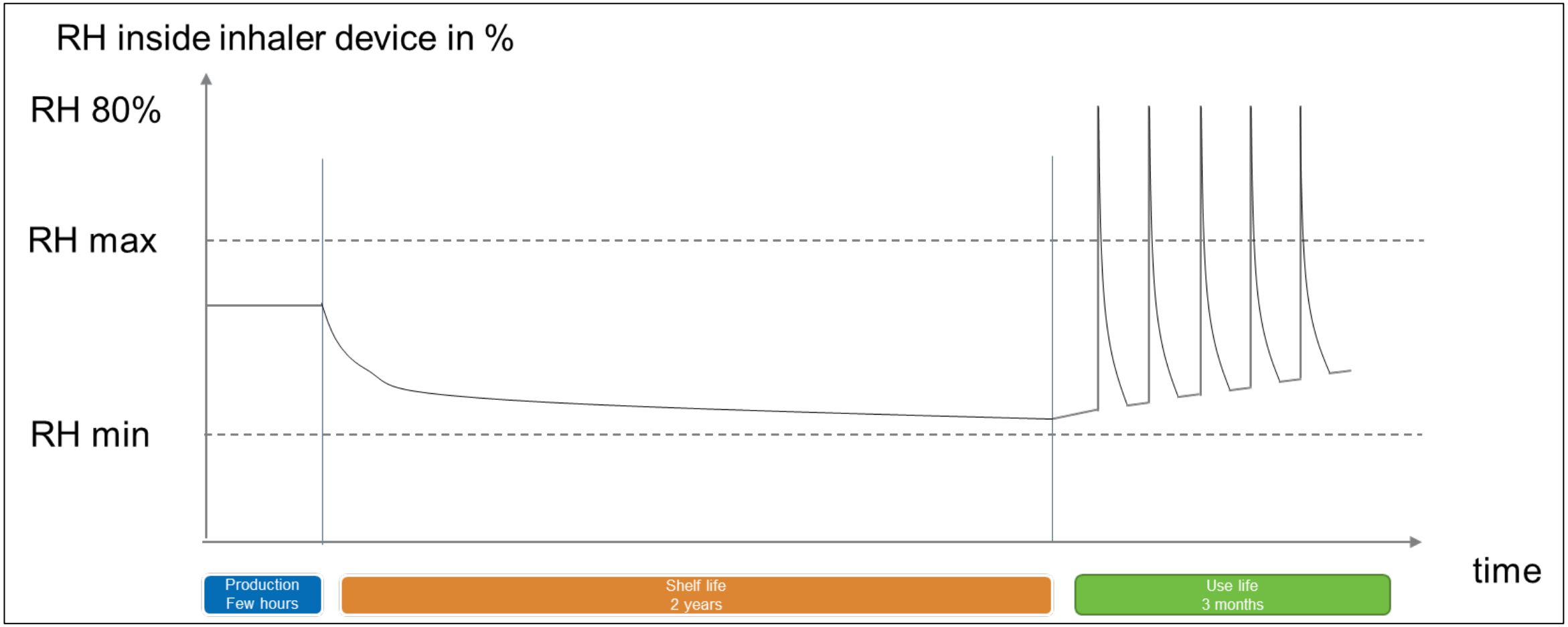


Oxygen “Pull-Down” Performance



Buffered RH Solutions for Products Susceptible to Over-Drying

RH inside inhaler using a custom Aptar CSP 3-Phase Activ-Polymer™ component throughout storage and use life of device

