FUMED METAL OXIDES

CAB-O-SIL® FUMED SILICAS

FOR PHARMACEUTICAL AND NUTRACEUTICAL APPLICATIONS

CABOT®

Cabot Corporation: A proud history of innovation and quality

Cabot Corporation has been a global manufacturer of specialty chemicals and performance products since 1882. We continue to innovate and find applications for our materials in new fields, where they help improve existing products and create exciting new offerings. We are committed to the reliable delivery of pharmaceutical materials of the highest quality and consistency. Our global reach enables us to work closely with our ever-growing list of customers in order to become their supplier of choice for quality materials, performance and service.

Current challenges in pharmaceutical and nutraceutical tablet production

Producing tablets and capsules of uniform quality in an efficient manner can be challenging. The biggest issues tend to occur during the following stages of the production process:

Flow through hopper

- Powders may stick to metallic walls due to static charges that affect flow patterns
- Agglomerates may form in the hopper and this may result in uneven flow as well as bridging

Die or capsule filling

The manufacture of tablets and capsules on high speed machinery requires the powder to exhibit optimal flow. If optimal flow is not achieved, the following issues can arise:

- Segregation of active or inactive ingredients due to powder cohesiveness
- Non-uniformity in tablet content
- Tablet weight variation

Tablet compaction

Variable tablet hardness caused by poor powder compaction can lead to capping, lamination, chipping, and tablet breakage

CAB-O-SIL® product description

- CAB-O-SIL M-5P (pharmaceutical grade) fumed silica is an excipient of extremely high purity used as a multi-functional additive in the pharmaceutical and nutraceutical industries.
- CAB-O-SIL M-5DP fumed silica is a higher bulk density fumed silica offering lower freight and storage costs, easier handling while retaining all the performance advantages of CAB-O-SIL M-5P.

CAB-O-SIL fumed silica acts in the following ways to address significant issues involved in tablet production:

Improved tableting operations

Flow aid

- CAB-O-SIL fumed silica's **glidant** and **anti-static properties** help improve the flow properties of powders and **reduce friction and static charges** in high speed tablet and capsule machines.
- Additionally, CAB-O-SIL fumed silica helps prevent **bridging**.

Greater uniformity in tablet weight

Die or capsule or filling aid

- Uniformity in **tablet weight and active ingredient content** result from formulations that flow evenly into the die cavity during the tableting operation.

Greater tablet hardness and density

Flow through hopper

- CAB-O-SIL fumed silica can aid in particle rearrangement within the die during the early stages of compression and can increase bonding strength between powder particles that form a solid tablet, helping to more effectively compact tablets/capsules.
- **Increased tablet hardness at lower compression forces** results from formulations that are effectively compacted.

Physical-chemical properties

CAB-O-SIL fumed silica is compatible with many pharmaceutical ingredients. It adheres readily to hydrophilic ingredients, functioning as an excellent glidant.

Pharmaceutical product	Surface area	Bulk density	Features
CAB-O-SIL M-5P fumed silica	200 m^2/g	‹60 g/l	Easy to disperse
CAB-O-SIL M-5DP fumed silica	200 m^2/g	80 to 130 g/l	Higher bulk density

The data above are typical test values intended as guidance only, and are not product specifications. Product specifications are available from your Cabot representative.

Purity – CAB-O-SIL fumed silica versus precipitated silica

CAB-O-SIL fumed silica is produced through a pyrogenic process that results in one of the purest commercially available forms of synthetic amorphous silica (99.8% pure). In contrast, the production of precipitated silica requires the addition of a mineral acid to an alkaline silicate solution, resulting in a lower purity product that contains higher moisture, sulfates and chloride impurities. These impurities can impact the product in significant ways, including:

- High sulfates and chloride content can affect the stability of some active ingredients. Fumed silica has a much lower level of ionic chlorides than precipitated silica and very low to no ionic sulfate species as there are no sulfur containing species in the pyrogenic process.
- High levels of moisture can affect moisture-sensitive compounds. Fumed silica has a lower level of moisture than precipitated silica.

Regulatory compliance

CAB-O-SIL® fumed silica is produced in a manner consistent with Good Manufacturing Practices appropriate for pharmaceutical excipients.

