CABOT

Influence of CAB-O-SIL® M-5P on the Angle of Repose and Flow Rates of Pharmaceutical Powders

Introduction

The manufacture of tablets and capsules on high speed machinery requires the granulation to exhibit optimal flow in order to produce a pharmaceutial product with uniform properties. Fine particles will, in general, exhibit cohesive or nonfree-flowing properties which can result in caking or agglomeration of particles during storage. This may result in uneven flow as well as bridging of the granulation in the hopper of the machine.

CAB-O-SIL® M-5P (pharmaceutical grade) fumed silica is a white, free-flowing powder of extremely high purity that is widely used as a glidant in tablet and capsule formulations to promote the flow of granulations. The basic physical and chemical properties of CAB-O-SIL M5P fumed silica are discussed in the scientific reports, *Properties of CAB-O-SIL® M-5P Fumed Silica* and *Applications of CAB-O-SIL® M-5P Fumed Silica in the Formulation and Design of Solid Dosage Forms.*[1,2] The influence of CAB-O-SIL M-5P fumed silica on the angle of repose and flow rates of pharmaceutical powders will be presented in this scientific report.

Background

Glidants are intended to promote flow of granulations or powder materials by reducing the friction between the particles. CAB-O-SIL M-5P is a very effective glidant that can also function as an anti-adherent. Calcium and magnesium stearate are widely used lubricants in tablet technology. Stearic acid is less effective than the salts and it also has a lower melting point. Although magnesium stearate has been used as a glidant, it will, however, interfere with effective bond formation between the granules during the compaction process and may significantly influence the tensile strength and the disintegration properties of the tablet compact. The influence of magnesium stearate on reducing the tensile strength of tablet compacts has been previously reported.[3,4] The time of the blending process will also exacerbate the deleterious effect that magnesium stearate will exert on the binding functions of other excipients. This lubricant can also decrease the *in vitro* dissolution rates of drug initially or after aging.[4] CAB-O-SIL M-5P has been shown to increase the tensile strength of tablet compacts and it will contribute to strong bond formation between granules in the compact.[2]

Pharmaceutical processing of solid dosage forms can present two significant problems to the pharmaceutical scientist: 1) segregation of active or inactive ingredients leading to content uniformity problems and 2) large powder agglomerates in the granulation may not be broken down during the mixing cycle (since cohesion of particles will impair the mixing process). Agglomerates may alternatively form in the hopper during the tabletting process. Some of these problems may be eliminated with the addition of a micronized glidant that possesses intrinsic cohesive properties such as CAB-O-SIL M-5P. Glidants as well as micronized drugs and lubricants have been shown to adhere to large particles of a second constituent in the formulation, a process often referred to as “ordered mixing.”[5,6] CAB-O-SIL M-5P is also used in capsule and tablet granulations where static charge has presented flow problems. Charge transfer between two solids by contact electrification will depend on the nature of the solids in the granulation as well as the surface properties and environmental conditions during contact. Since sliding/frictional forces are generally involved, the term “triboelectrification” has been employed. Although the literature contains conflicting reports on the effects of moisture on triboelectrification of powders, most researchers have reported that the particle charge will be reduced as the relative humidity is

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increased, due possibly to the adsorbed moisture by the powder.[7,8]

Adhesion of powders to metal surfaces is another problem that will compromise product quality. For low melting point solids and for effervescent granulations, adhesion to the tips of the punches is of great concern and this will result in tablets with a rough surface. These problems are magnified as the level of moisture in the atmosphere is increased.[9] Low moisture levels in a fluidized bed coating unit may also induce a static charge to powders and pellets, causing these materials to adhere to the plastic or stainless steel walls of the coating chamber.

The objectives of the study in this report were to further investigate the properties of CAB-O-SIL® M-5P as a pharmaceutical glidant by studying the angles of repose and flow rates of pharmaceutical excipients and drug substances. The rate with which a powder will exit a tube or cylinder through an orifice is denoted by the flow rate of the powder, given the geometry of the flow constraint.[9] Some preliminary results concerning the angles of repose of powders containing CAB-O-SIL M-5P have previously been reported.[2]

In the current report, the relationship between the angle of repose and flow rates (Table 1) was explored in more detail. The method to determine the angle of repose was the same technique as used previously.[2] The flow rates of the powders were determined using a Hanson's FLODEX™ apparatus, and a schematic for this apparatus is shown in Figure 1. The material was added through a loading funnel into a cylinder that contains two disks. The upper disk has a circular aperture of known diameter. The lower disk was removed and the time taken for the powder to flow through the cylinder into the receiving funnel was accurately determined and reported as ml/sec. Volume flow was preferred as a comparison over mass flow determinations since the filling of a die cavity in a tablet press in based on volume, rather than mass. The "bridging" point may be determined with this apparatus by determining the aperature size at which no flow of material will occur into the lower graduated cylinder.

