TECHNICAL BRIEF

ENHANCING STABILITY OF PHARMACEUTICAL MICRO-TABLETS AND POWDERS IN STICKPACKS USING MOISTURE ADSORBING ACTIVE FILM

Julien Klein & Flavien Paquin, *Aptar CSP Technologies*
Holger Merz, *Merz Verpackungsmaschinen Gmbh*
Roland Heinemann & Werner Schmid, *Ivers-Lee*
Elmar Maus, *Constantia Flexibles*

Introduction

Pediatric drug formats play a crucial role in ensuring the safe and effective treatment of children, addressing their unique requirements and improving medication compliance and outcomes. To address these needs, pharmaceutical companies are developing microtablets and granulates to adapt dosages to children. Microtablets, mini-tablets, and granulate products packaged in stickpacks offer a convenient, safe, and precise drug delivery system for pediatric patients, addressing many of the challenges associated with administering medications to children. Specifically, this drug format offers a range of benefits:

- **Accurate Dosage:** Microtablets allow for precise dosing tailored to pediatric patients' needs. Each microtablet typically contains a small, standardized dose of the medication, making it easier to adjust doses based on the child's age, weight, and condition.
- **Ease of Administration:** Stickpacks provide a convenient and portable packaging format for microtablets. Patients and caregivers can easily carry stickpacks with them and administer medication when needed, without additional measuring devices or preparation.
- **Reduced Risk of Choking:** Microtablets are small and easy to swallow, reducing the risk of choking, especially in younger children who may have difficulty swallowing larger tablets or pills.
- **Improved Compliance:** The convenience of stickpacks and the small size of microtablets may improve medication compliance among pediatric patients. Children may find it easier to take medications in this format, leading to better treatment outcomes.
- **Customized Formulations:** Microtablets can be formulated with specific flavors or coatings to improve palatability and mask any unpleasant tastes, making them more appealing to children.
- **Reduced Waste:** Stickpacks typically contain individual doses of medication, reducing the risk of overuse or waste compared to bulk packaging formats.
- **Safety and Hygiene:** Stickpacks provide a hygienic and tamper-evident packaging solution, ensuring the safety and integrity of the medication until it is administered.

IDEA IN BRIEF

THE PROBLEM

Pharmaceutical powders, granulates, and microtablets packaged in stickpacks or sachets can face stability challenges associated with residual humidity or residual oxygen.

THE CHALLENGE

Minimal headspace in the small stickpack format limits the use of traditional moisture or oxygen scavengers in sachet or canister formats.

THE SOLUTION

Aptar CSP's proprietary 3-Phase Activ-Polymer™ technology, deployed as Activ-Film™ material, can be seamlessly integrated into these packaging formats to create a precise microclimate inside the package that extends API shelf life and ensures product stability and efficacy, and mitigates degradation risk.

Problem: Stability of Microtablets or Granulates

Despite the many benefits of powders, mini-tablets, and granulate products packaged in stickpacks, these drugs also face unique challenges when it comes to maintaining shelf life and assuring drug product stability and efficacy. Like any pharmaceutical formulation, the stability of microtablet drugs is a critical aspect that pharmaceutical companies consider during development and manufacturing. Several factors influence the stability of microtablet drugs, including:

- **Chemical Stability:** Microtablets must maintain chemical stability over time to ensure that the active pharmaceutical ingredient (API) remains intact and effective. Factors such as pH, temperature, moisture, and exposure to light can affect the chemical stability of the API. Proper formulation, packaging, and storage conditions are essential to minimize degradation.
- **Physical Stability:** Physical stability refers to the maintenance of the physical properties of the microtablets, such as size, shape, hardness, and disintegration characteristics. Changes in physical stability can affect the drug's dissolution and bio-availability. Formulation excipients, manufacturing processes, and storage conditions play crucial roles in maintaining physical stability.
- **Moisture Sensitivity:** Microtablets may be sensitive to moisture, leading to changes in their physical and chemical properties. Proper packaging, such as moisture-barrier materials and desiccants, can help protect microtablets from moisture absorption and maintain stability.

Challenge: Maintaining API Integrity in Stickpack Format

When a drug requires moisture or oxygen protection to assure efficacy and mitigate risk of degradation, pharmaceutical developers may look to packaging-based solutions, often in the form of high-barrier foil packaging and drop-in desiccants or scavengers in a sachet or canister format. However, the small packaging footprint of a stickpack solution for microtablets, powders, and granulate products make it challenging to incorporate protection beyond the barrier properties of the foil. The limited headspace inside a stickpack package prohibits the use of a basic desiccant or scavenging sachet. Developers of these small format drugs need an alternative active packaging solution to manage moisture and oxygen exposure and protect against drug degradation.

