

# Adding SYLOID® Mesoporous Silica to Improve Run Time and Yield for Micronization Processes

Microsize has been a pioneer in enhancing dissolution and bioavailability of Active Pharmaceutical Ingredients (APIs) via particle size reduction using micronization technologies. Grace manufactures APIs and pharmaceutical excipients, including its SYLOID® mesoporous silica product line. Powder flow and other physical properties of these materials significantly impact their processability.

Feed rate is one of the two main operating parameters in a jet milling process and consistent feed rates lead to a more homogeneous final product. Adding SYLOID® mesoporous silica at low percentages to a micronization process improves feed rate consistency. Mill retention can also lead to low yields and long run times. The addition of silica can reduce mill retention, increase yields, and improve process efficiencies.

## Key Takeaways

- Low percentage additions of SYLOID® mesoporous silica can improve the run time and yield when jet milling APIs that are difficult to process
- Pre-blending SYLOID® mesoporous silica with a poor flowing API leads to a blend with good flow properties and a more consistent inlet feed rate

## Introduction

Micronization is important early in the pharmaceutical manufacturing process and it improves the dissolution rate of DCS Class IIa APIs and, ultimately, the bioavailability of small molecule OSD products. Micronized API is often blended downstream with pharmaceutical excipients to produce these solid oral dosage forms. A low percentage additive can be incorporated into the API micronization process due to this dilution of the active ingredient in the final formulation.

Feed rate and manifold pressure are the most important jet milling process parameters with the greatest impact on the final particle size. A consistent feed rate ensures that

the milling chamber is not starved or overfed, which can impact the final particle size results. Adding an excipient with good flow properties, such as SYLOID® mesoporous silica, can lead to a more consistent feed rate.

Material flow through the mill is another important aspect of micronization. Materials with strong cohesive and adhesive properties may build up inside the mill and block several areas such as the outlet or the nozzles in the ring. Materials will not micronize if the buildup blocks the gas flowing through the nozzles. Severe blockages reduce yield and throughput by causing operators to shutdown the process and clean the mill.

These experiments aimed to evaluate whether the addition of SYLOID® mesoporous silica would prevent buildup inside a jet mill, thereby improving both run time and yield. The active ingredient selected for these micronization trials was Cholesterol, a waxy solid that

is difficult to process, akin to the physical properties of many of the more complex small molecules currently under development. SYLOID® 63 FP and SYLOID® XDP 3050 mesoporous silica grades were selected for this study at concentration levels 1%, 2%, and 8%.

## Equipment and Parameters

Micronization Equipment and Parameters	
Mill	Non-GMP 4" Spiral Jet Mill
Feeding Method	Dual screw Microfeeder
Pressure	Injector: 120 PSI, Manifold: 120 PSI
Feed Rate	300 g/hr
Blending	Turbula Mixer for 10 minutes prior to milling

**Table 1.** Run Time Experiment

Micronization Equipment and Parameters	
Mill	Non-GMP 2" Loop-style Jet Mill
Feeding Method	Bulk Solids Feeder
Pressure	Injector: 120 PSI, Manifold: 120 PSI
Feed Rate	Varied, Feeder Setting kept constant
Blending	Turbula Mixer for 10 minutes prior to milling

**Table 2.** Yield Experiment

## Results

### Run Time

The first experiment focused on increasing Cholesterol's run time in a 4" spiral jet mill. When Cholesterol is micronized at maximum pressure (120 PSI), the process reaches failure mode in 2 minutes, which involves blowback and full obstruction of the mill. Different grades of SYLOID® mesoporous silica at different concentrations were added and tested at two milling pressures. Cholesterol was preblended with SYLOID® mesoporous silica in a suitably sized plastic jar using a Turbula Mixer for 10 minutes prior to micronization. Results are shown in Table 3.



**Figure 1.** 4" Spiral Jet Mill with Dual Screw Microfeeder

Trial	Material	SYLOID Grade	Manifold Pressure (PSI)	Run Time (min)	Increase in Run Time
1	100% Cholesterol	N/A	120	2	N/A
2	98% Cholesterol 2% SYLOID® mesoporous silica Blend	63FP	120	33	16.5x
3	98% Cholesterol 2% SYLOID® mesoporous silica Blend	63FP	60	46	23x
4	92% Cholesterol 8% SYLOID® mesoporous silica Blend	XDP	60	26	13x

**Table 3.** Run Time Results

All trials were run until failure mode was reached. Run time was significantly increased for all trials with SYLOID® mesoporous silica added. For Trial 2, all operating conditions were kept the same as Trial 1 and 2% SYLOID® 63 FP mesoporous silica was added. For Trial 3, the manifold pressure was halved to see if the run time could be increased further. The run time did increase but decreasing the manifold pressure can increase the resulting particle size. For Trial 4, the level of SYLOID® mesoporous silica was increased to 8% and the SYLOID® XDP 3050 grade was used. The run time was significantly longer than Trial 1 however it was shorter than both Trial 2 and Trial 3. This result suggests that for a given API there may be an ideal SYLOID® mesoporous silica grade and optimal level of additive.