Table 1

Relationship between angle of repose θ and powder flow

Angle of Repose (theta) (degrees)	Flow
< 25	Excellent
25–30	Good
30–40	Passable
> 40	Very poor

Results and Discussion

The influence of CAB-O-SIL M-5P on the angle of repose of acetaminophen and hydroxyethylcellulose as well as several grades of lactose and microcrystalline cellulose, is shown in Figure 2. The poor flow properties of lactose 310 in the absence of CAB-O-SIL M-5P is seen in Figure 2a. The presence of 0.5% CAB-O-SIL M-5P resulted in a significant decrease in the angle of repose for lactose 310. The three grades of lactose demonstrated similar angles of repose at the 0.5% and 1% levels of CAB-O-SIL M-5P. The angle of repose of microcrystalline cellulose is inversely related to the average particle size (Figure 2b). Avicel® PH-200 with a mean particle size of 180 µ has a low angle of repose while Avicel® PH-105 (mean particle size = 20 µ) has a high angle of repose. This is due to the greater cohesive nature of the smaller particles. However, with the addition of 0.5% M-5P, the angle of repose for the smaller particle microcrystalline cellulose materials drops significantly (from greater than 50° to less than 40°) and will thus improve the flow rate. A similar reduction in the angle of repose was observed for the hydroxyethyl cellulose (Natrosol®) and acetaminophen in the presence of 0.5% CAB-O-SIL M-5P (Figure 2c).

The influence of CAB-O-SIL M-5P fumed silica on the flow rates of microcrystalline cellulose (PH-101, PH-105) and hydroxyethyl cellulose (Natrosol®) is seen in Figure 3. The flow rates are a function of the orifice diameter in the circular disk of the Hanson's FLODEX™ apparatus used for these studies. For Avicel® PH-101, with a mean particle size of 50 µ, bridging was evident when an aperture diameter of 22 mm was