Solution: Innovations in Active Material Science Technologies

Despite the challenges the small stickpack format presents when it comes to managing moisture and oxygen exposure, there is a solution. Advancements in active material science technologies have enabled the development of a new class of highly-engineered compounds that fully integrate moisture adsorption, oxygen scavenging, or other active properties into product packaging.

Leveraging 20+ years of material science expertise, Aptar CSP Technologies' 3-Phase Activ-Polymer™ platform technology provides premier product protection for sensitive drug products, probiotics, medical devices, drug delivery systems, and even foods. It incorporates active chemistries to provide moisture control, gas scavenging (Oxygen, CO_2, Ethylene, Formaldehyde, Nitrosamines, etc.), microbial pathogen reduction, and aroma reduction or emission.

The proprietary technology is delivered in a unique formulation comprised of a base majority polymer, a minority polymer (channeling agent), and active particles (Figure 1). The majority polymer serves as the base component and provides the physical structure for the final product. The active particle provides the desired characteristics, such as ***absorption*** or ***adsorption*** of moisture, gasses, or odors, ***release*** of

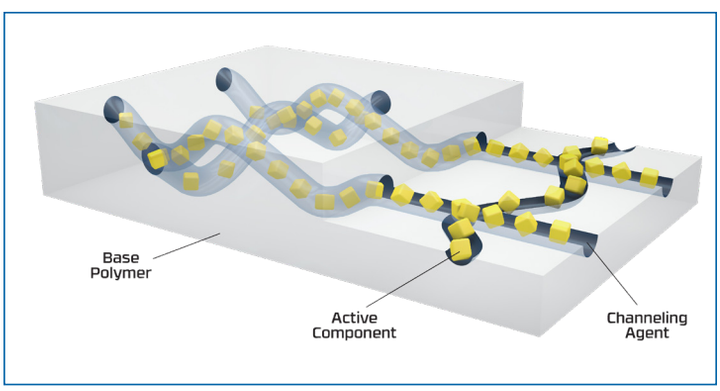

Figure 1: 3-Phase Activ-Polymer™ Technology Matrix

aromas or antimicrobials, or ***transmittal*** to enhance the gas transmission rate of the polymer. The minority polymer or channeling agent is immiscible (non-mixing) in the majority polymer and has a chemical attraction to the active particle, creating pathways for complete access to the active particles.

Activ-Polymer™ technology has the 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, which can be extruded into a film or injected in a molded part. Additionally, the solution can be formulated to manipulate the kinetics of adsorption, absorption, or release of gasses, increasing or decreasing uptake rate and capacity to offer a customized solution that maximizes shelf life and product protection.

When deployed as an extruded Activ-Film™ material (configured as a continuous roll or die cut), 3-Phase Activ-Polymer™ technology enables a unique solution to the challenges stickpack packaged drugs face. The film can be formulated to adsorb moisture, scavenge oxygen, VOCs, etc., or combine functionalities and is applied to the stickpack foil pouch in line via a proprietary heat-staking process, without use of adhesives.

ACTIV STICKPACK®

In order to enable simple adoption of Activ-Film™ technology to protect stickpack packaged drugs, Aptar CSP Technologies partnered with Merz Verpackungsmaschinen GmbH, a leader in stickpack innovation, and Ivers-Lee, a CMO. As heatstaking needs to provide a strong bond, Constantia Flexibles joined the team to provide expertise and laminates to guarantee a tight seal as well as a safe and lasting bond of the Activ-Film™ material to the inside of the laminate. Merz has successfully integrated a Film Applicator Module (Figure 2) in a vertically operating, fully automatic forming, filling, and sealing machine for stickpack production, delivering up to 40 stickpacks per minute per filling line with weighing control. The Activ-Film™ material is heat staked to the foil (Figure 3) without adhesives before stickpack forming. The machine is located at Ivers-Lee to support pre-stability and proof of concept samples for pharma companies wishing to leverage this innovative "ACTIV STICKPACK®" technology.