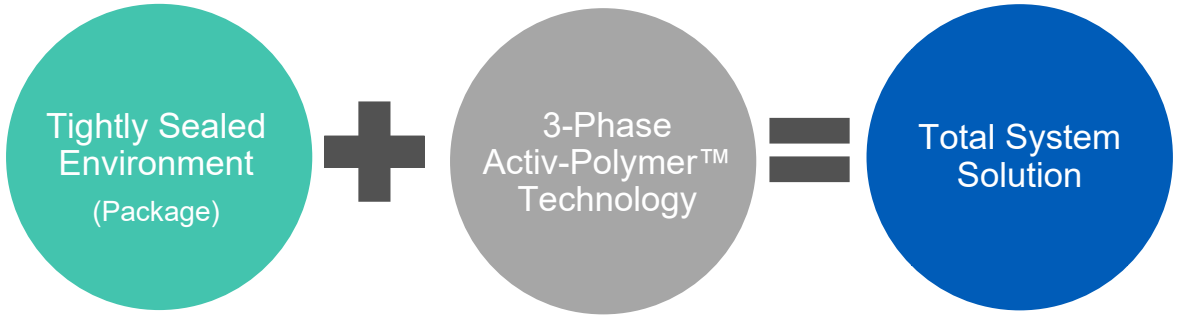


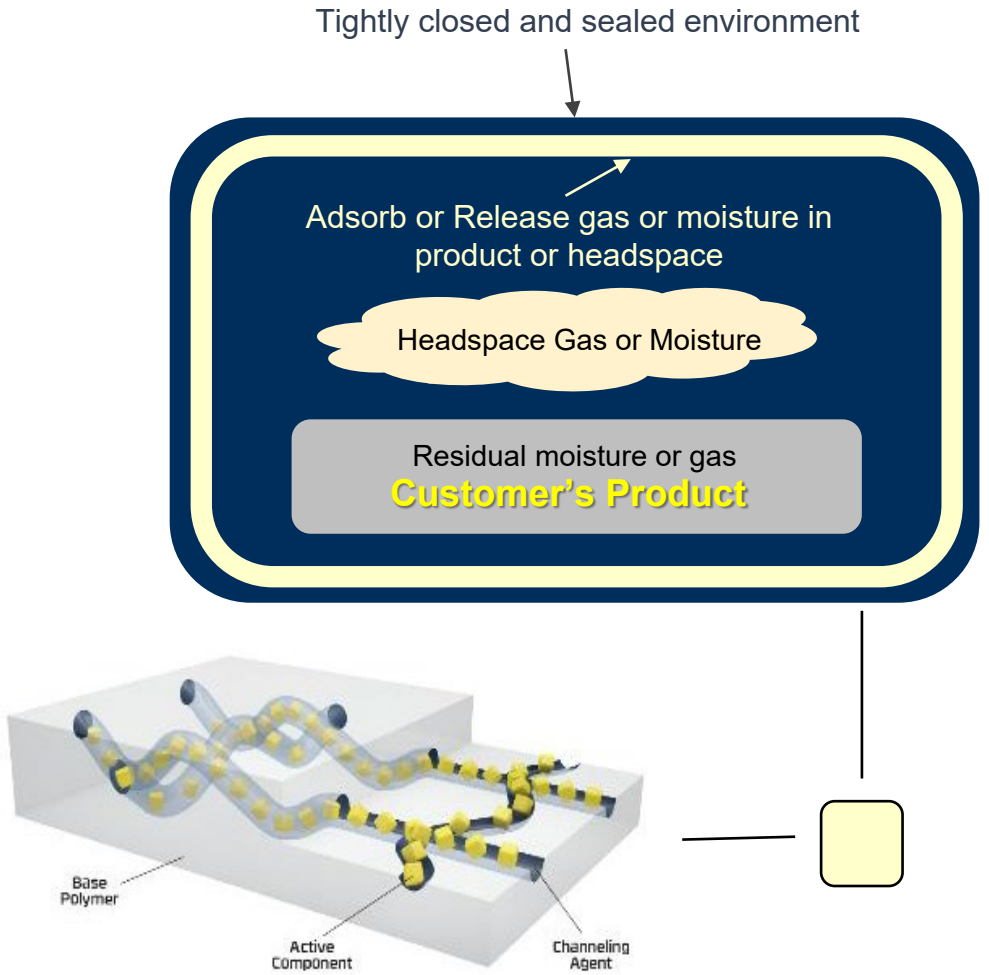
Active Packaging – Putting Chemistry into Polymers