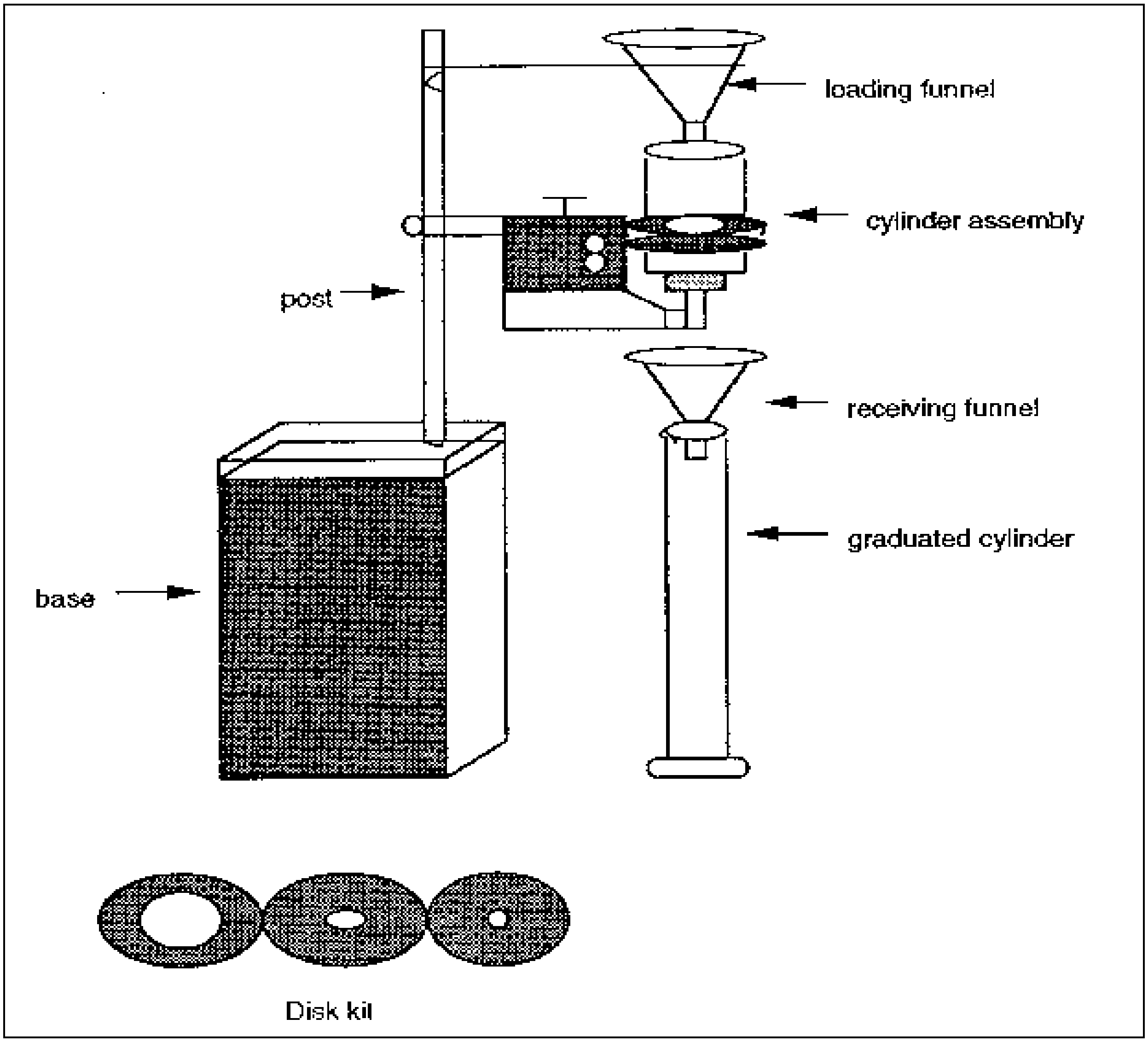


Figure 1

Hanson’s FLODEX™ apparatus for determination of flow rates of powder blends

used. Flow will not occur when the cohesive forces in the powder located over the oriface in the disk will offset and be greater than the gravitational forces.[10] The inclusion of CAB-O-SIL® M-5P will decrease these cohesive forces and promote flow as seen in the figure. The bridging point for this excipient in the presence of the CAB-O-SIL M-5P occurred with disks containing apertures less than 16 mm. The influence of the glidant on the bridging point for Avicel® PH-105 is clearly evident in Figure 3b. Doelker and co-workers investigated the flow and tableting properties of six Avicel® products including Avicel® PH-105, PH-101, and 200.[11] The flow properties were investigated using a vibratory hopper technique. Although no CAB-O-SIL M-5P was included in these studies, similar findings on these three grades of microcrystalline cellulose were found. The flow properties improved as the particle size of the microcrystalline cellulose increased.[11]

Excellent flow rates for Natrosol® were seen in powder blends containing 0.5% and 1% CAB-O-SIL M-5P. No flow through the apparatus was evident in the absence of the glidant and bridging was still evident with the disk having an aperture diameter of 24 mm. The hydrophilic cellulosic polymers including HPMC, HPC and

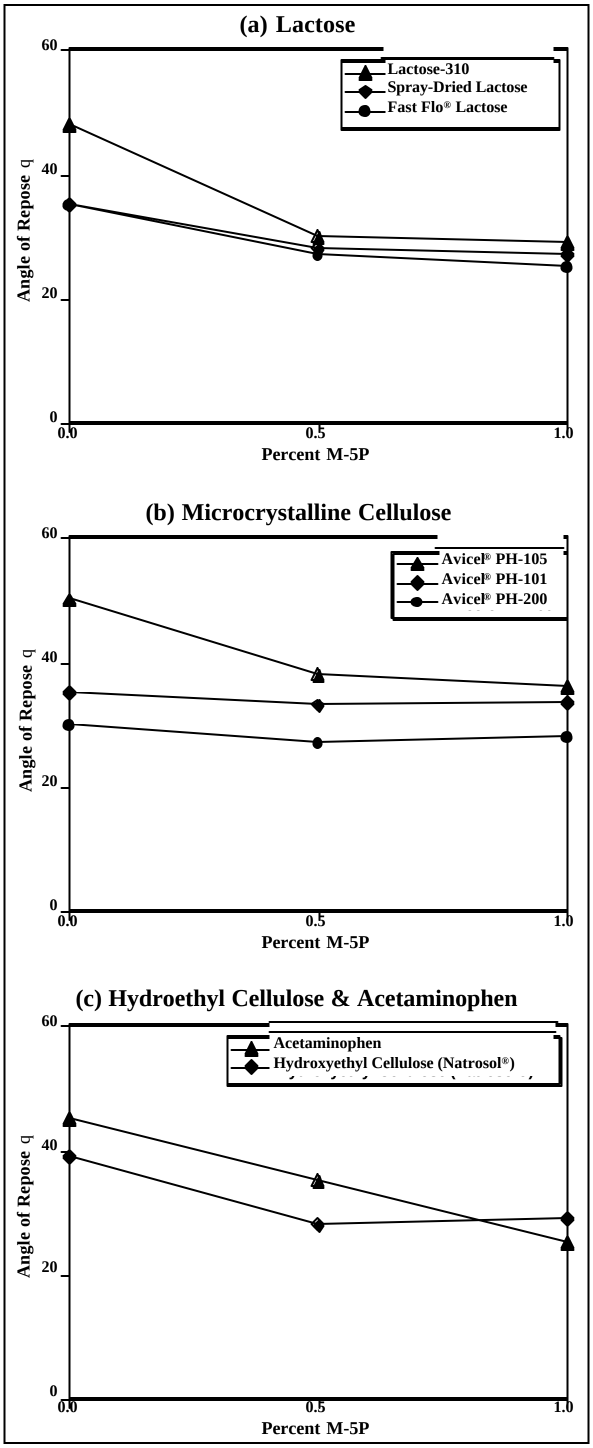


Figure 2

Influence of CAB-O-SIL® M-5P fumed silica on the angle of repose of: (a) lactose, (b) microcrystalline cellulose and (c) hydroxyethyl cellulose and acetaminophen