Figure 3: ACTIV STICKPACK® with Activ-Film™ Material Heatstaked to Foil

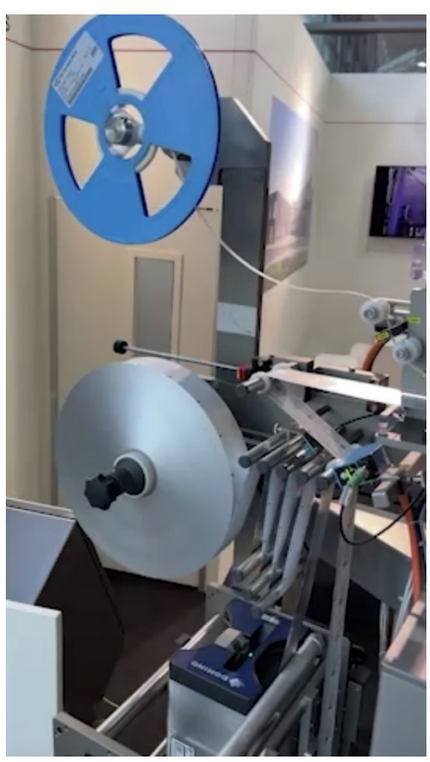

Figure 2: Integrated Film Application Module

Study Design

To validate the feasibility of and interest in integrating Activ-Film™ technology in a stickpack format, Aptar CSP Technologies, Merz Verpackungsmaschinen, Ivers-Lee and Constantia Flexibles designed an experimental study to observe the impact of Activ-Film™ on Water Activity inside a stickpack over time.

This study used Lactose Monohydrate and Semolina as surrogate powders and included two types of stickpack foils with different aluminum barrier film thicknesses (9 µm and 20 µm). Half of the stickpacks contained Activ-Film™ material and half did not.

In total, the study had 8 different branches (2 foils, 2 types of powders, each with or without Activ-Film™ material).

Material & Methods

Stickpack Materials *(Figure 4)*

- Stickpack format: 30 mm W, 70 mm L (Stickpack drawing FZ-1013)
- Stickpack foils:
  Constantia PATZ 47435 (12PET/9AL/50PE)
  Constantia PATZ 47436 (12PET/20AL/50PE)
- Activ-Film™ material:
  Reference M-0035 (moisture adsorption)
  Desiccant strip dimensions:
  35 mm L | 7.5 mm W | 0.6mm Thick
- Activ-Film™ total moisture adsorption capacity: 23.1 mg

Stickpack Equipment

- Stickpack Machine Type: SBL50 No. 120 (Fig. 5)
- Strip supply ACTIV STICKPACK® SZ730 No. 001 (Fig. 6)
- Feed Activ-Film™ strips in stickpacks, suitable for moisture-sensitive products
- Powder Dosing system SD550 Nr. 019 (Fig. 7)

Materials: Lactose and Semolina

- Stickpacks were filled with 0.5g of Lactose Monohydrate (Excipress GR150 – Armor Pharma, France) or Semolina.
- Initial Moisture Content:
  Lactose: 4.5% to 5.5% (according to COA)
  0.15% (Ivers-Lee measurement)
  Griess Semolina: Unknown (no technical sheet)
  10-12% (Ivers-Lee measurement)

Methods: Testing Equipment at CMO

The moisture level of the products was tested at Ivers-Lee with a Halogen Moisture Analyzer HS153, which was used to measure the residual moisture of the material. Before the bulk material was filled into the hopper of the dosing unit, three samples of 10g bulk material was taken manually. This sampling was taken before each run, and all results were recorded.

Methods: Stickpack Moisture Ingress*

Stickpack samples were identified and introduced into a climatic chamber at 40°C and 75%RH. These aggressive testing conditions were used to evaluate sealing performance. Measurements were taken at T0 and every 4 weeks afterward.

* The amount of moisture coming through the seal and wall side of the stickpack for defined temperature and humidity conditions.

Figure 4: Stickpack Materials


Figure 5: ACTIV STICKPACK® Machine

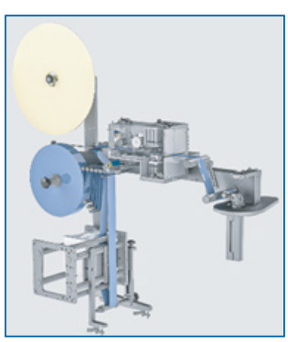
Figure 6: ACTIV STICKPACK® Strip Supply


Figure 7: Powder Dosing System

Material & Methods *(continued)*

Methods: Activ-Film™ Moisture Adsorption Capacity
Residual moisture adsorption was measured on stickpack samples after the measurement of the water activity. The water activity was measured on the powder, and the remaining moisture adsorption was measured on the empty open stickpack. Weight gain of the Activ-Film™ was measured until total capacity was reached.

