Syloid® FP Silica

Pharmaceutical Excipient

Free Flow and Anti-Caking Application Note

formulation and delivery

Syloid® FP Silica Improves Flow Properties and Helps Prevent Caking

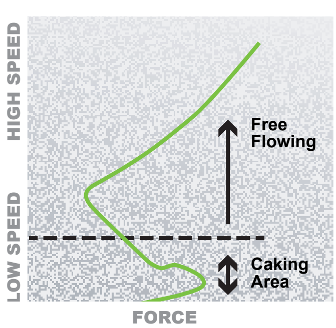
For the proper handling of active ingredients or excipients in powder form, good flow properties are very important. Clumpy or poor flowing powders are difficult to transport and dose. Homogeneous mixing with APIs and other ingredients is compromised when caking, sticking (to walls), or electrostatic conditions occur. Powder flow properties can be improved by adding Syloid® FP silica to formulations.

Syloid® 244 FP, AL-1 FP (EU), and 63FP (US) excipients are synthetic and amorphous silicas. They are produced under controlled conditions, guaranteeing high chemical purity. Grace is the manufacturer of Syloid® FP silicas facilitating supply chain custody and traceability. Syloid® FP silicas are certified to meet the specific test requirements as published in the latest editions of the United States Pharmacopoeia-National Formulatory (USP-NF) for Silicon Dioxide, Japanese Pharmaceutical Excipients (JPE) for Hydrated Silicon Dioxide and the European Pharmacopoeia (EP) for Colloidal Hydrated Silica.

Characteristics of ingredients, how they interact with each other, and the surfaces they come in contact with, and various environmental factors can all affect flow behavior. Common flow challenges include caking, sticking, and static behavior. This is illustrated in the graph below, where the force required to get a powder to move is compared to the moving speed of the powder.

Figure 1.

When powder is at rest, increased force is required to initiate powder flow. Once in motion, force decreases. Caking is common at the initial high force low speed stage. As speed increases, free flowing behavior improves



Important parameters that determine free flowing properties include:

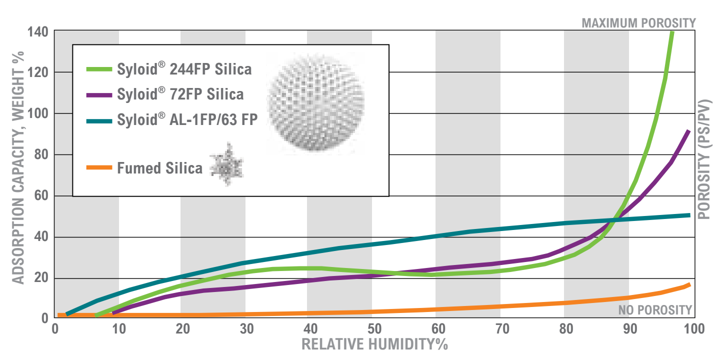
- **Moisture**
- **Particle Shape and Size**
- **Temperature**
- **Pressure**
- **Composition**

A. Moisture

Hygroscopic products, such as plant related API's, anti-infectives, lyophilized products, probiotica, and many others can adsorb moisture from the air, adhere together, and become sticky depending on the Relative Humidity (RH) in the environment. Caking can also occur when powders are not completely dry or when moisture migrates towards the outer surface after drying in wet granulation. Syloid® FP silica is a highly porous, micronized silica powder. When added to a formulation, the high porosity of Syloid® FP silica is capable of adsorbing a considerable amount of moisture, keeping the product dry and improving the stability. This can be best illustrated by the moisture adsorption capacity as represented in **Figure 2**. The moisture adsorption capacity

Figure 2.

The higher surface area and internal porosity gives Syloid® FP silicas greater moisture adsorption than other silicon dioxide excipients



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at different RH conditions is shown for different various free flowing enhancing additives. The best additive for moisture control can be selected according to the RH conditions. Keeping your formulation dry helps maintain its stability by preventing moisture transfer towards the API.