The addition of SYLOID® mesoporous silica improved run time for Cholesterol and this result is even more encouraging for scaleup to larger spiral jet mills with a greater volume in the grinding chambers. Extended run times translate to more efficient manufacturing times and less cleaning events with minimized material loss.

## Yield

The second experiment was focused on improving the yield for the Cholesterol micronization process by increasing the level of SYLOID® mesoporous silica additive. A 2" loop jet mill was used to prevent the failure mode seen in the first experiment because the volume of the grinding chamber is much larger. Results are shown in Table 4.

The feeder setting was kept constant for all trials and the resulting feed rate increased at an almost linear rate with respect to the percentage of SYLOID® XDP 3050



**Figure 2.** 2" Loop Jet Mill

mesoporous silica in the blend. This increase in feed rate can be attributed to the improved flow properties of each blend as compared to Trial 1. With improved flow properties, a more consistent feed rate and mass flow can be achieved and ultimately a more homogenous final product can be generated.

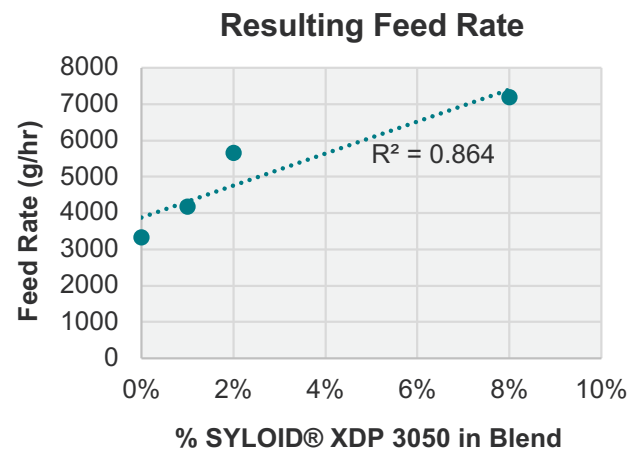
For Trial 1, a jet milling process with a yield below 60% presents a high level of loss to a customer and suggests that there is excessive buildup in the mill. The yield significantly improved by over 20% at the 1% and 2% levels of SYLOID® XDP 3050 mesoporous silica in the Cholesterol blend. Increasing the level of SYLOID® XDP 3050 mesoporous silica to 8% improved the yield again, however it was a minor gain which implies that there may be a practical limit for adding SYLOID® mesoporous silica for yield improvement. For a material that is difficult to process, yield greater than 75% represents a substantial process improvement.

Trial	Material	Manifold Pressure (PSI)	Feeder Setting	Resulting Feed Rate (g/hr)	Yield (%)
1	100% Cholesterol	120	850	3327	58.5%
2	99% Cholesterol 1% SYLOID® XDP 3050 mesoporous silica Blend	120	850	4179	78.9%
3	98% Cholesterol 2% SYLOID® XDP 3050 mesoporous silica Blend	120	850	5664	78.7%
4	92% Cholesterol 8% SYLOID® XDP 3050 mesoporous silica Blend	120	850	7197	84.5%

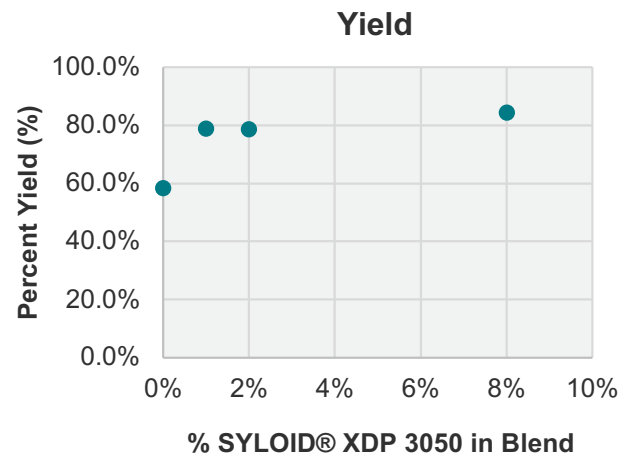
**Table 4.** Yield and Feed Rate Results

## Conclusion

The run time and yield for a difficult to micronize API were both significantly improved with low level percentage additions of SYLOID® mesoporous silica. These benefits can be attributed to the improvement in the powder flow properties of the material that is fed into jet mill. If an API can have its particle size reduced but has other processing issues, this approach of pre-blending in low levels of SYLOID® mesoporous silica should be pursued. Establishing a consistent micronization process with this technique provides substantial value to both CDMOs and their clients.



**Figure 3.** Feed Rate vs % SYLOID® XDP 3050 mesoporous silica



**Figure 4.** Yield vs % SYLOID® XDP 3050 mesoporous silica