Methods: Testing Equipment at Stability Establishment
*Product Water Activity***
Stickpack samples were identified and introduced into a climatic chamber at 30°C and 65%RH (Zone IV ICH conditions). The water activity was then measured with Awmeter LabTouch-aw Advanced (NOVASINA). Measurements were taken at T0 and every 4 weeks afterward.

** *Water activity (aw) is expressed as the ratio of the vapor pressure in a food (P) to the vapor pressure of pure water (P0). It predicts whether water is likely to move from the food product into the cells of microorganisms that may be present. The water activity has no unit as it's a ratio between P/P0.*

Testing Results: Moisture Ingress

Moisture ingress testing was conducted on stickpack samples containing Lactose and Semolina (Figure 7). Both sets of samples were stored for three months at room temperature before beginning the moisture ingress testing. Results of testing for both the Lactose and the Semolina showed a normal population with moisture ingress lower than 20µg per day at 40°C/75% RH (Figures 8 & 9). The stickpacks were considered tightly sealed.

Population	Comment	Foil Type	Powder Type
3 "O"	without desiccant	12PET / 9AL / 50PE	Lactose
4 "W"	with Activ-Film™	12PET / 9AL / 50PE	Lactose
5 "O-2"	without desiccant	12PET / 20AL / 50PE	Lactose
6 "W"	with Activ-Film™	12PET / 20AL / 50PE	Lactose
7 "O"	without desiccant	12PET / 9AL / 50PE	Semolina
8 "W"	with Activ-Film™	12PET / 9AL / 50PE	Semolina
9 "O"	without desiccant	12PET / 20AL / 50PE	Semolina
10 "W"	with Activ-Film™	12PET / 20AL / 50PE	Semolina

Figure 7: Tested Population Table

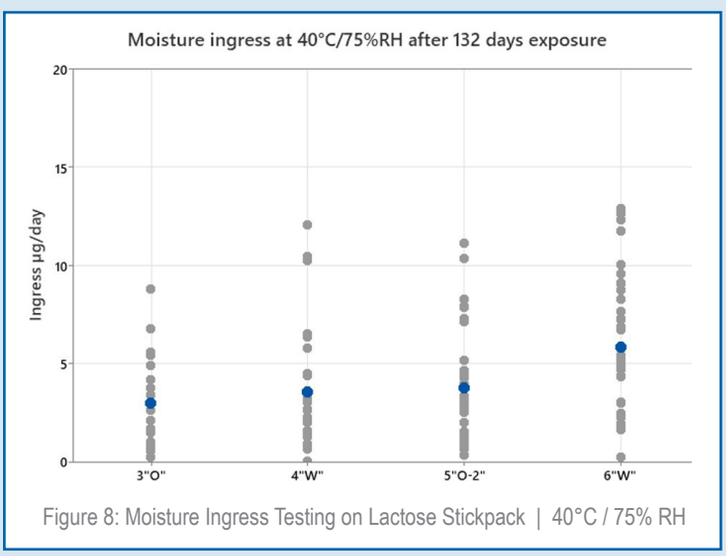

Figure 8: Moisture Ingress Testing on Lactose Stickpack | 40°C / 75% RH

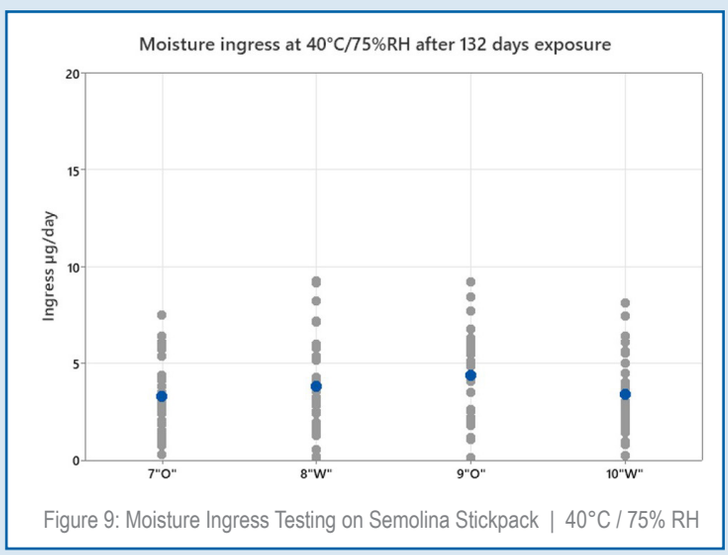

Figure 9: Moisture Ingress Testing on Semolina Stickpack | 40°C / 75% RH

Testing Results: Water Activity

Sample stickpacks containing Lactose and those containing Semolina were stored for 3 months at room temperature before running the water activity test. The initial Aw of the Lactose was 0,40 and showed a decrease of up to 0,2 in the samples packaged with Activ-Film™ material.