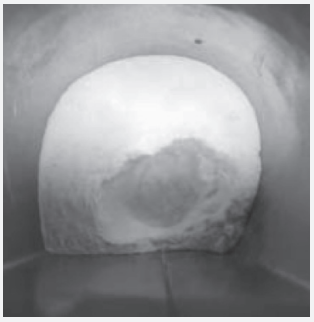
Pharmacopeia status				
	Meets all requirements for **Colloidal Silicon Dioxide**	Meets all requirements for **Silica Colloidal, Anhydrous**	Meets all requirements for **Light Anhydrous Silicic Acid**	Meets all requirements for **Colloidal Silicon Dioxide**
Pharmacopeia	US Pharmacopeia/ National Formulary	European Pharmacopeia	Japanese Pharmacopeia	Chinese Pharmacopeia
CAB-O-SIL M-5P fumed silica	Yes	Yes	Yes	Yes
CAB-O-SIL M-5DP fumed silica	Yes	Yes	–	–

Please contact your Cabot technical representative for current pharmacopoeia editions cited in this document.

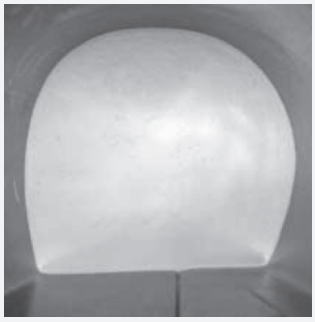
Performance

CAB-O-SIL fumed silica as flow aid

The formation of a powder bridge in a hopper of a tablet press can lead to a phenomenon known in powder flow as "bridging." The image to the right illustrates this phenomenon:



Powder bridging in hopper



Even powder flow in hopper

How is flow measured?

The angle of repose provides a useful correlation to the flow properties of powders. The relationship between the angle of repose and powder flow is shown in Table 1 on the right.

Table 1: Correlation of powder flow to the angle of repose

Angle of repose (degrees)	Flow
25 - 30	Very free flowing
30 - 38	Free flowing
38 - 45	Fair / passable flow
45 - 55	Cohesive
>55	Very cohesive

Source: Bodhmage, A. (2006). Correlation between physical properties and flowability indicators for fine powders (Unpublished doctoral dissertation). University of Saskatchewan, Saskatoon, Saskatchewan.

Figure 1 illustrates the flow properties of APAP (acetaminophen or N-acetyl-p-aminophenol), ibuprofen (isobutylphenylpropanoic acid) and aspirin (acetylsalicylic acid) tablets when tested with various concentrations of CAB-O-SIL® fumed silica. The results indicate that as the concentration of CAB-O-SIL M-5P fumed silica increases, the flowability of the powder mix improves, going from 'cohesive' to 'passable flow' to 'free flowing'.

Figure 1: Effect of CAB-O-SIL M-5P fumed silica on APAP, ibuprofen and aspirin flowability at various concentration levels

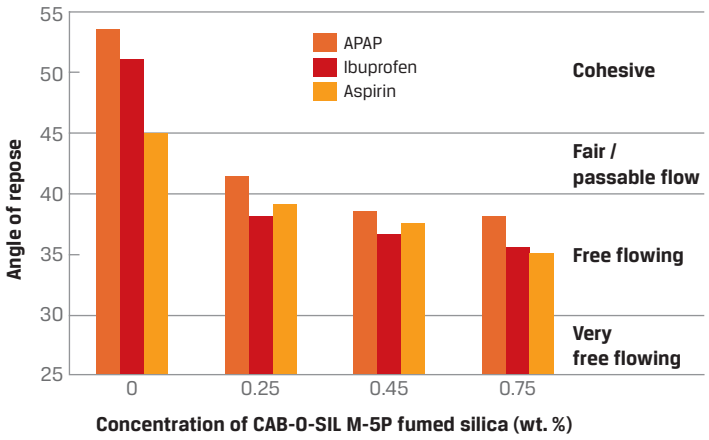


Figure 2 illustrates how the level of CAB-O-SIL M-5P fumed silica in an APAP mixture influences the flowability of the mixture. The results indicate that CAB-O-SIL M-5P fumed silica improved flow properties of the APAP mixture, taking it from a cohesive powder to fair/passable flow.

