

Materials for Pharmaceutical Manufacturing

Syloid® FP Silica Excipients

2-Step Mixing Process Improves API Stability, Flow, and Uniformity

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Two-Step Mixing Process

Tablet preparation through Direct Compression is preferred over wet and dry granulation due to its reduced complexity, fewer steps, lower cost, and faster development time. The steps involved in direct compression are blending the API with excipients (e.g.: filler, disintegrant, binder) and compaction of the total mixture into tablets. Direct compression is particularly beneficial for APIs that are sensitive to moisture and heat by avoiding granule preparation process.

The three most important factors for successful tableting by direct compression are flow, compactability of the compression mix and drug content uniformity in the final mix and tablets. Flowability of the powder is the most important factor and unfavorable flow affects the tablet weight uniformity and processability. Flowability of the final mixture is a big concern in the case of high dose drugs and the content uniformity is in the case of low dose drugs. The drug properties also influence the flow and compactability of the final mixture for tablet preparation.

Glidants are added to the formulation to improve flow properties of the mixture for tableting. The effect of glidants on the flow of granules depends on the shape and size of the glidant particle and the granule. Flow of the final mixture depends on a combination of particle size, molecular interactions, tribo-electrostatic charges, presence of polar groups and capillary forces. The procedure used for the addition of glidant can also influence the flow of the mixture. Porous silica gel, such as Syloid® 244 FP silica, is advantageous for flow improvement compared to other

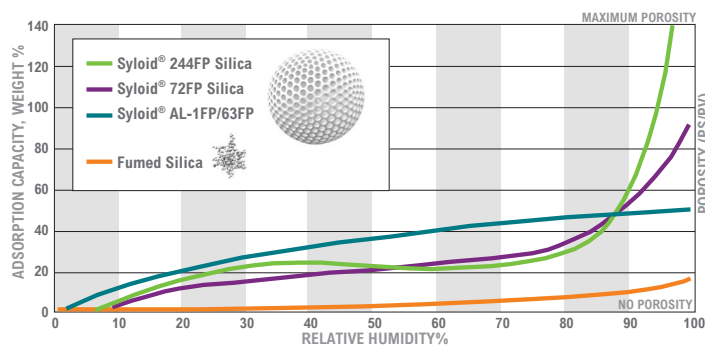


Figure 1. The higher surface area and internal porosity gives Syloid® FP silicas greater moisture adsorption than other silicon dioxide excipients. Having a range of adsorption capacities makes Syloid® FP silicas the ideal choice for both the API mixing and the excipient mixing stages of a two-step mixing process.

glidants because of its porous nature and reduced dust due to its high density. Apart from improving flow properties, porous silica gel can also promote uniformity and improve stability of the API by adsorbing moisture present in the final formulation. Specifically, Syloid® AL-1FP/63FP excipients are recommended for stability improvement of moisture sensitive APIs.

It has been shown [Abe et al, Chem. Pharm. Bull. 57(7) 647—652 (2009)] that addition of a glidant separately to both the API and the excipients mixture can have a beneficial effect on the flow property. When the glidant was added separately to the API and excipient mixtures (two-step glidant mixing), flow improvement was more pronounced than if the glidant was added as a single step to the entire API and excipient formulation mixture (one-step glidant mixing).

In this work, we will demonstrate the use of Syloid® FP silicas for flow improvement through a two-step glidant mixing process. Also, we demonstrate that the two-step mixing strategy can be used to impart additional benefits to the formulation such as moisture control, stability, and uniformity through the use of appropriate types of porous silicas.



Before considering special packaging to protect moisture sensitive formulations, first consider selecting the right excipients and formulation techniques to help stabilize moisture sensitive APIs. Porous silica gel, such as Syloid® FP silicas, can help improve the stability of moisture sensitive APIs by adsorbing moisture in the final formulation.

Using Syloid® AL-1FP/63FP Silica to Protect Moisture Sensitive APIs...