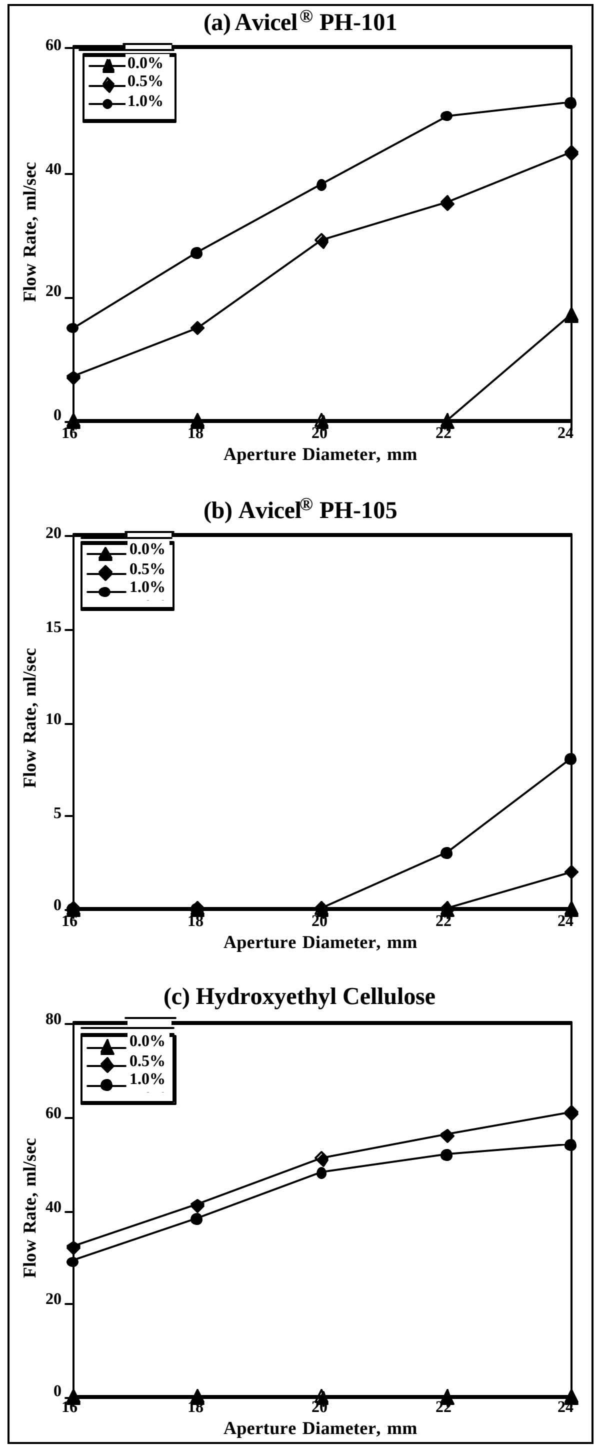


Figure 3

Influence of CAB-O-SIL M-5P fumed silica on the flow rate of microcrystalline cellulose and hydroxyethyl cellulose using the FLODEX™ apparatus

HEC have been used in matrix tablets as retardant polymers. Since the high molecular weight grades of these polymers tend to form viscous dispersions, the cellulosic derivatives are often dry blended with the granulation prior to compaction. Polysaccharides such as the alginates and xanthan gums may be added in a similar manner. These materials tend to have poor flow properties and preblending with 0.5% CAB-O-SIL® M-5P will significantly improve their flow properties and promote a uniform distribution of the retardant throughout the matrix tablet. The flow rates of lactose 310 and spray dried lactose are seen in Figures 4a and 4b, respectively. For both materials, the flow rates of the powder blends containing the CAB-O-SIL M-5P fumed silica were higher than lactose alone. Poor flow was seen with the lactose 310 in the absence of CAB-O-SIL M-5P and these data were in agreement with the angle of repose results reported in Figure 2a.

The influence of CAB-O-SIL M-5P on the flow properties of powder blends containing two different particle size fractions of theophylline with Avicel® PH-101, is shown in Figure 5. Although the angle of repose results were very similar, the flow studies in the FLODEX™ apparatus using an aperture diameter of 22 mm showed that the CAB-O-SIL M-5P increased the flow rate of material through the apparatus. Powder blends containing the larger particles of theophylline from the #100 mesh screen had faster flow rates than the blend containing drug that had been passed through a #200 mesh screen. Powder blends containing the larger mesh fraction of theophylline had the fastest flow rates. Bridging occurred in samples containing CAB-O-SIL M-5P levels of 0.1% or below. There was a gradual increase in flow rates in samples containing 0.2% to 0.5% glidant. These results are reported in Table 2.

Flow rate studies and angle of repose measurements have been demonstrated to be very useful in optimizing the flow properties of materials that have poor flow. It should be pointed out, however, that not all materials used in capsule and tablet formulations exhibit flow problems.