Tightly Sealed Environment

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

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



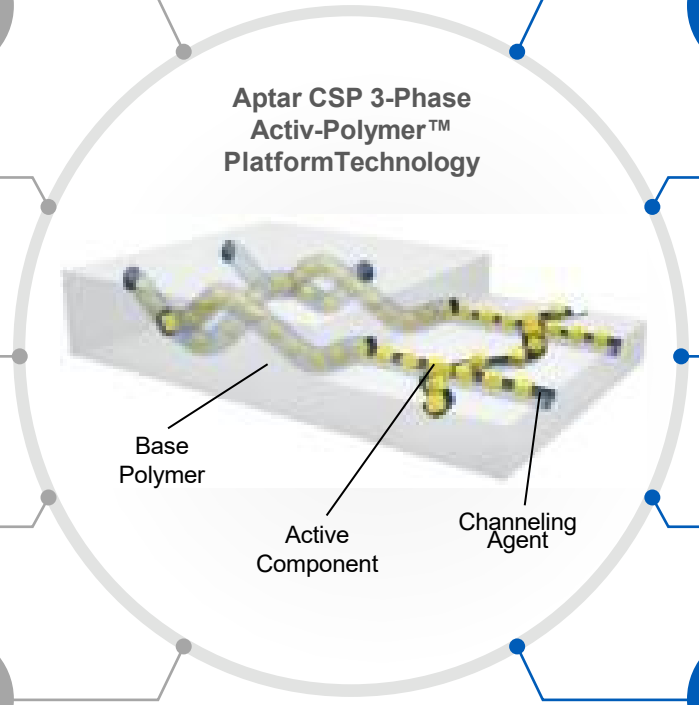


Active Material Science Platform Technology

Ability to incorporate single or multiple chemistries into a polymer solution that retains the performance of the chemistries while maintaining the physical properties of the polymer

Incorporate Desired Chemistry

- Moisture Control
- Scavenging - Oxygen, CO_2, Ethylene, Formaldehyde
- Antimicrobial
- Emitters
- Odor Removers



Commercial Applications

- Injection molding
- Thermoforming
- Extrusion Film
- Extrusion Blow Molding*
- Hot melt*

*Applications in development

Microneedle and Transdermal Applications

Microneedle and Transdermal Applications

Microneedle/Micro-Array Patches

- Protection vs moisture
- Protection vs oxygen
- Combo
- Control of Relative Humidity within the headspace
- Sterilization of devices via biocide degassing

Transdermal Patches

- Protection vs moisture
- Protection vs oxygen (reducing the need for N_2 flush or antioxidant compound)
- Dual protection vs moisture and oxygen

Xcelerate Development Services for Transdermal Applications

Complete Solution Service, from Stability Challenge to Product Launch

Xcelerate Development Services awards:

Pharma Manufacturing magazine 2019 All-Star Innovator Award

Medicine Maker magazine 2019 Innovation Award

Case Study

Case Study Introduction

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CHALLENGE

- If the RH is too high, Micro-Array shape could be affected
- If the RH is too low, Micro-Array may become brittle

SOLUTION

- Protection of a Micro-Array Patch within a buffered Relative Humidy

Case Study User Requirements

Sponsor Product: Micro-Array Patch (MAP) for Transdermal Drug Delivery Systems

- Moisture protection for target shelf life (24 months at 25°C /60% RH)
- Mechanical protection during transport and use
- Functional performance with applicator device
- Clean room and automated equipment compatible; particulate level and particulate generation control

Additional items:

- All concepts will be bi-injection design with Activ-Polymer™
- Color options available
- Surface finish options available for improved grip
- Interior features will be designed for compatibility with activation device