Figure 2: Effect of CAB-O-SIL M-5P fumed silica on APAP mixture flowability

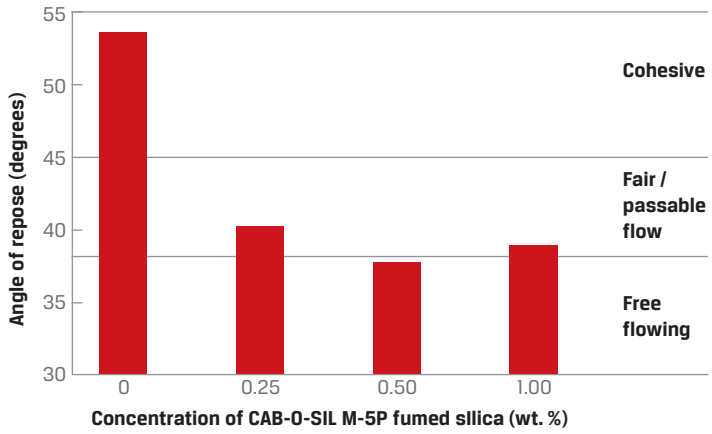
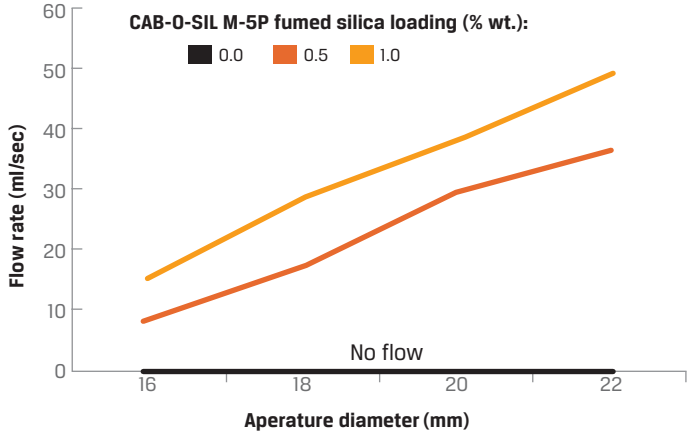


Figure 3 shows the different flow rates of Avicel® PH-101 Micro Crystalline Cellulose (FMC Corporation) when combined with different loading levels of CAB-O-SIL M-5P fumed silica. Note that without the addition of fumed silica, the powder does not flow.

The data in **Figure 3** was measured using the Hanson's FLODEX™ apparatus, which measures flow rates as a function of aperture diameter. The "bridging" point may be determined with this apparatus by determining the aperture diameter at which no flow of material will occur into the lower graduated cylinder.

Figure 3: Effect of CAB-O-SIL M-5P fumed silica on Avicel™ PH-101 micro crystalline cellulose flow rate



Highly hygroscopic materials or materials with static charge problems

For highly hygroscopic materials or materials that exhibit poor flow due to static charge, the amount of added CAB-O-SIL M-5P fumed silica may need to be 3-4 times more than that required for materials that are less prone to static.

CAB-O-SIL® fumed silica as a die filling aid

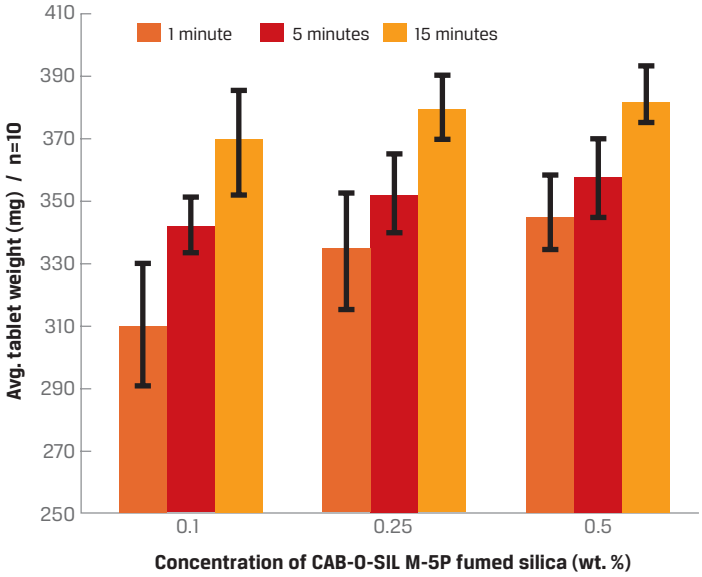
Uniform tablet weights and uniform doses of active ingredients are dependent on the ability of the powder mix to feed into the dies in a reproducible manner. Fumed silica can be added to the formulation in order to improve the flow properties of the material and to aid particle rearrangement within the die during the early stages of die filling and compression.