In Formulation: Moisture sensitive APIs are prone to caking, flow issues, and inconsistent dissolution

For Shelf Life: Moisture sensitive APIs can degrade quickly, reducing their shelf life if not protected from moisture

Part A: Improving Flow Property and Uniformity by Adding Glidant (Syloid® 244FP silica) in Two-Step Mixing Process compared to One-Step Mixing.

Here, we tested the flow improvement by using one-step versus two-step incorporation of Syloid® silica as a glidant, with two high-dose API formulations (Paracetamol 50% and Ascorbic Acid 40%).

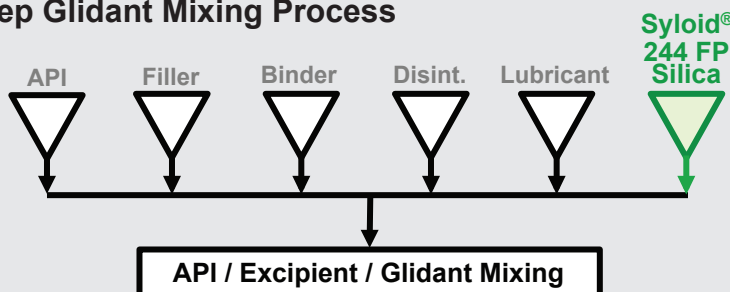
The assumption here is that in one-step mixing, the amount of Syloid® FP silica as a glidant is diluted by the total excipient mixture and is insufficiently available to form a layer and protect the API particle. In a two-step process, the amount of Syloid® FP silica is sufficiently available to form a layer around the API particle, thus improving flow, uniformity, and stability. In addition, Two-step mixing ensures uniform distribution of the API throughout the formulation due to the micronized excipient/ excipient and excipient/API particle compatibility, which prevents segregation.

Procedure for preparation of samples for two step glidant mixing:

Initially, we determined the percentage of Syloid® 244 FP silica required for separately improving the flow of fine powder drugs such as ascorbic acid (passed through 40 Mesh), Paracetamol (passed through 60 Mesh) and the excipient portion present in the respective formulations. Fine APIs and the excipients were separately mixed with Syloid® 244 FP silica at different amounts. The optimum percentage of Syloid® 244 FP silica was identified with respect to the individual API and with respect to the excipient mixture (see **Chart 1** on the following page).

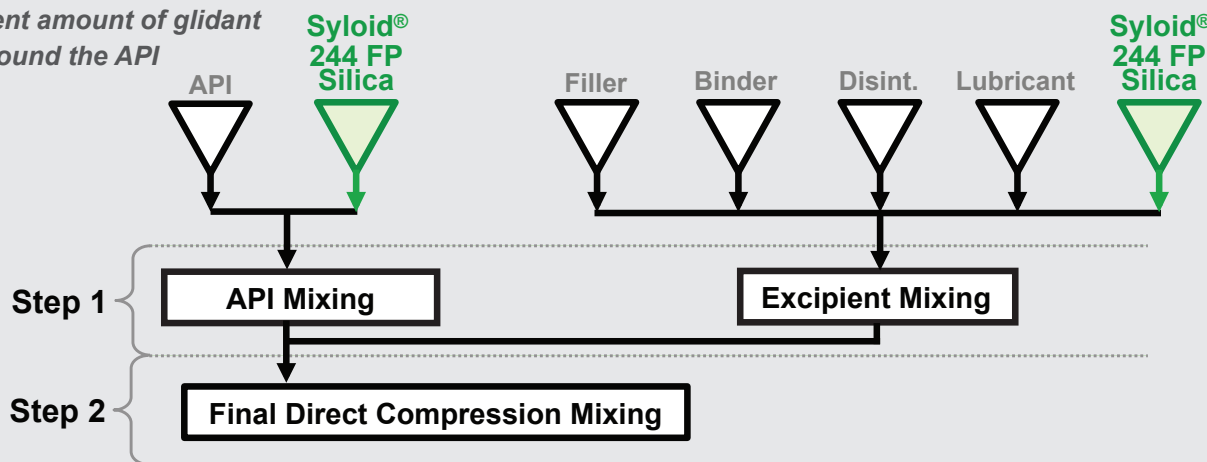
**Figure 2:
One-Step Glidant Mixing Process**