Co-Development Process for MAP Protective System

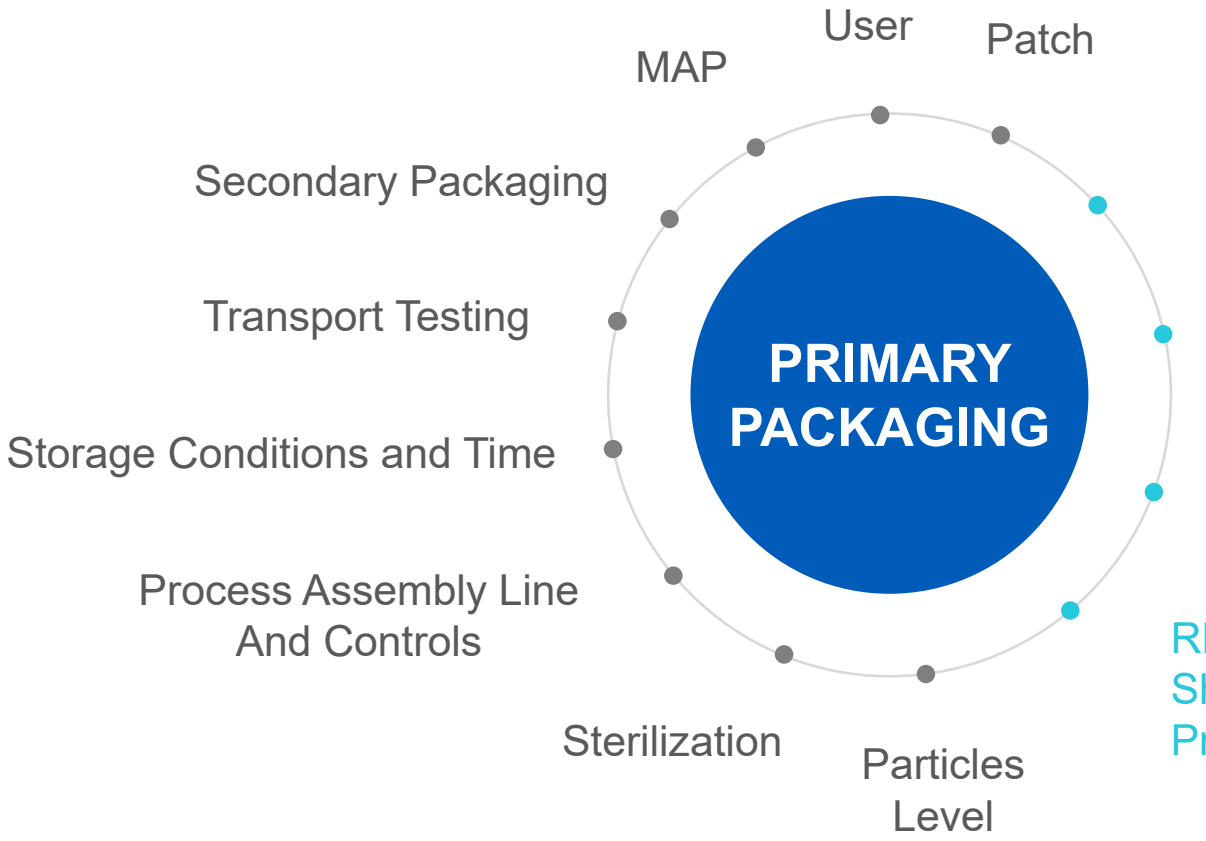
Steps in the Process with Established Milestones and Deliverables to Sponsor

PHASE I		PHASE II	PHASE I	PHASE III	PHASE IV	PHASE V
STAGE 1	STAGE 2	STAGE 1	STAGE 2		STAGE 5	STAGE 6
RH Assessment & Specification Development	**System Development**	**Clinical Stability Study Product Development**	**NDA Submission & Commercial Planning**		**Commercial Production**	**Post Market Surveillance**
• Moisture specification determination • RH characterization and MAP performance • Moisture budget creation • Proxy study	• Demo samples • Characterization and MAP performance study • Mechanical performance and testing • Product and package design freeze & verification	• Moisture specification determination • 3 parts with manual assembly • Prototype production and tool validation • Moisture budget creation • DMF desiccant product • Lab scale for moisture pre-loading process • Environmental controls	• Demo samples • Characterization and MAP performance study • Mechanical performance and testing • DMF access • Product and package design freeze & verification • Capacity plan		• Production tool and process • Industrial moisture pre-loading process • Quality and supply agreement • Validation master plan • Process FMEA	• Risk evaluation and mitigation strategy (when required) • Investigation management • Change control management (internal maintenance) • Perform data trending for Critical Quality Attributes (CQA) - to be negotiated with the sponsor • Annual product review (APR)