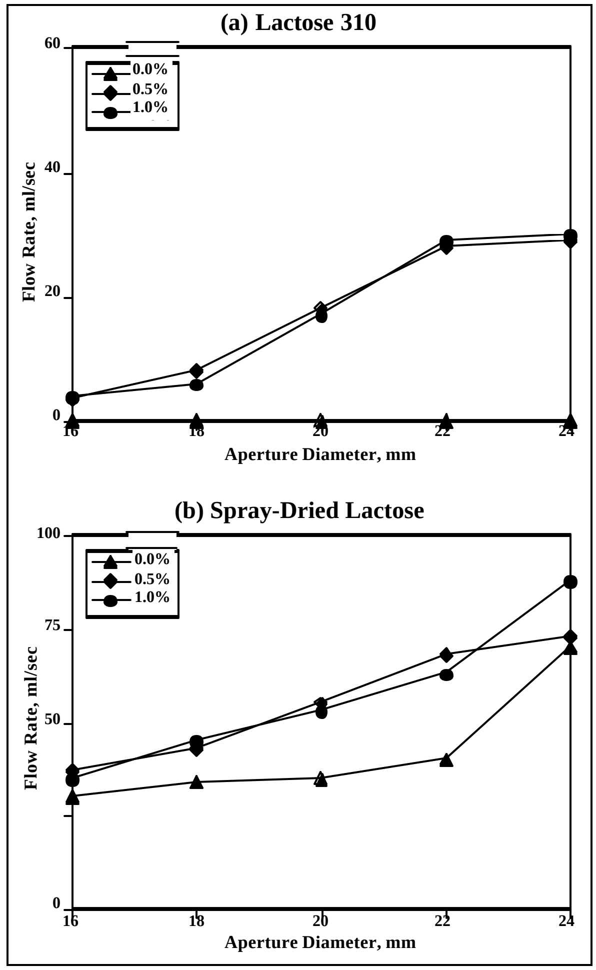


Figure 4

Influence of CAB-O-SIL M-5P fumed silica on the flow rate of lactose: (a) lactose 310 and (b) spray-dried lactose using the FLODEX™ apparatus

Table 2

Influence of the concentration of CAB-O-SIL M-5P fumed silica on the angle of repose and the flow rate of a mixture of theophylline (100 or 200 mesh) with Avicel® PH-101 (1:1) at an aperture diameter of 22 mmm (mixing time = 15 min)

	100 mesh		**200 mesh**	
M-5P % w/w	**repose angle** q	**flow rate ml/sec**	**repose angle** q	**flow rate ml/sec**
0.1	34.85	0.000	32.04	0.000
0.2	30.85	63.31	29.38	51.92
0.3	29.07	71.90	29.07	51.28
0.4	27.07	73.46	29.07	65.33
0.5	27.07	84.55	29.07	74.24

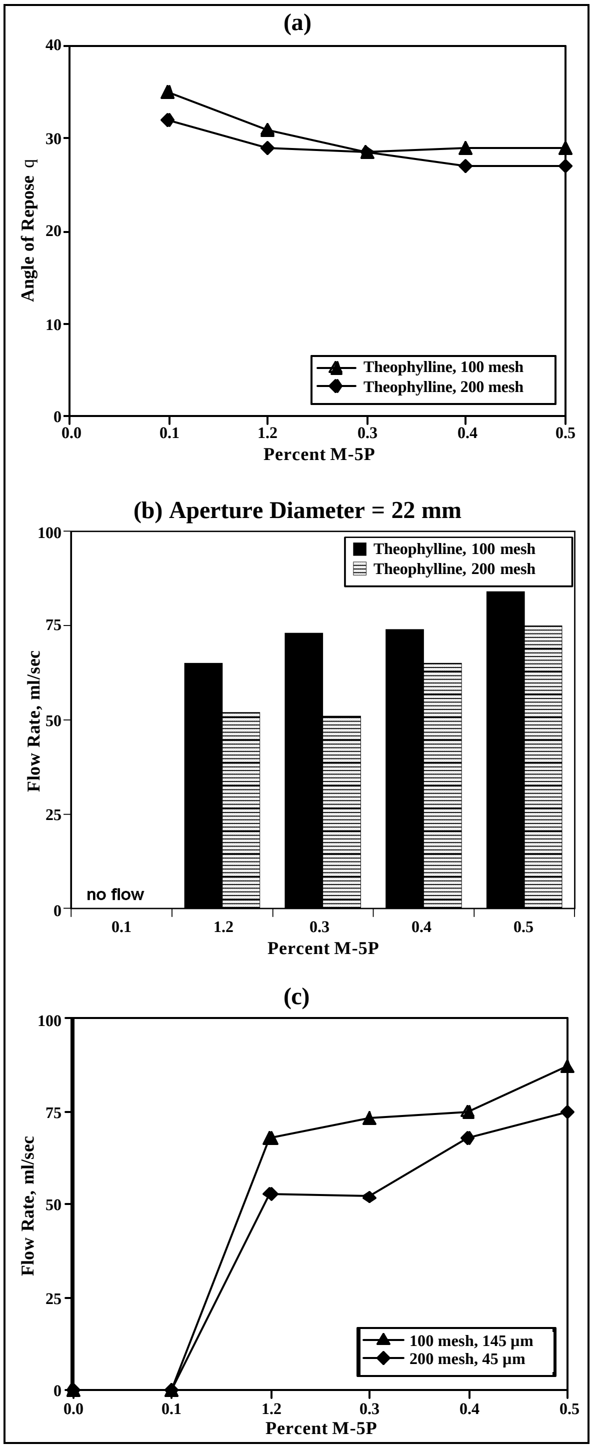


Figure 5

Influence of CAB-O-SIL M-5P fumed silica on the angle of repose and flow rates of a 1:1 blend of microcrystalline cellulose (Avicel® PH-101) and theophylline