In a one-step glidant mixing process, there is an insufficient amount of glidant to surround the API and protect it from moisture due to the fact that the glidant is distributed throughout the formulation mixture



**Figure 3:
Two-Step Glidant Mixing Process Using Syloid® 244 FP Silica**

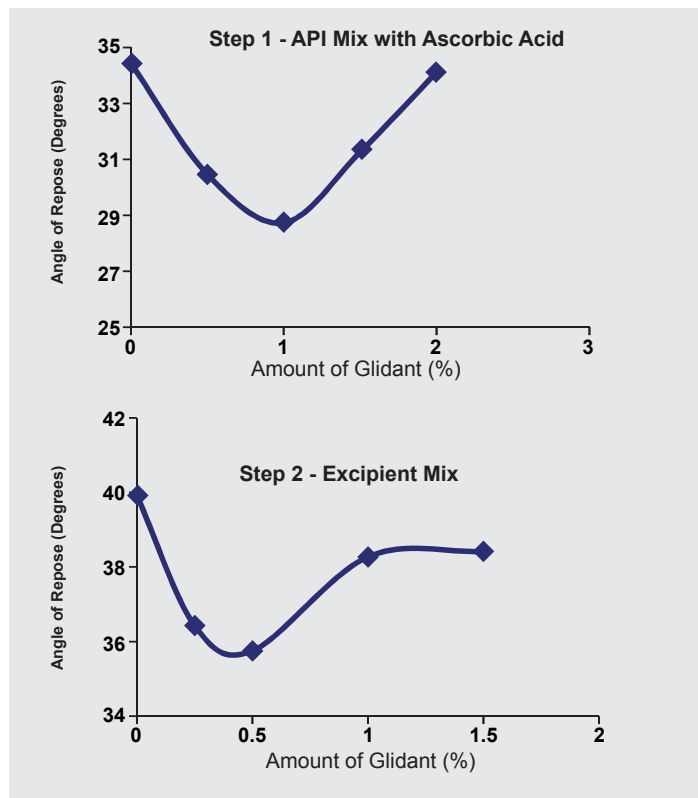
In a two-step glidant mixing process, there is a sufficient amount of glidant to surround the API



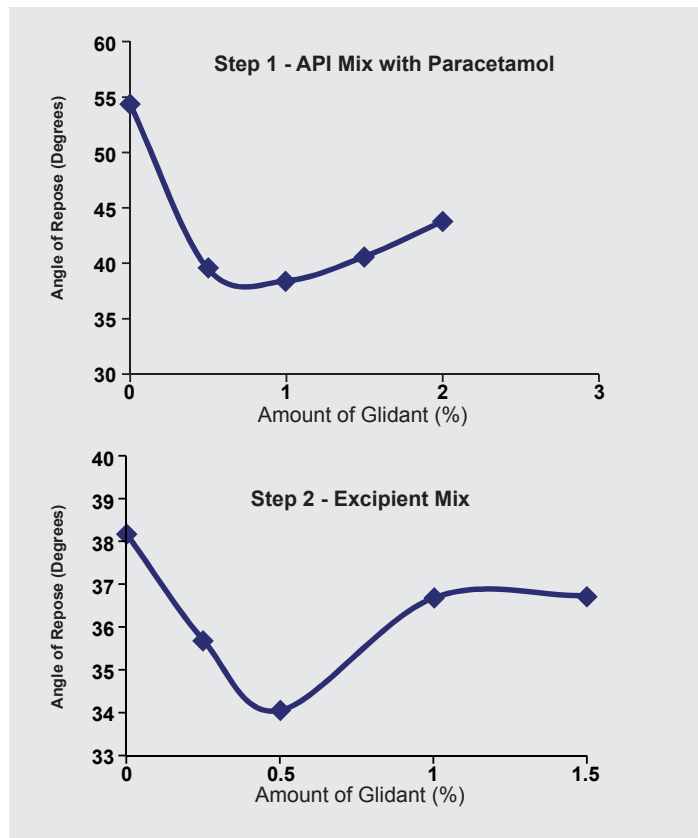
1-Step vs 2-Step Mixing - Flow Properties