Stage 1: RH Assessment & Specification Development

Draft Requirements / Specifications

To Define Primary Functions and Secondary Functions



Sealing
Material MVTR*
Surfaces*

*Ingress

Plastic Material*
Thickness*
MVTR

*Ingress

Volume Head Space

RH
Shelf Life
Process Time

Activ-Polymer™ Solution

- Formulation
- Weight
- Moisture Pre-loading
- Format of Activ-Polymer™ (molded component, bi-injection, film, etc.)

3D design

Draft Drawing

Stage 1: RH Assessment & Specification Development

Specification

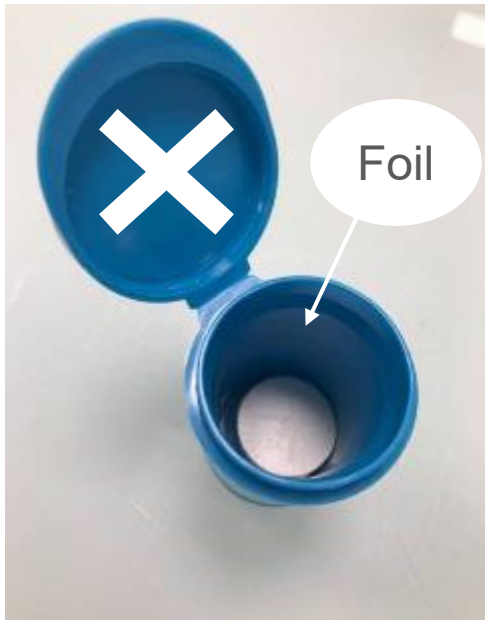
- Meeting and/or teleconference with partners to determine functionality of product

Deliverables

- Recommendation based on Proxy Study
  - Defined RH range for MAP at specific conditions
- Establish product requirement list including:
  - Specification of each component of the primary packaging: desiccant, molded parts and potential adhesive
  - Description of process (conditions, requirements)
  - Conditions of packaging, storage and use
  - Specification of tertiary packaging of each component and final product

Proxy Study: 24 ml Vial and Activ-Polymer™

“Proxy vial” is an existing container: Use a foil sealed on the top (cap will be removed)