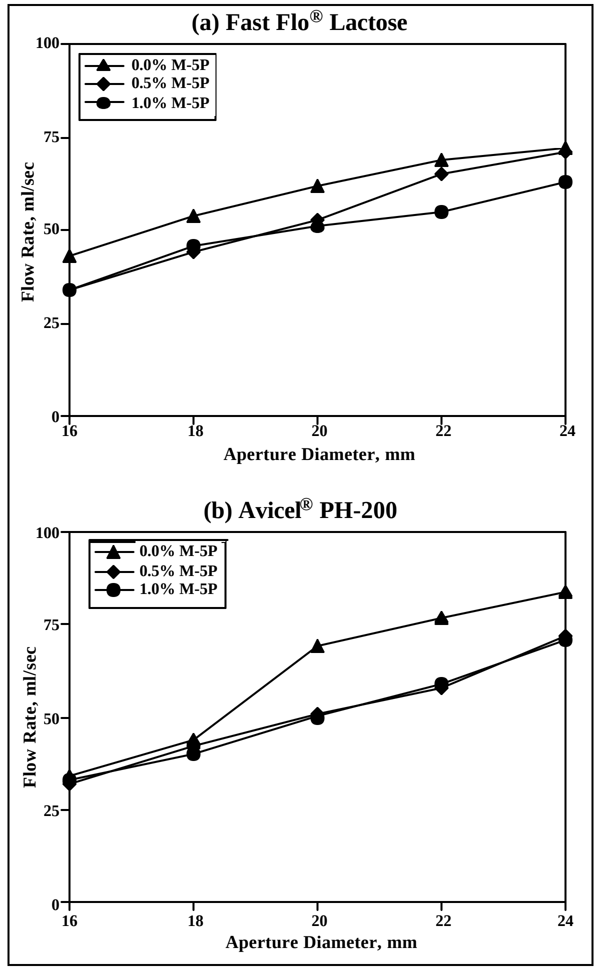


Figure 6

Influence of CAB-O-SIL M-5P fumed silica on the flow rate of: (a) Fast Flo® lactose and (b) Avicel® PH-200 using the FLODEX™ apparatus

Our studies demonstrated that Fast Flo® lactose and Avicel® PH-200 exhibited excellent flow properties. As shown in Figure 6, the addition of CAB-O-SIL® M-5P at the 0.5% and 1% level, appears to hinder the flow properties of the material when compared to the excipient in the absence of the glidant. The addition of the glidant to both of these materials produced powdered blends that displayed excellent flow properties and were less dense and more fluffy. However, due to the higher volume of the powder, it took longer for the powder to pass through the FLODEX™ flow meter, which would explain the decrease in flow rates with the addition of the CAB-O-SIL M-5P fumed silica.

The formation of a powder bridge in a hopper of a tablet press can lead to a phenomenon known as “rat-hole” formation. The photographs shown in Figure 7 illustrate this phenomenon. In Figure 7a, the surface morphology of a tablet granulation in a hopper is shown. This granulation con-

(a)

(b)