Chart 1. 2-Step Mixing and effect of Syloid® 244 FP silica % on flow property in the API Mix (Step 1) and the Excipient Mix (Step 2)

Ascorbic Acid Formulation:



Paracetamol Formulation:

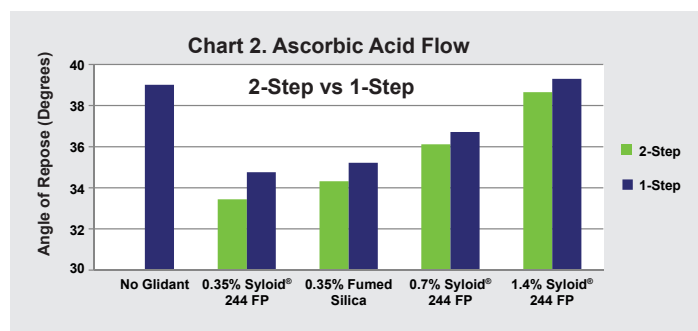


Optimum amounts of Syloid® 244 FP silica were determined for the API Mix (Step 1) and the Excipient Mix (Step 2). They were then blended and the resulting mixtures were evaluated for flow parameters.

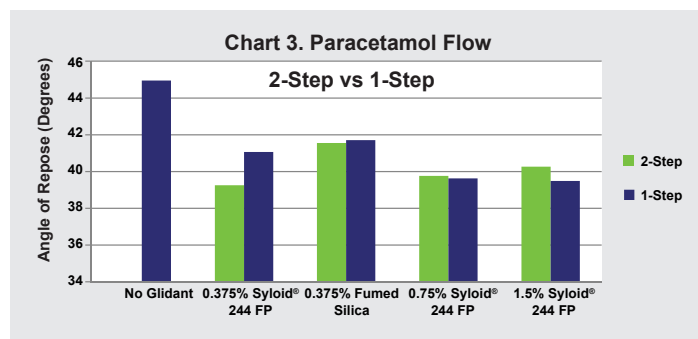
A typical direct compression formulation was prepared with 40% Ascorbic acid, 2.5% PVP K 30, 3.3% croscarmellose sodium, 0.75% stearic acid, and 0.35-1.4% glidant. The remaining amount was MCC PH 102 to bring the mixture to 100g.

As seen in Chart 2 below, there is a significant improvement in flow property when glidant is added to the ascorbic acid formulation. Furthermore, adding glidant in two separate steps to the API and excipient mixtures provides better flow behavior than a single-step process.

Syloid® 244 FP silica was also compared with fumed silica at the optimized amounts. Flow improvement with Syloid® 244 FP silica was similar or slightly better than fumed silica.



To confirm the above observations, a similar procedure was used on a Paracetamol formulation with 50% API, 5% PVP K 30, 2.5% croscarmellose sodium, 0.5% Mg stearate, 0.35-1.4% glidant. The remaining amount was MCC PH 102 to bring the mixture to 100g.



From the results above, we conclude that Syloid® 244 FP silica can be used as a glidant in a two-step mixing process to obtain maximum glidant benefits. In comparison to fumed silica, Syloid® 244 FP shows similar or slightly better flow improvement.