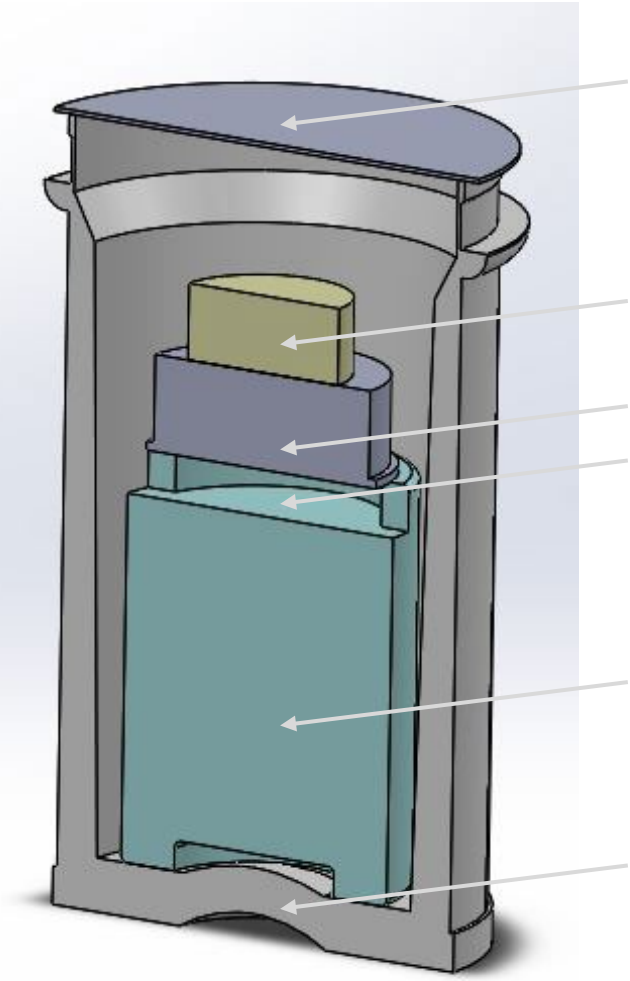


- 24ml Vial
- Ingress 50 µg/day with aluminum foil seal (TBC)

- Add Activ-Polymer™ piece with requested weight
- Fill with beads or a spacer made of PP (same material as vial) to achieve air volume of 3ml

Proxy Vial: 24ml with Components

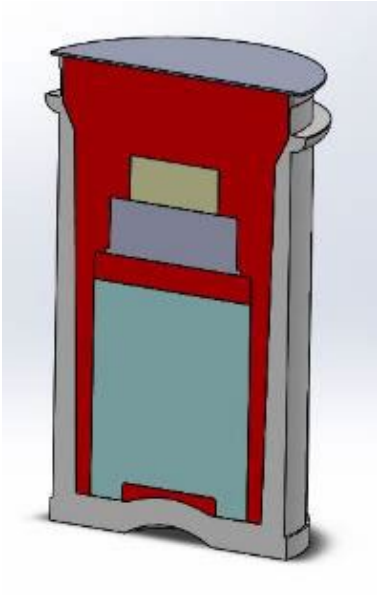
With space for sponsor Micro-Array Patch



Micro-Array:

- Diameter: approx. 10mm
- Height: approx. 1mm

With components, headspace is 1,45cm^3



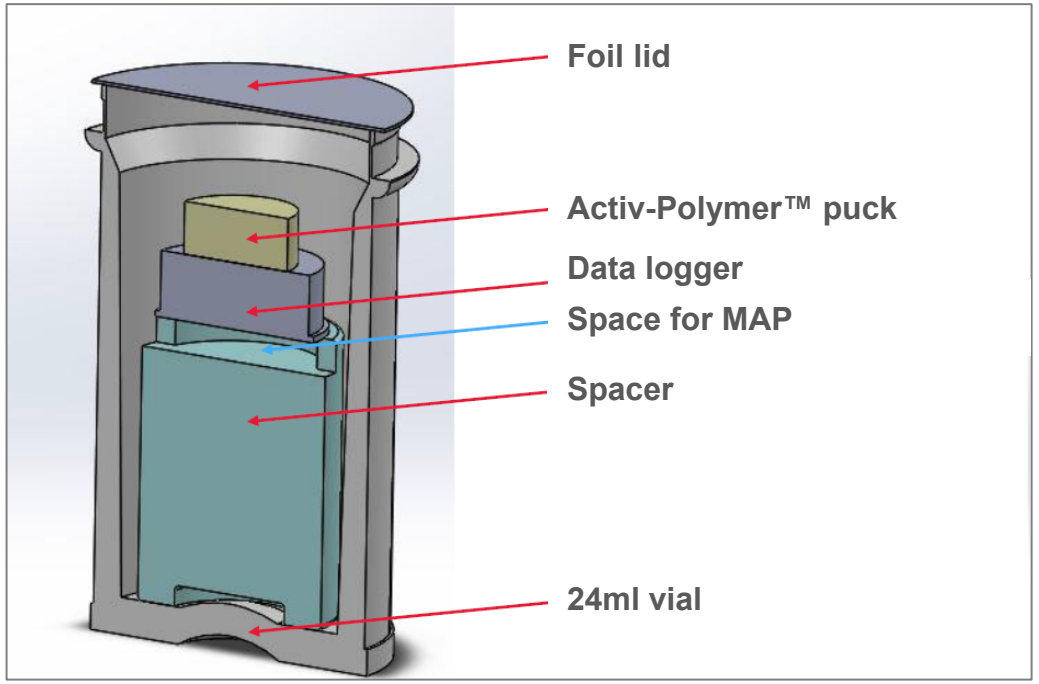
Stage 1: RH Assessment & Specification Development