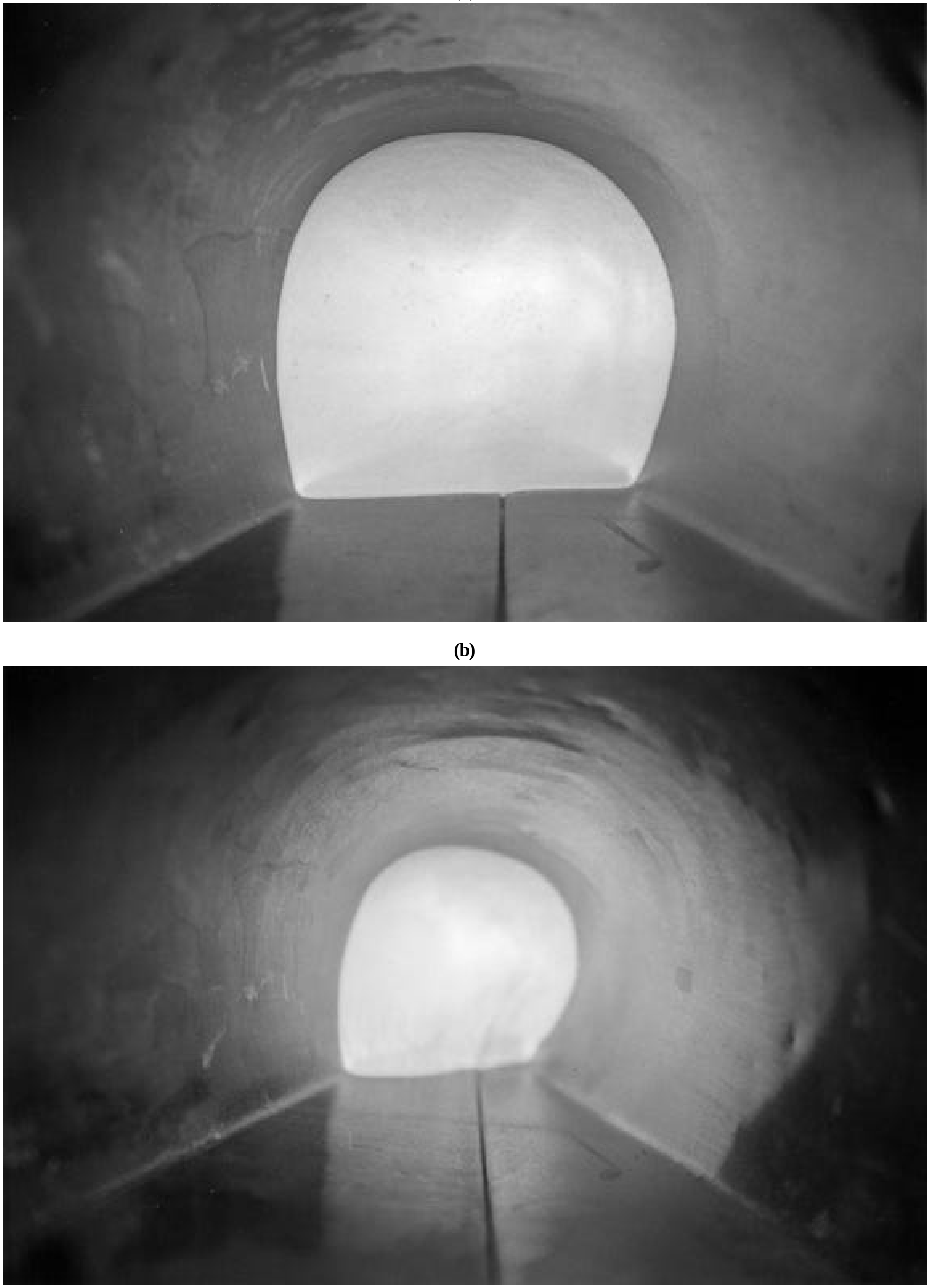
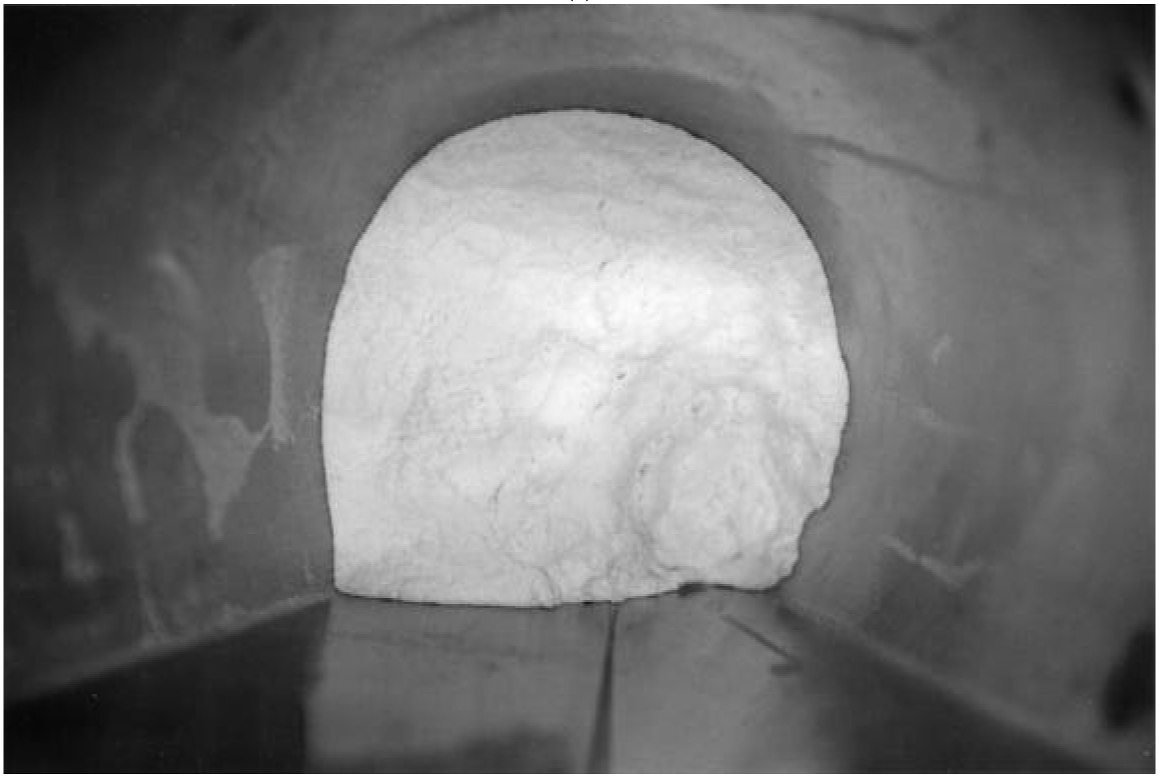


Figure 7

Optical photographs of granulation in tablet hopper: (a,b) granulation containing 0.5% CAB-O-SIL® M-5P fumed silica and (c,d) “rat-hole” formation in granulation (no glidant)

(a)



(b)