We also observe that flow improvement depends on the percentage of the API as well as the particle size of the API.

2-Step Mixing Process - Protecting Moisture Sensitive APIs

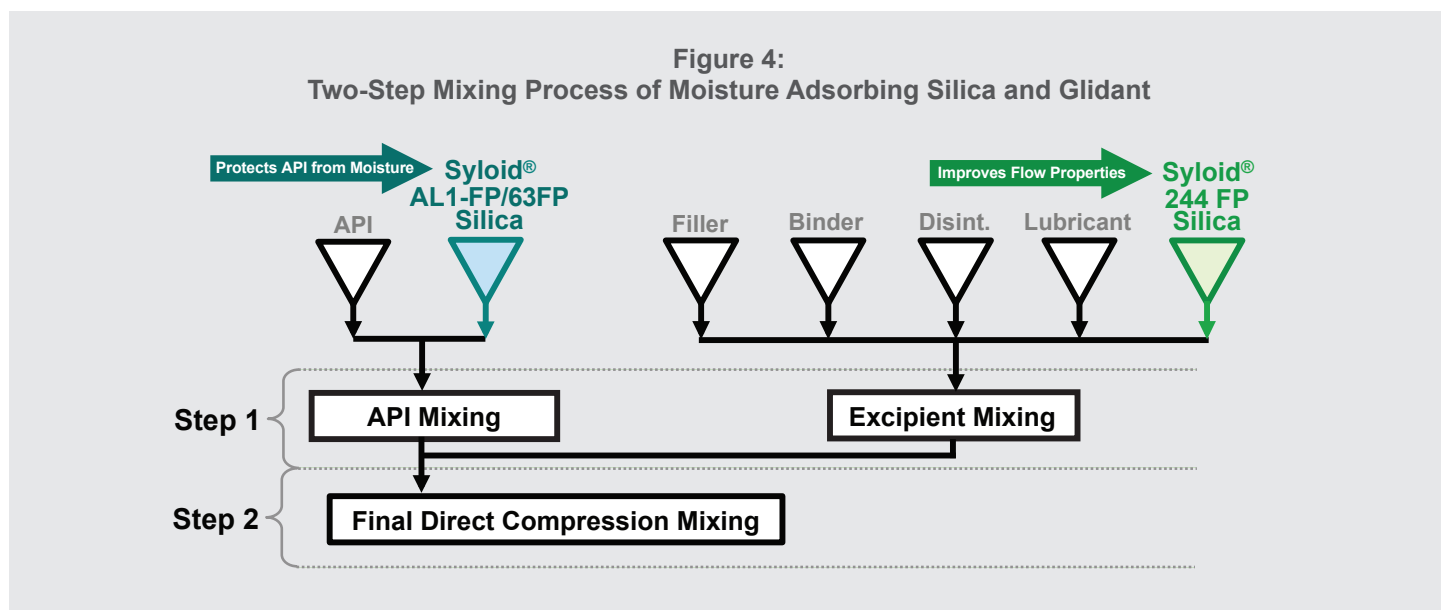
Part B: Adding Different Silica Grades in a Two-Step Mixing Process to Protect Moisture Sensitive APIs, Improve Uniformity and Stability While Maintaining Good Flow Behavior

In addition to flow improvement, porous silica gel, can also help improve the stability of moisture sensitive APIs by absorbing moisture present in the final formulation.

Porous silica gel, such as Syloid® 244 FP silica, is typically used as a glidant in formulations in small amounts (up to 2%). However, for adequate moisture protection, such low quantities are not sufficient. Another grade of porous silica, Syloid® AL-1 FP/63FP (AL-1FP for EU, 63FP for US) silica, is particularly effective for providing moisture protection and can be incorporated in larger amounts depending on the critical relative humidity as well as the nature and amount of API in the formulation.