Tablet weight and mixing time

Formulations that flow evenly into the die cavity during the tableting operation will result in uniform tablet weight and drug content.

Figure 4 demonstrates that the weight of APAP tablets can be influenced by the concentration of CAB-O-SIL M-5P fumed silica in the formulation, as well as the time of mixing.

Figure 4: Effect of CAB-O-SIL M-5P fumed silica on tablet weight at various concentrations and mixing times



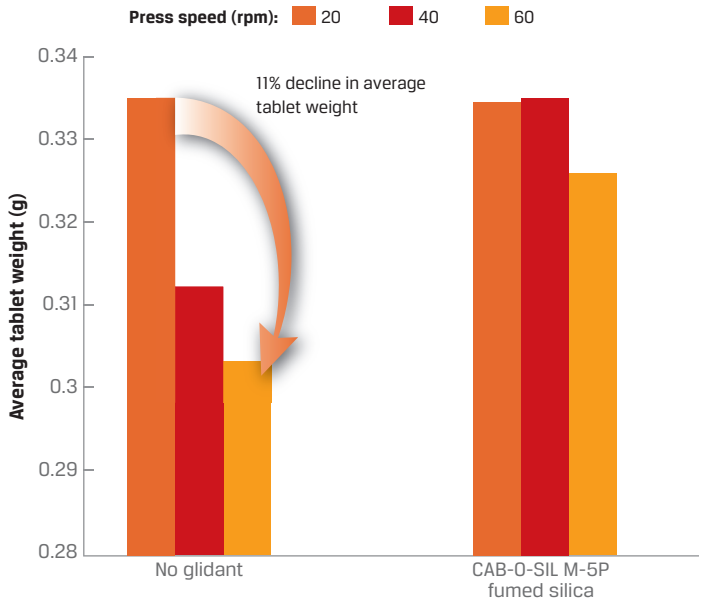
Note: The formulation includes: 10% APAP and balanced lactose. Bars correspond to minimum and maximum tablet weight.

Tablet weight and production speeds

The addition of CAB-O-SIL M-5P fumed silica allows tablet manufacturers to produce high quality tablets at higher tablet press speeds than they otherwise could, therefore improving productivity.

Figure 5 illustrates that at high production speeds, the tablet weight of formulations that do not include fumed silica decreases by 11%, showcasing issues with the powder's flow and die filling. In contrast, tablets that include 0.25% CAB-O-SIL fumed silica preserve a more consistent weight under higher press speeds.

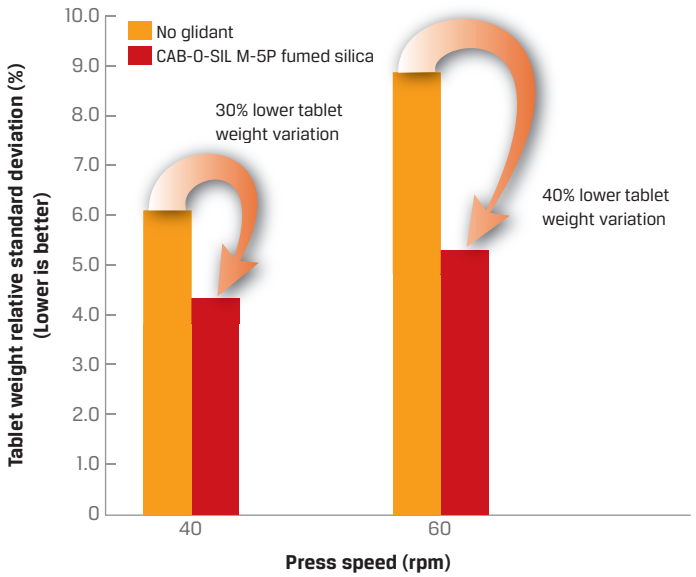
Figure 5: Effect of CAB-O-SIL M-5P fumed silica and press speed on tablet weight



Note: Ibuprofen tablets with 0.25% CAB-O-SIL fumed silica.

Figure 6 illustrates that at high production speeds, the addition of 0.25% CAB-O-SIL® M-5P fumed silica reduced tablet weight variation anywhere from 30% to 40% when compared to the same powder mix without a glidant.