Key Components:

- Proxy Study: 24ml vials, Activ-Polymer™ puck and data logger
- Foil sealing to close Proxy Vial
  - Variable headspace and RH levels
  - Testing without MAP

Deliverables to sponsor:

- Design proxy product and raw material recommendation (3D model)
- Production of components (vial, puck and spacer) for proxy study
- RH characterization in proxy product at 3 different external conditions and 3 different durations.
- Moisture Budget Assessment based on study results.
- Supply same proxy product to sponsor for MAP performance and moisture specification determination for primary package



Stage 1: RH Assessment & Specification Development

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PREDICTED VIAL PERFORMANCE

Produced on 12/03/2019 BY: GRF
Updated on BY:

Assumptions and notes

Customer Name	IIS
Product Description	Proxy product
# sensors/vial =	1
# of openings @ CSP	1
# of openings @ Customer	1
Vial Inner Diameter	22 mm
Vial Inner Height	8 mm
Plug Inner Diameter (for standard vials enter 0)	0 mm
Plug Height (for standard vials enter 0)	0 mm
Vial Internal Volume	3,041 cm^3
Desiccant Weight	0,64 g
Minimum Molecular Sieve Loading	60 %
Usable Desiccant Capacity to maintain 15% RH	20 %
Minimum Capacity	77 mg
Ingress USL @ 30 °C / 75% RH	100 (µg/day)

Input
Calculated result

Instructions:
1. Choose calculation result in gray box
2. Adjust inputs to change