Direct compression offers several advantages over other processes including greater stability and a less costly and easier manufacturing process. Successful direct compression requires an API/excipient blend that is both free-flowing and compressible which can be challenging. However, 2-step glidant mixing can be used to achieve such a blend. This process helps achieve both optimal flow and compression properties for direct compression while maintaining the homogeneity and stability of the formulation.

Syloid® FP excipients can be used in both parts of 2-step glidant mixing. In the API mixture, use Syloid® AL-1 FP (EU) or Syloid® 63FP (US) excipient to help maximize stability of the API. Its extremely high surface area creates a hydrogen bond with moisture resulting in stable water. For the second mixture, use Syloid® 244 FP to prevent caking and segregation during blending and processing. Syloid® 244 FP silica adsorbs the right amount of moisture to create a free-flowing powder mixture, while the internal porosity retains just enough physically adsorbed water for plasticizing and binding properties needed for processing.

B. Particle Shape and Size

Particle shape and size have a major effect on free-flowing properties, segregation and uniformity. In general, spherical particles have better flow properties than non-spherical particles and larger particles have better flow properties than smaller particles. In addition, the more homogeneous the particle, the better the flow properties will be. Syloid® FP silica provides a narrow particle size distribution which helps maintain uniformity in direct compression.

The micronization of Syloid® FP silica particles prevents segregation and contributes to better flow properties with micronized API's or other micronized excipients. Such improved flow properties facilitate processing in general but especially with co-processing and pre-mixing.

C. Temperature

An elevated temperature can have a negative influence on free flowing behavior or cause caking problems. Especially for oil and lipid containing formulations, a temperature increase can lead to severe caking. In addition, temperature changes can lead to changes in adsorption capacity and condensation on cold surfaces which can lead to caking.

D. Pressure

Prolonged storage of packaged products under the influence of pressure (primarily in combination with moisture) can lead to caking.

E. Composition

Binders, hygroscopic and oil containing products are susceptible to caking. Lyophilized, freeze dried products (probiotica, peptides, etc.) often encounter electrostatic problems. In the case of electrostatic problems, the porous nature and capillary forces of Syloid® 244 FP silica can take up the charges to reduce static behavior and attraction to instruments. When a formulation has a tendency of sticking, adding a fine milled silica powder such as Syloid® FP silica coats the surface of the other ingredients to reduce adherence and prevent caking and sticking.