Here, we demonstrate that incorporating the two different grades of porous silicas (Syloid® AL-1/63FP silica and Syloid® 244 FP silica) through two-step mixing can provide the combined benefits of moisture protection and flow improvement to the formulation. We also demonstrate that greater quantities of porous silica (5-20%) required to provide moisture protection can be used, while maintaining compressibility of the formulation mixture.

Syloid® 244 FP silica is used here in the excipient part of the formulation, to lend its glidant property to the mixture. Syloid® AL-1/63FP silica, which is specifically for moisture control of sensitive molecules, is mixed with the API to absorb moisture and provide stability to the formulation mix.



Ascorbic acid was used as a model drug in a direct compression formulation to demonstrate the effects of different amounts of silica on flow and tablet parameters. We evaluated the effect of different amounts of Syloid® AL-1/63FP silica on the flow behavior and the compressibility of the final formulation, with both 10% and 40% drug loading.

Syloid® 244 FP silica is used at 1% in all the formulations to provide optimum glidant benefits. The amount of Syloid® AL-1/63FP silica was varied from 5% up to 20% of the formulation.

Table 1. Formulations containing different amounts of Syloid® AL-1FP/63FP silica

Formulation (%)	A		B		C		D		E	
Syloid® AL-1/63FP Silica	0		5		10		15		20	
Ascorbic Acid	10	40	10	40	10	40	10	40	10	40
MCC PH 102	82.3	52.3	77.3	47.3	72.3	42.3	67.3	37.3	62.3	32.3
PVPK 30	2.5		2.5		2.5		2.5		2.5	
Cross Povidone	3.35		3.35		3.35		3.35		3.35	
Syloid® 244 FP Silica	1		1		1		1		1	
Stearic Acid	0.85		0.85		0.85		0.85		0.85	
Total	100		100		100		100		100	

2-Step Mixing - Tableting Results

Results and Discussion:

We first tested the flow parameters of the final formulation with and without Syloid® AL-1/63FP silica at different percentages. The mixtures were then compressed into tablets by direct compression. The resulting tablets were evaluated for various parameters such as hardness, friability, weight uniformity, etc.



Chart 4. Effect of different amounts of Syloid® AL-1/63FP silica on flow property

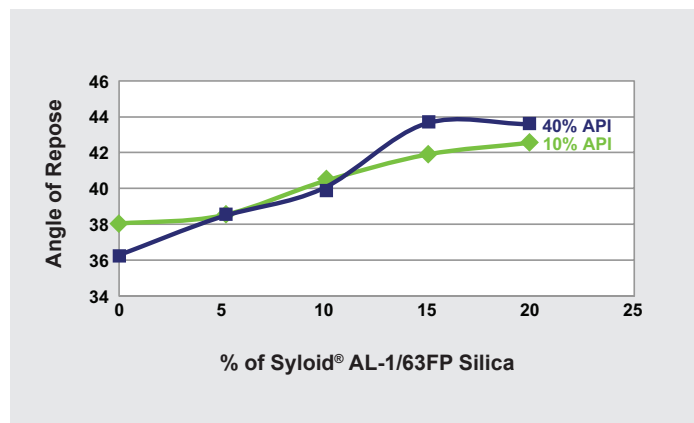


Table 2. Tablet parameters with different amounts of Syloid® AL-1/63FP silica

Formulation (%)	A		B		C		D		E	
Syloid® AL-1/63FP Silica	0		5		10		15		20	
Ascorbic Acid (%)	10	40	10	40	10	40	10	40	10	40
Weight (mg)	500	500	500	500	500	500	500	500	500	500
Weight Uniformity, RSD %	0.48	0.79	0.33	0.96	0.82	0.6	0.5	1.64	0.8	1.5
Hardness (Kg/Cm ²)	12.5	10	12	7.5	11	5.5	9	3.5	7	2
Disintegration Time (min)	24	8.1	19.5	5.3	14.05	1.54	5.34	0.47	4.3	0.25
Friability (%)	0	0	0	0	0	0	0	0.033	0	1 >
Compression Force (KN)	27-28	40-42	27-28	40-42	27-28	40-42	27-28	40-42	27-28	40-42

For formulations with lower loading of API, Syloid® AL-1/63FP silica can be added for moisture protection up to 20% of the total formulation, while still maintaining good flow of the resulting mix and good tablet properties.