For the Semolina samples, the initial Aw was recorded at 0,65. Samples packaged with Activ-Film™ material showed a decrease in Aw of up to 0,35 before reaching the total capacity of the Activ-Film™ material.

With both sets of samples, the thickness of the two types of aluminum foil used for the stickpack had no significant impact on the Aw values (Figures 10, 11, 12, 13).

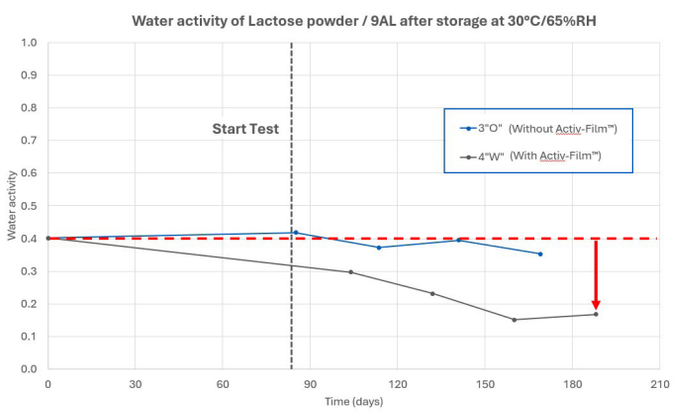

Figure 10: Water Activity of Lactose Powder / 9AL After Storage at 30°C / 65% RH | Initial Aw Lactose 0,400

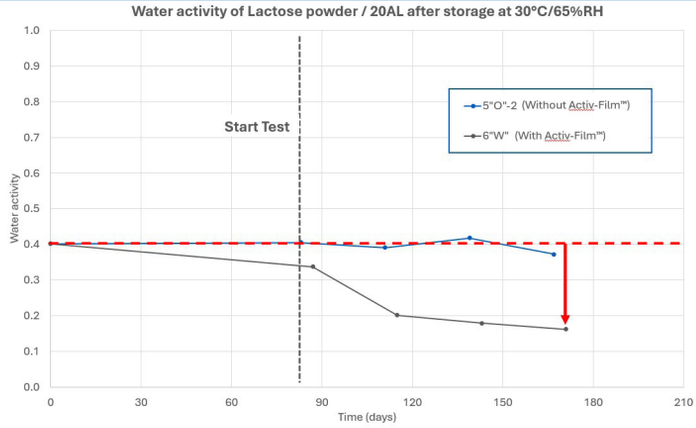

Figure 11: Water Activity of Lactose Powder / 20AL After Storage at 30°C / 65% RH | Initial Aw Lactose 0,400

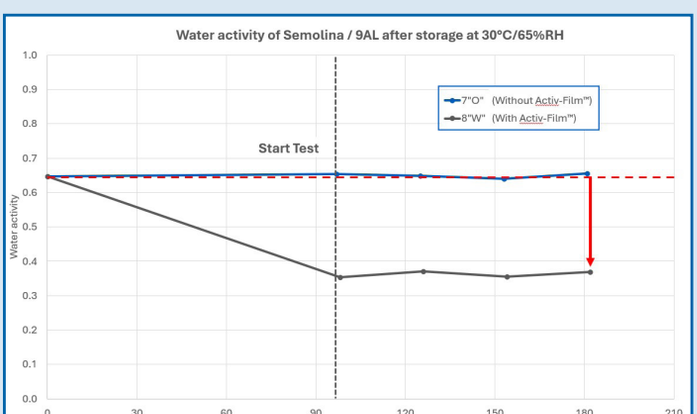

Figure 12: Water Activity of Semolina / 9AL After Storage at 30°C / 65% RH | Initial Aw Semolina 0,650

