

# APPLICATION NOTE



## Protecting Moisture-Sensitive Compounds From Chemical Degradation – Performance of SYLOID® AL-1FP Silica on Potassium Clavulanate

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# PHARMACEUTICAL SOLUTIONS

## Introduction

A number of APIs are sensitive to moisture and formulating these drugs into stable oral dosage forms can be a challenging task for formulators. Several potential problems are associated with moisture sensitive drugs, such as caking and poor flow properties, chemical degradation, and decrease in shelf life of the drug. Instead of solely considering special packaging to protect moisture sensitive formulations, selecting the right excipients and formulation techniques to help stabilize moisture sensitive APIs should be taken into consideration, too. Porous silica gel, such as SYLOID® AL-1FP silica gel, can help to improve the stability of moisture sensitive APIs by acting as a moisture scavenger in the final formulation.

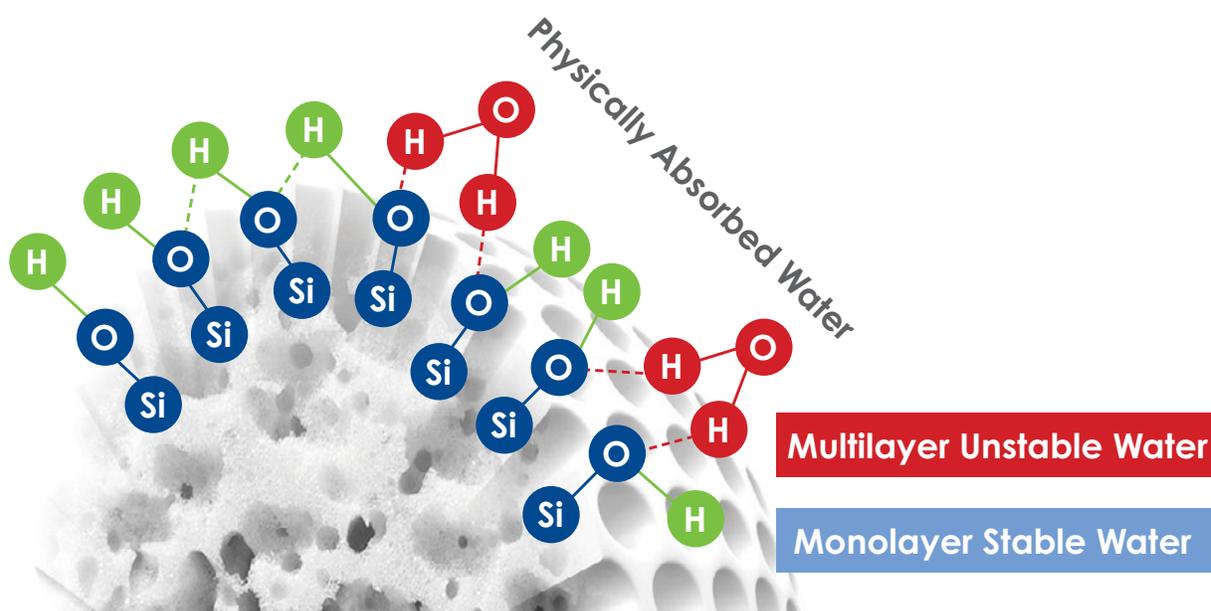
Silica gels adsorb moisture on the surface either in the form of monolayer or multilayer coverage. Water adsorbed through monolayer binds on the surface via a very energetically favorable (strong) hydrogen bonding interaction with silanol groups on the surface of the silica. As a result, it is more stable than the water adsorbed through multilayer. In addition, the highly

energetically favorable monolayer adsorption allows the reaction to occur even at low partial pressure of water, thus providing protection when low water partial pressure is required. To maximize monolayer adsorption and subsequent stabilization, the pore structure of the silica gel needs to be optimized, and the surface area is to be maximized.

SYLOID® AL-1FP silica is designed with optimized structure and exceptionally high internal surface area for maximum monolayer moisture adsorption capacity and stabilization. It can be used to provide maximum protection for compounds that is sensitive to even low partial pressure of water. The moisture adsorbed is stabilized through the strong interaction and should not adversely affect the water sensitive compounds in admixture.

This document summarizes the results of the determination of the protective effect on a highly moisture sensitive compound and compares the performance of SYLOID® AL-1FP silica with a competitor product.

**Figure 1.** Monolayer vs. multilayer capacity of a mesoporous silica gel.



## Experimental

### Description of SYLOID® AL-1FP silica

SYLOID® AL-1FP silica food additive and pharmaceutical excipient is a synthetic amorphous silica appearing as a white free flowing powder. It has a very high purity and is taste and odor free.

SYLOID® AL-1FP silica is a fine-sized, low pore volume gel with a huge internal surface area. Its very strong affinity for moisture along with its ease of incorporation can effectively contribute to the processability, stability, and shelf life of moisture-sensitive products in many pharmaceutical and food applications.

### Pharmacopeia compliance (USP, EP, etc.)

- SYLOID® AL-1FP silica (as indicated on the CoA, cf. attachment 1)
- U.S. Pharmacopeia-National Formulary (USP-NF) for Silicon Dioxide
- ICH Guideline on Elemental Impurities Q3D
- Japanese Pharmaceutical Excipients for Hydrated Silicon Dioxide
- Food Chemical Codex (FCC)
- Regulation (EU) No. 231/2012 for E 551
- Japan's Specification on Standard for Food Processing Aids, Silicon Dioxide

### Development of a model formulation

SYLOID® AL-1FP silica is an effective moisture scavenger in pharmaceutical formulations containing moisture sensitive APIs.