○ Calculate Ingress USL
◉ Calculate Theoretical Shelf Life

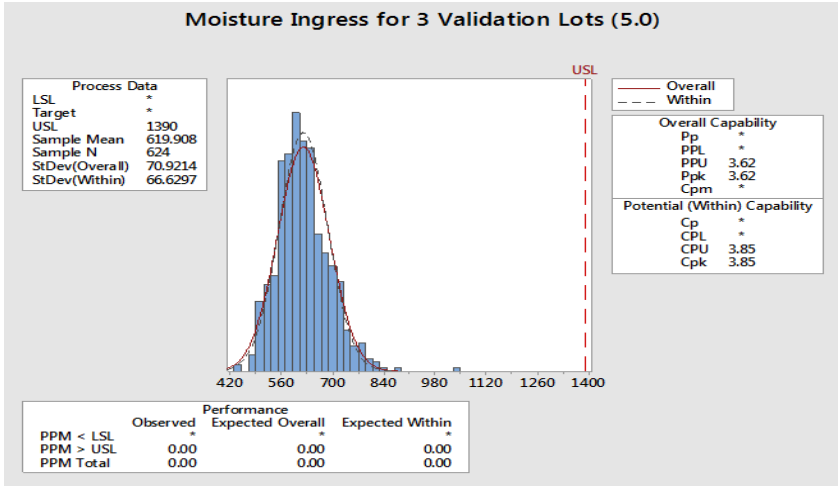
Maximum Ingress at Different Conditions

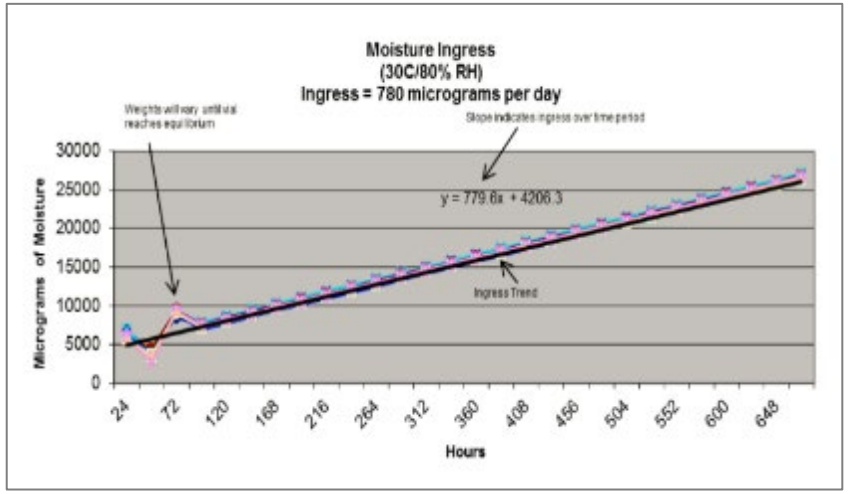
22 °C / 80% RH	68 (µg/day)
25 °C / 60% RH	61 (µg/day)
30 °C / 65% RH	87 (µg/day)
30 °C / 70% RH	93 (µg/day)
25 °C / 93% RH	94 (µg/day)
30 °C / 75% RH	100 (µg/day)
30 °C / 80% RH	107 (µg/day)
40 °C / 75% RH	168 (µg/day)

	Temperature and Humidity	Mass of Water Vapor (g/cm^3)	Maximum Ingress (µg/day)	Foil Bag (Y/N)
CSP Manufacturing conditions	25 °C / 60% RH	0,00001387	61	N
CSP Storage Conditions	25 °C / 60% RH	0,00001387	61	Y
Customer Storage Conditions	25 °C / 60% RH	0,00001387	61	Y
Customer Manufacturing conditions	25 °C / 60% RH	0,00001387	61	N
Shelf conditions	30 °C / 75% RH	0,00002284	100	N

I. Calculations

1	Vial/lid		0,1 mg
2	CSP Manufacturing Life Opening		
	Mass water vapor, in vial after open		42 µg
	Number of openings		1
	CSP Manufacturing Life Opening load		0,042 mg
3	Storage @ CSP		
	Maximum Number of Years of Storage		1 years
	Storage @ CSP load		0,4 mg
4	Storage @ Customer		
	Maximum Number of Years of Storage		1 years
	Storage @ Customer load		0,4 mg
5	Customer Manufacturing Life Opening		
	Mass water vapor, in vial after open		42 µg
	Number of openings		1
	Customer Manufacturing Life Opening load		0,042 mg
6	Moisture in Each Sensor		0,05 mg
	Total Moisture from Sensors		0,05 mg
7	Moisture From Patient Opening 1 Time		0,069 mg
	Total Moisture from Use Life Openings		0,1 mg
8	Shelf Storage		
	Minimum Number of Potential Years of Storage @	30 °C / 75% R	2,08 years
	Shelf Storage load		
	Grand total moisture load		77 mg





Sample data: Moisture ingress

Stage 2: System Development

Stage 2: System Development

Key Components:

- Rapid prototype models of selected designs
- Proxy Study II: Demo samples
- Material development and selection with compliance statement
- Test methodology development
- Moisture budget (updated)
- Package/Specification development
- Product and packaging spec and drawings

Deliverables:

- Demo samples
- RH characterization and MAP performance study
- Moisture pre-loading process development
- Mechanical performance and specifications
- Bulk package design and related shelf-life
- Design freeze & verification with regulatory review

CoDev End of Phase I

PHASE I

STAGE 1

RH Assessment & Specification Development

- Moisture specification determination
- RH characterization and MAP performance
- Moisture budget creation
- Proxy study

STAGE 2

System Development

- Demo samples
- Characterization and MAP performance study
- Mechanical performance and testing
- Product and package design freeze & verification

- Ready for Phase 2 – Stage 3 (pilot mold for stability studies)
- Limit risks due to Proxy Study and validation of the specifications
- Expedite time to market

Thank You For Your Attention!

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