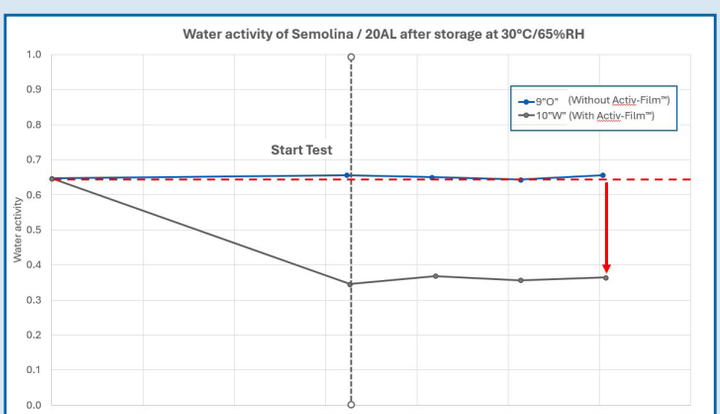

Figure 13: Water Activity of Semolina / 20AL After Storage at 30°C / 65% RH | Initial Aw Semolina 0,650

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Testing Results: Residual Moisture Adsorption Capacity

Finally, we studied the residual moisture adsorption capacity of the Activ-Film™ in the Activ-Stickpack format. The stickpacks were stored at room temperature before being placed in a climatic chamber at 30°C/65% RH for testing. After four months, the Activ-Film™ in the stickpack with Semolina reached its full capacity, while the Activ-Film™ in the stickpack with Lactose did not reach full capacity and continues to dry the product inside (Figure 14).

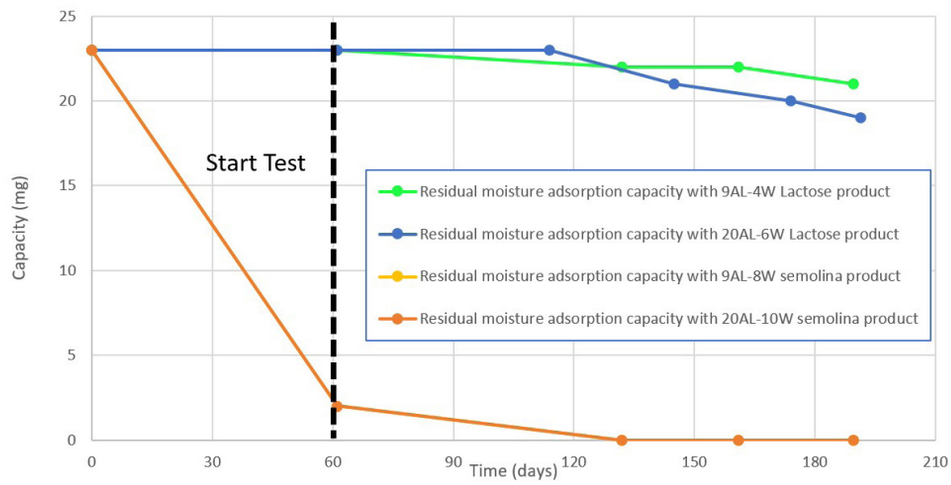

Figure 14: Residual Moisture Adsorption Capacity | 30°C / 65% RH
Note: Yellow and orange data lines are overlaid.

Conclusion

The study findings clearly demonstrate that Activ-Film™ material adsorbs residual moisture in both Lactose and Semolina, and the stickpack seal delivers excellent moisture tightness. As shown in the data, Activ-Film™ inside the stickpack with Semolina is saturated and assures the Aw is stable, while Activ-Film™ inside the stickpack with Lactose continues adsorbing moisture and is expected to deliver a continuous decrease in Aw over time.

As Aw is linked to drug product stability, we can conclude that the ACTIV STICKPACK® solution can extend shelf life and enhance stability and efficacy of microtablets. The size, thickness, and capacity of Activ-Film™ material can be customized to meet specific drug product requirements, delivering premier product protection versus traditional stickpack solutions.

The small, easy-to-integrate format can manage the microclimate in the headspace of the stickpack, offering a smart way to mitigate stability risks linked to moisture, oxygen, or nitrosamines and other VOCs. The collaboration between Aptar CSP, Merz, Constantia and Ivers-Lee provides pharmaceutical companies with expert guidance and support from R&D through commercialization to expedite speed to market.

For more information, contact:
Francois Bidet, Vice President Business Development, EMEA
Aptar CSP Technologies
Francois.Bidet@Aptar.com // (mobile) +33 6 2078 8153

Aptar
CSP Technologies