To illustrate this effectiveness, a model formulation of a dry oral suspension containing amoxicillin (as amoxicillin trihydrate) and clavulanic acid (as potassium clavulanate) have been developed (cf. Table 2). Potassium clavulanate ( $\beta$ -lactamase inhibitor) protects  $\beta$ -lactam antibiotics like amoxicillin from enzymatic degradation. However, potassium clavulanate is known to quickly decompose upon contact with moisture.

The formulation contained either SYLOID® AL-1FP silica or a competitor product as scavenger to protect clavulanic acid from moisture induced degradation.

The ratio of Silica: Clavulanic acid was 1:1.2 in the formulation, equaling 14% weight fraction in the formulations. Both formulations contained additional silica gel (SYLOID® 244FP silica) as glidant and anti-caking agent for maintaining the flow properties of the dry powder upon storage.

**Table 1.** Particle size and pore parameters of SYLOID® AL-1FP silica (typical values).

Spec.	Unit	SYLOID® AL-1FP Silica
D (v,0.1)	[ $\mu$ m]	2,7
D (v,0.5)	[ $\mu$ m]	7,5
D (v,0.98)	[ $\mu$ m]	22,5
Span98		2,62
BET	[m <sup>2</sup> /g]	700
PV	[ml/g]	0,4

**Table 2.** Composition of model formulations of Amoxicillin and Clavulanic acid for stability testing.

Ingredient	Dose: 400 mg Amoxicillin + 57mg Clavulanic acid in 5ml [mg/30 ml bottle]			
	F1	%w/w	F2	%w/w
Amoxicillin Trihydrate (equivalent to Amoxicillin free acid 400mg)	2788	51,6	2788	51,6
<b>Pot. Clavulanate premix (equivalent to clavulanic acid 57mg) +10% overages</b>	<b>902,88</b>	<b>16,7</b>	<b>902,88</b>	<b>16,7</b>
Xanthan gum	80	1,5	80	1,5
Succinic acid	4	0,1	4	0,1
Silicon Dioxide (SYLOID® 244FP silica)	122	2,3	122	2,3
HPMC	391	7,2	391	7,2
Flavor	355,9	6,6	355,9	6,6
<b>Silicon dioxide (SYLOID® AL-1FP silica)</b>	<b>756,22</b>	<b>14,0</b>	-	-
<b>Competitor product</b>	-	-	<b>756,22</b>	<b>14,0</b>
<b>Total (mg)</b>	<b>5400</b>	<b>100,0</b>	<b>5400</b>	<b>100,0</b>

## Stability testing

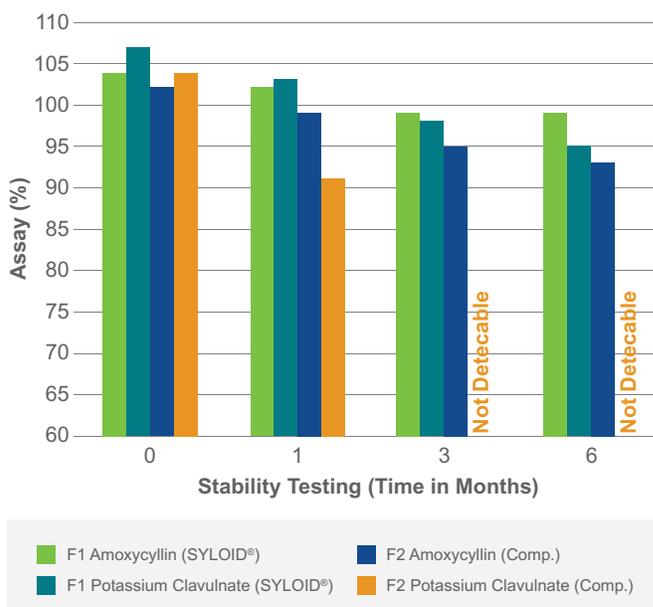
Both formulations were subjected to a six-month stability testing study under standard accelerated conditions at a temperature of 40°C and a constant relative humidity of 75%.

Sample assays were performed at t=0 and after 1, 3, and 6 months in order to determine the API content (amoxicillin and potassium clavulanate) in the formulations (cf. Figure 2) using the HPLC method as described in the USP. In addition, the appearance of the powder mixtures was checked after 3 months (cf. Figure 3).

The highly moisture sensitive potassium clavulanate in formulation F2 (containing the competitor product as moisture scavenger) degraded completely and could not be detected after three months of accelerated stability testing conditions. In contrast, 95% of the potassium clavulanate was still active after six-month in F1 (containing SYLOID® AL-1FP silica).

**Figure 2.** Amoxicillin and clavulanic acid assays at t=0, 1, 3 and 6 months of formulations F1 and F2 during stability testing under accelerated conditions (40°C/75% RH).

**Stability Testing (40°C/75%RH) of Amoxy/Clav Formulations with SYLOID® AL-1 FP or Competitor Product as Moisture Scavenger**



**Figure 3.** Appearance of formulations F1 (SYLOID® AL-1FP silica) and F2 (competitor product) after 3 months under accelerated conditions (40°C/75%RH).



Whereas F1 maintained its off-white color, the yellowish color of F2 at the end of the 3-month testing period indicates the chemical degradation of potassium clavulanate, a finding that is supported by the stability data (Figure 2).

## Conclusions

The results of the stability testing of the model formulation as described in this application note show that SYLOID® AL-1FP silica is a very effective moisture protectant. Strong evidence has been found that it outperforms a recently marketed competitor product.

Obviously, the porosity parameters (as related to pore volume and internal surface area) are optimized in SYLOID® AL-1FP silica.

The high internal surface area of SYLOID® AL-1FP silica provides a high monolayer capacity. This results in a pronounced stabilizing effect on moisture sensitive compounds and is reflected in the results of the stability testing.

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