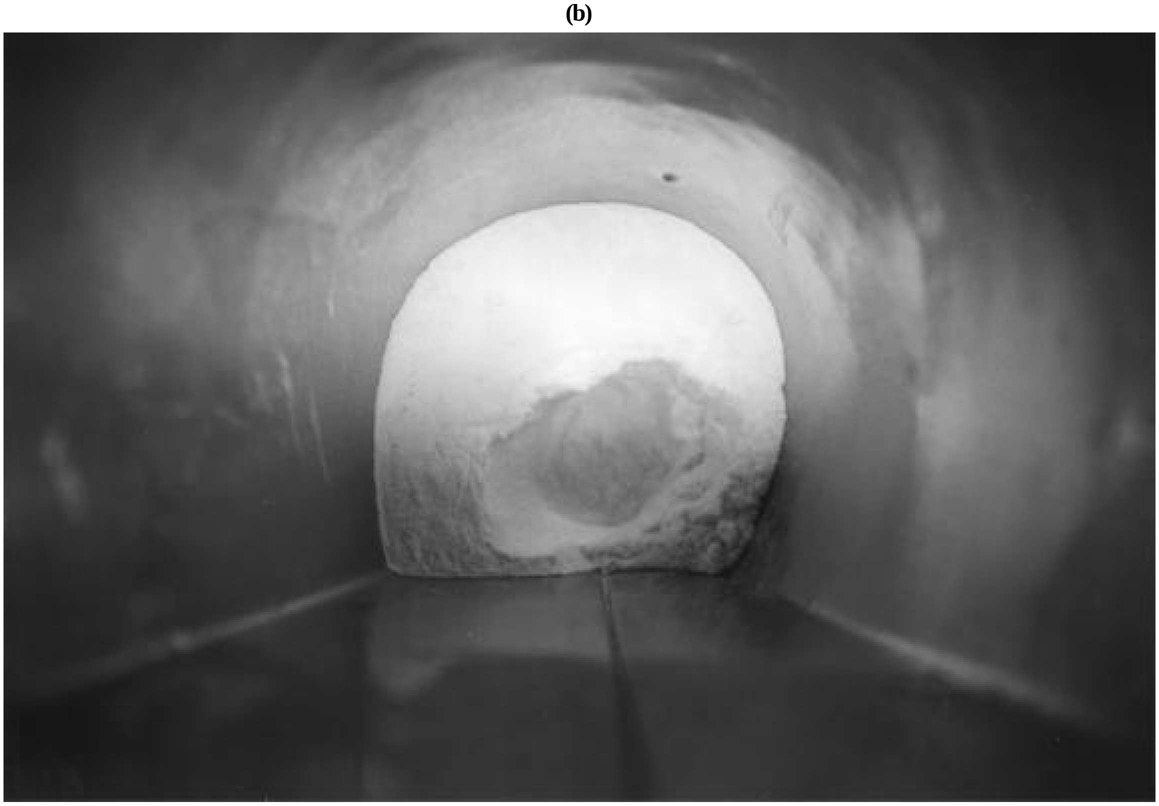


Figure 7

Optical photographs of granulation in tablet hopper: (a,b) granulation containing 0.5% CAB-O-SIL® M-5P fumed silica and (c,d) “rat-hole” formation in granulation (no glidant) tained 0.5% CAB-O-SIL® M-5P fumed silica and flowed evenly through the hopper into the tablet press. In Figure 7b, the photograph shows the granulation at a later stage of the tableting process. Figure 7c shows the first signs of "rat-hole" formation at the edge of the granulation. As the process is continued, a well defined orifice in the granulation appears in Figure 7d. For granulations that have extremely poor flow, this orifice will continue down to the feed shoe. Vibration of the hopper has been used to assist in the flow of such poorly formulated granulations. The phenomenon of "rat-hole" formation is schematically presented in Figure 8.

In summary, it has been demonstrated that low levels of CAB-O-SIL M-5P in a powder blend will have a dramatic effect on the flow properties of powders and granulations. The fumed silica will also increase the tensile strength of tablet compacts, contribute to strong bond formation between granules and reduce the static charge of the powders.

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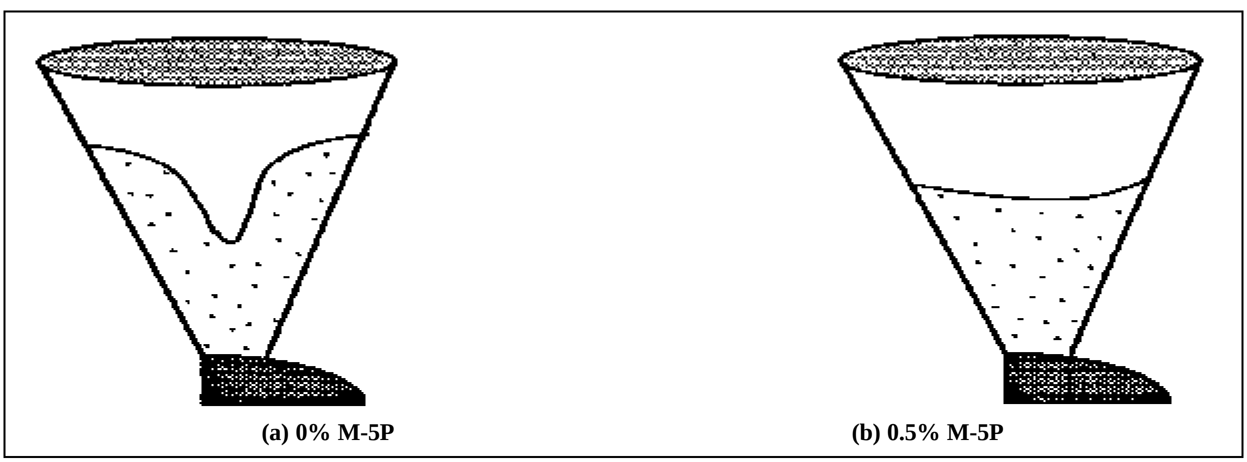

Figure 8

Schematic representation of granulation in hopper of tablet machine: (a) "rat hole" formation in granulation and (b) granulation containing 0.5% CAB-O-SIL M-5P fumed silica.

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