Figure 6: Effect of CAB-O-SIL M-5P fumed silica on ibuprofen tablet weight variation



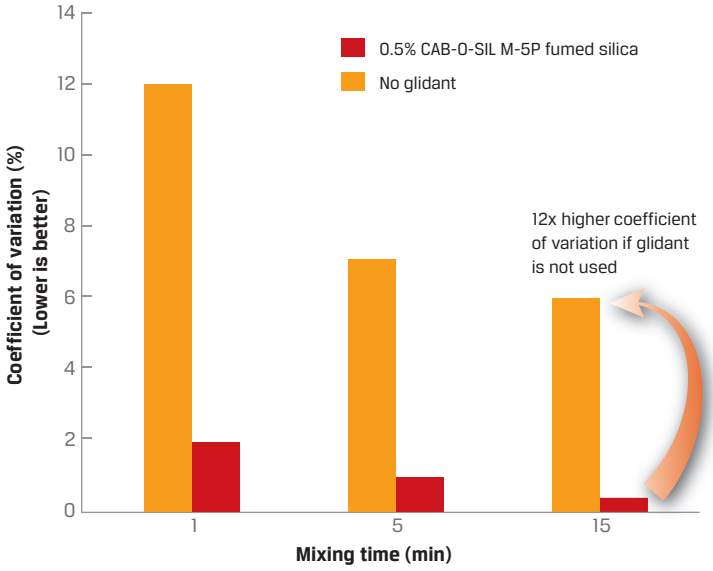
Note: Ibuprofen tablets with 0.25% CAB-O-SIL fumed silica.

API content uniformity

Addition of fumed silica reduces segregation of active and inactive ingredients, promoting content uniformity.

The data in **Figure 7** demonstrates that the presence of CAB-O-SIL M-5P fumed silica in a tablet formulation can decrease the coefficient of variation of active pharmaceutical ingredient (API) content in a batch of tablets. Very low variations in drug content were observed with APAP tablet formulations containing 0.5% CAB-O-SIL M-5P fumed silica after blending for 15 minutes. Tablets without fumed silica mixed for 15 minutes exhibited a coefficient of variation of 6%, which is 12 times higher than the variation seen in tablets that did contain CAB-O-SIL fumed silica.

Figure 7: Effect of CAB-O-SIL M-5P fumed silica on coefficient of variation of API in tablet formulations



Note: These tablets contained 10% APAP, 89.5% lactose and 0.5% CAB-O-SIL M-5P fumed silica. The tablet formulation without fumed silica contained 90% lactose and 10% APAP.

CAB-O-SIL® fumed silica as compaction aid

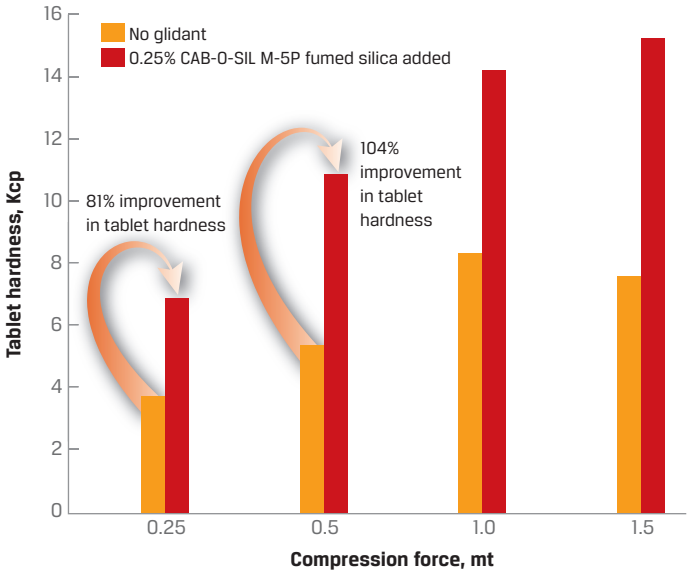
Tablet hardness

CAB-O-SIL fumed silica was added to ibuprofen tablets in order to test its influence on tablet hardness. The results of this testing under various compression force levels indicate the following conclusions and are illustrated in **Figure 8** below:

- The addition of only 0.25% of CAB-O-SIL fumed silica at 0.25mt of compression force facilitates an 81% improvement in tablet hardness compared to tablets formulated without a glidant. Adding 0.25% CAB-O-SIL fumed silica increases tablet hardness by 104% when compression forces reach 0.5mt.
- The addition of CAB-O-SIL fumed silica can double tablet hardness when compared to tablets formulated without a glidant.