We successfully demonstrate that tablets can be prepared by direct compression method using Syloid® AL-1/63FP silica from 5% to 20% at different API loading 10% and 40%.

We found that the tablet properties are very good with 10% API loading at all percentages of Syloid® AL-1/63FP silica from 5% to 20%. For 40% API loading, the tablet properties are good with up to 15% Syloid® AL-1/63FP silica.

Chart 5. Effect of different amounts of Syloid® AL-1/63FP silica on tablet hardness

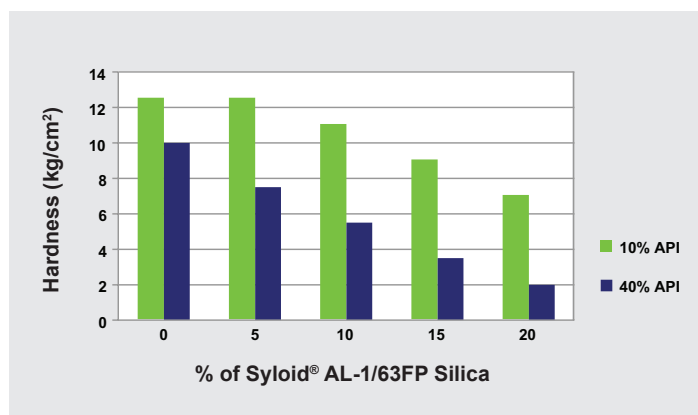
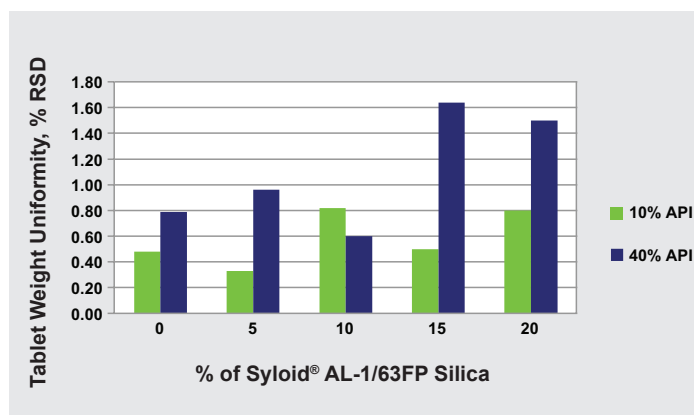


Chart 6. Weight uniformity of tablets containing different amounts of Syloid® AL-1/63FP silica



*Tablet weight variation is measured as a function of RSD% of the tablet weights. Lower weight variation and better uniformity results in lower RSD%.

Conclusions:

Syloid® FP silicas can provide the dual benefits of flow improvement and moisture protection when incorporated into formulations in a two-step mixing process. The tablet parameters such as hardness, friability, and weight uniformity were found to depend on both percentage of API and percentage of Syloid® AL-1/63FP silica in the tablets.

By optimizing these ratios for different drugs, sufficient amounts of porous silicas can be incorporated for direct compression to provide optimal moisture protection to the formulation.

We are currently investigating the effects of large amounts of silica on other parameters like disintegration times and dissolution rates.

Abbreviations:

A.R. - Angle of Repose

CI - Carr's Index or Compressibility Index

HR - Hausner's Ratio

SD - Standard Deviation

RSD - Relative Standard Deviation

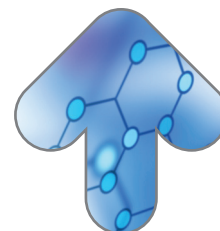
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