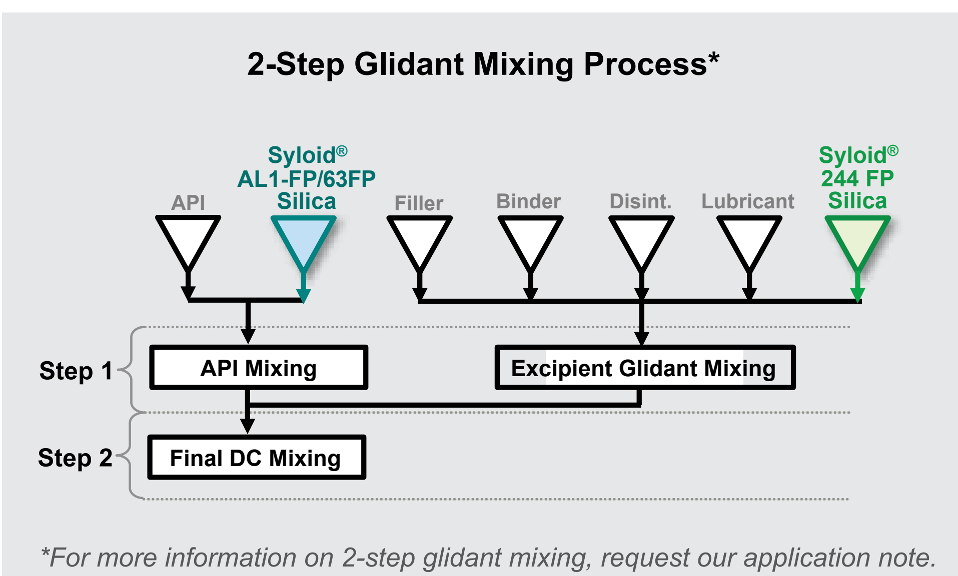


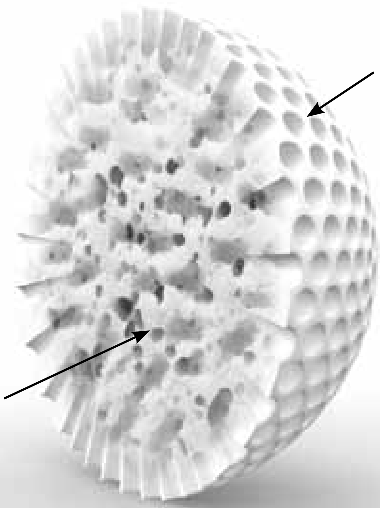
Figure 3.

API Mixing - Use Syloid® AL-1 FP (EU) or Syloid® 63FP (US) to help maximize stability of the API. Its extremely high surface area creates a hydrogen bond with moisture resulting in stable water.

Excipient Glidant Mixing - Use Syloid® 244 FP silica to prevent caking and segregation during blending and processing. Syloid® 244 FP silica adsorbs the right amount of moisture to create a free-flowing powder mixture, while the internal porosity retains just enough physically adsorbed water for plasticizing and binding properties needed for processing.

Conclusion:

The addition of small amounts (0.2-2%) of Syloid® FP silica can improve flow properties of formulations. The controlled porous morphology of Syloid® FP silica can create unique interactions, charges, and capillary forces resulting in improved free-flow, glidants, and anti-caking behaviors.



Syloid® FP Silica - Unique Attractions and Interactions

- Interparticulate attractions
- Triboelectrostatic & permanent electrostatic charge
- Presence of polar functional groups in the surface
- Molecular interactions (dipole dipole, vanderwaals)
- Capillary forces (Washburn's equation)

Reference Information - Predicting Powder Wettability

Washburn's Equation can be used to predict wettability of powders. Potential applications include calculation of drug release, formulation optimization, and determination of adhesion during manufacturing processes.

Washburn's Equation: $L^2 = (C * r) * \gamma * \cos \Phi / 2 * \eta$

L = the length of flow in time t
C = constant to account for randomly oriented capillaries
r = the radius of the capillary
γ = the surface tension of the liquid
Φ = the advancing contact angle of viscosity of liquid
η = the viscosity of the liquid

Reference Information - Table of Excipient Selection Considerations

API Property	Impact on Tablet Formulation	Excipient Selection Considerations (QbD)
Dose	Low dose may have content uniformity effects. High dose may result in direct physical impact of the API on tablet properties.	Choose excipients that improve uniformity and those that improve the physical and chemical stability of your API
Particle size	Particle size of API will influence flow properties, segregation, and uniformity. This may also contribute to capping problems in tablets.	Choose glidants with controlled and narrow particle size distribution that improve tabletting properties and prevent segregation (mostly micronised).
Flow properties	Poor flow of API may lead to decreased tablet hardness and weight inconsistencies.	This may require granulation techniques or micronised glidants. Choose glidants that do not decrease dissolution and compaction.
Bulk density	Density plays a significant role in the blend uniformity of API along with other excipients.	In general, for a high density API, the diluent selected should have a high density and vice versa in order to avoid segregation issues in a directly compressible formulation.Controlled particle size should be considered.
Moisture content	High moisture content of API may result in sticking issues during tablet compression.	Select glidants or hydrophilic lubricants with the ability to adsorb excessive moisture without diffusion to the surface.
Hygroscopicity	Highly hygroscopic API's may have tablet punch issues. Choosing the right manufacturing process under low humidity conditions can become critical for such API's.	Select excipients with dessicant properties (highly hygroscopic) and the functionality to improve the stability of your API under any relative humidity preventing degradation.
Excipient compatibility	Certain API's may be incompatible with specific excipients and may limit their selection.	Excipient/API and excipient/excipient compatibility testing (QbD) help determine the best excipient considering API and other excipients used.
Compactability	Certain API's have a poor ability to compact. Compactability simplifies direct compression.	This may require granulation techniques or the use of coprocessed/coblended excipients as a means of formulation development.

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