Figure 8 indicates that the highest tablet hardness is obtained at 1.5 metric ton of compression. This is relevant, because as the compression forces are reduced, the wear on press and dyes is reduced as well.

Figure 8: Effect of CAB-O-SIL fumed silica on tablet hardness at various compression force levels



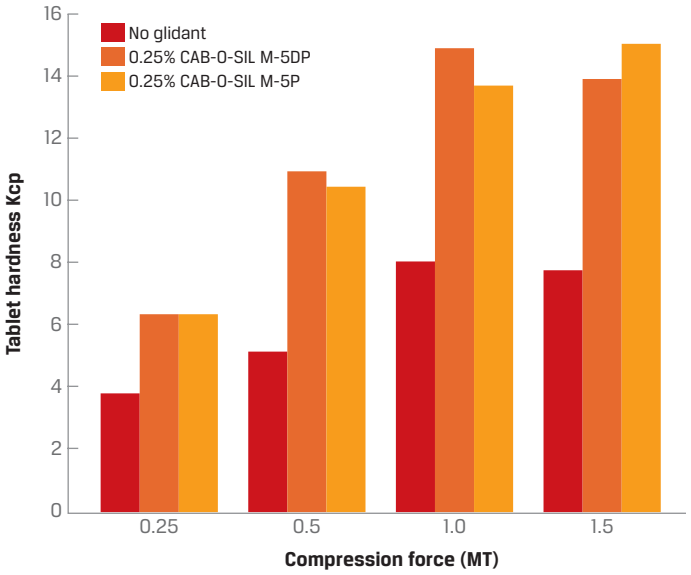
CAB-O-SIL® M-5DP or M-5P fumed silica yields:

- Greater tablet hardness and density reducing tablet chipping and breakage during handling, coating, packaging and shipping.
- Greater uniformity In both tablet weight and size — reduced tablet weight and thickness variability.
- Improved tabletting operations — high quality tablets at lower ejection force and faster press speeds.

The addition of as small an amount as 0.25% of CAB-O-SIL M-5DP or M-5P fumed silica shows a significant improvement in tablet hardness.

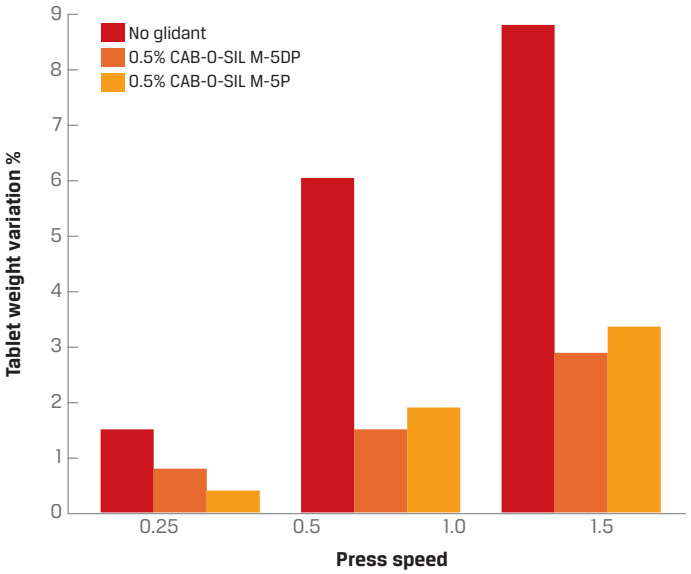
- Relative to tablets formulated without a glidant, CAB-O-SIL 5DP or M-5P fumed silica doubles the tablet hardness and increases productivity.
- Reduced compression force is an indicator of wear reduction on the presses and dyes.
- Best tablet hardness is obtained at 1 metric ton of compression.

Harder tablets at lower compression forces



- The addition of 0.5% of CAB-O-SIL M-5DP or M5P fumed silica allows table manufacturer to produce high quality tables at higher tablet press speed, hence improving productivity.
- At 60 rpm, CAB-O-SIL M-5DP fumed silica reduces table weight variation below 3%.

Reduced variation at higher press speeds



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